Contemporary Rhinology: Science and Practice

Andrew C. Swift
Sean Carrie
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Editors
Andrew C. Swift
Liverpool Head and Neck Centre
Liverpool University Hospitals
Foundation Trust
Liverpool, UK

Sean Carrie
Otolaryngology
Freeman Hospital, Newcastle upon Tyne
Hospitals NHS Foundation Trust
Newcastle upon Tyne, UK

Christopher de Souza
Department of Otolaryngology
Tata Memorial Hospital
Mumbai, Maharashtra, India

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Foreword

Since the 1980s, rhinology has genuinely experienced its "Golden Age" with the advent of new diagnostic techniques, medical treatments, and surgical approaches. This has been underpinned by an increasing understanding of the anatomy, physiology, and pathophysiology of the respective conditions and an appreciation of the interplay of the nose and sinuses with the lower respiratory tract and the rest of the body. Furthermore, rhinology has embraced the application of an evidence-based approach with an exponential rise in randomized controlled trials and prospective cohorts, enabling individualized precision medicine and surgery.

This book offers not only a contemporary approach to rhinology but also one which is comprehensive. It covers both the scientific aspects of the speciality but also provides clear practical advice on clinical management in both adults and children. It is, therefore, of use to a broad constituency of readers and practitioners from the motivated medical student, through the ENT trainee, interested primary care physician, to the general otorhinolaryngologist and tertiary care rhinologist. It is increasingly recognized that optimum management of many rhinologic conditions, such as recalcitrant allergic rhinitis or chronic rhinosinusitis, sinonasal neoplasia, and rarities such as vasculitis and hereditary hemorrhagic telangiectasia, is ideally undertaken by multidisciplinary teams that provide the widest range of expertise and greatest benefit to patients and clinicians alike. Similar synergies exist at the sino-orbital interface and skull base. All of these topics are addressed in this book, so there are also allergists, immunologists, pulmonologists, oncologists, ophthalmologists, neurosurgeons, gastroenterologists, and rheumatologists among many others who would find the contents of this book of value.

In commissioning this book, the editors have spread their net widely to include an array of experts from many countries and subspeciality interests so the advice represents a distillation of up-to-date information, irrespective of the healthcare system.

It is happenstance to be in the right place at the right time and that is certainly true for those of us with an interest in the nose and sinuses in recent decades. However, one should recognize that it is more important to know how to take advantage of being in the right place at the right time, and this book facilitates that aspiration.

Professor Valerie J. Lund, CBE
Royal National Ear, Nose and Throat
and Eastman Dental Hospital, UCLH
London, UK

Preface

A complete understanding of the nose, paranasal sinuses, and the respiratory tract is best regarded as a work in progress and a subject that is constantly developing. Whilst the ongoing pandemic was a major setback, it also provided opportunities for discovery and became an important landmark in rhinological and olfactory knowledge. We have used this to our advantage and included the newly learnt knowledge about the SARS-CoV-2 coronavirus within this book.

Medical technology and computing have continued to rapidly improve, enabling high-quality imaging and visualization of previously obscured structures to be seen with outstanding clarity.

In parallel with this, our understanding of the basic science, the physiology, and medical disorders of the nasal and paranasal passages greatly improved, facilitating better understanding of treatment strategies and modalities that led to better patient outcomes.

From the historical perspective, the field of rhinology has gained much scientific acclaim. In the 1970s and 1980s, studies on mucociliary flow, instigated by Professor Walter Messerklinger and aided by Heinz Stammberger, underpinned a novel concept of surgical techniques for the nose and sinuses, leading to the term "Functional Endoscopic Sinus Surgery (FESS)." This term has stood the test of time but is now used loosely to describe any minimally invasive sinus surgery, even when extensive resection is performed.

The year 2004 marks a landmark event, when Linda Buck and Richard Axel were awarded the Nobel Prize for their work on olfaction. The SARS-CoV-2 virus subsequently led to a huge expansion in olfactory research and a whole wealth of new information.

The heightened profile of rhinology has led to a whole new generation of endoscopic sinus surgeons, who have been at the forefront of a dramatic expansion in the scale and scope of various endoscopic techniques. Surgical procedures that were once considered "challenging and fraught with danger" are now rendered as routine operations. This advance has been achieved by certain more serious procedures being focused in specialist centers dedicated to controlling risk and minimizing complications, leading to improved patient outcomes.

The net effect of the above changes has been to place rhinology at the forefront of surgery. This incredible journey began with the development of the rigid endoscope, alongside dedicated CT and MRI imaging techniques. We can only wonder as to what other advancements lie on the horizon, how

these will affect our current management protocols and the outcomes for the wide range of rhinological disorders.

We, the editors, are immensely grateful to our contributory authors, who are all experts within their fields. Each author has produced a state-of-the-art, extremely valuable contribution, each taking many hours of planning, research, development, and writing. We thank each and every one of the authors for their commitment and support.

We hope the readers of this book will be filled with awe and wonder at the extreme complexity of the nose and the paranasal sinuses. We also hope that this will lead to an unending desire to study this fascinating, complex, and specialist organ that continues to surprise us all. We would strongly encourage our younger colleagues to develop an interest into the art and science of the diseases of the nose, and hope that this book will be the catalyst for this dedicated journey.

Liverpool, UK — Andrew C. Swift
Newcastle, UK — Sean Carrie
Mumbai, Maharashtra, India — Christopher de Souza

Contents

Contributors

Shahzada Ahmed University Hospitals Birmingham NHS Trust, Birmingham, UK

Mikkel C. Alanin Department of Otorhinolaryngology-Head and Neck Surgery and Audiology, Copenhagen University Hospital, Copenhagen, Denmark

Isam Alobid Department of Otorhinolaryngology, Rhinology and Skull Base Unit, Hospital Clinic, Universitat de Barcelona, Barcelona, Spain

Centro Médico Teknon, Barcelona, Spain

Department of ORL-HNS, Hospital Clinic, Barcelona, Spain

Emily Anderson Liverpool Centre for Genomic Medicine, Liverpool Women's Hospital, Liverpool, UK

Peter Andrews Royal National Throat Nose and Ear Hospital and National Hospital of Neurology and Neurosurgery, London, UK

Wout Backaert Department of Otorhinolaryngology, University Hospitals Leuven, Leuven, Belgium

Department of Microbiology, Immunology and Transplantation, Allergy and Clinical Immunology Research Unit, KU Leuven, Leuven, Belgium

Stephen Ball Department of Surgery, The University of Auckland, Auckland, New Zealand

Hazan Basak Department of Otorhinolaryngology—Head and Neck Surgery, Ankara University, Medical School, Ankara, Turkey

Paolo Battaglia Division of Otorhinolaryngology, Department of Biotechnology and Life Sciences, University of Insubria-Varese, ASST Sette Laghi, Ospedale di Circolo e Fondazione Macchi, Varese, Italy

Department of Biotechnology and Life Sciences, Head and Neck Surgery and Forensic Dissection Research Center (HNS and FDRc), University of Insubria, Varese, Italy

Manuel Bernal-Sprekelsen Department of ORL-HNS, Hospital Clinic, Barcelona, Spain

Christian Stephan Betz Department of Otorhinolaryngology, University Medical Centre Hamburg-Eppendorf, Hamburg, Germany

Rajiv K. Bhalla Manchester Foundation Trust and Salford Royal Hospital, Manchester, UK

Hans Rudolf Briner Center for Otorhinolaryngology, Head and Neck Surgery, Hirslanden Clinic, Zurich, Switzerland

Juan Carlos Ceballos Cantu Department of ORL-HNS, Hospital Clinic, Barcelona, Spain

A. Simon Carney, FRCS(ORL-HNS), FRACS, DM College of Medicine and Public Health, Flinders University, Adelaide, Australia

Adelaide Sinus Centre, Adelaide, Australia

Sean Carrie Rhinology and Skull Base Surgery, Newcastle upon Tyne Hospitals NHS Foundation Trust, Newcastle upon Tyne, UK

ENT Department, Ninewells Hospital, Dundee, UK

Paolo Castelnuovo Division of Otorhinolaryngology, Department of Biotechnology and Life Sciences, University of Insubria-Varese, ASST Sette Laghi, Ospedale di Circolo e Fondazione Macchi, Varese, Italy

Department of Biotechnology and Life Sciences, Head and Neck Surgery and Forensic Dissection Research Center (HNS and FDRc), University of Insubria, Varese, Italy

Russell A. Cathcart ENT Department, Jersey Hospital, Jersey, UK

Juan Carlos Ceballos Department of Otorhinolaryngology, Rhinology and Skull Base Unit, Hospital Clinic, Universitat de Barcelona, Barcelona, Spain

Vasileios Chatzinakis Endoscopic Skull Base Center, Hygeia Hospital, Athens, Greece

Raymond W. Clarke Department of Ear, Nose and Throat, Alder Hey Children's NHS Foundation Trust, Liverpool, UK

Christopher de Souza Lilavati Hospital, Holy Family Hospital, Mumbai, India

Department of Otorhinolaryngology, SUNY Brooklyn, New York, NY, USA

Department of Otorhinolaryngology, LSUHSC, Shreveport, LA, USA

Mumbai, India

Rosemarie de Souza BYL Nair Hospital, Mumbai, India

Peter George Deutsch Department of Otolaryngology, Birmingham Women's and Children's Hospital NHS Foundation Trust, Birmingham, UK

Joanna K. Dixon Department of Radiology, Freeman Hospital, Newcastle upon Tyne Hospitals NHS Foundation Trust, Newcastle upon Tyne, UK

Richard Douglas Department of Surgery, The University of Auckland, Auckland, New Zealand

Stephen R. Ell Hull University Teaching Hospitals NHS Trust, Castle Hill Hospital, Cottingham, East Yorkshire, UK

Cecilia Ahlström Emanuelsson ENT-Department, Skane University Hospital, Lund, Sweden

Wytske J. Fokkens Department of Otorhinolaryngology and Head and Neck Surgery, Amsterdam University Medical Centres, AMC, Amsterdam, The Netherlands

Claire Frauenfelder Department of Paediatric Otolaryngology, Great Ormond Street Hospital for Children NHS Foundation Trust, London, UK

University of Adelaide, Adelaide, South Australia, Australia

Richard Wei Chern Gan Hull University Teaching Hospitals NHS Trust, Castle Hill Hospital, Cottingham, East Yorkshire, UK

Quentin Gardiner Department of Otolaryngology, Ninewells Hospital and Medical School, Dundee, UK

Christos Georgalas Endoscopic Skull Base Center, Hygeia Hospital, Athens, Greece

Medical School, Nicosia University, Nicosia, Cyprus

Nicholas Goncalves Division of Otolaryngology, Groote Schuur Hospital, University of Cape Town, Cape Town, South Africa

Richard Green ENT Department, Ninewells Hospital, Dundee, UK

Usamah Hadi Department of Otolaryngology Head and Neck Surgery, American University of Beirut, Beirut, Lebanon

Richard J. Harvey Rhinology and Skull Base Research Group, St. Vincent's Centre for Applied Medical Research, University of New South Wales, Sydney, NSW, Australia

Faculty of Medicine and Health Sciences, Macquarie University, Sydney, NSW, Australia

Darlinghurst, NSW, Australia

Stephen Hayes Rhinology and Facial Plastics, Portsmouth Hospitals University NHS Trust, Queen Alexandra Hospital, Portsmouth, UK

Claire Hopkins ENT Department, Guy's Hospital, London, UK

Haissan Iftikhar University Hospitals Birmingham NHS Trust, Birmingham, UK

Isma Z. Iqbal The Newcastle Hospitals NHS Foundation Trust, Freeman Hospital, Newcastle upon Tyne, UK

Forsan Jahshan Queen's Medical Centre, Nottingham, UK

Hisham S. Khalil University Hospitals Plymouth NHS Trust, Plymouth, UK

University of Plymouth, Plymouth, UK

Grace C Khong Department of Ear, Nose and Throat, Alder Hey Children's NHS Foundation Trust, Liverpool, UK

Raymond Kim Department of Surgery, University of Auckland, Auckland, New Zealand

Nirmal Kumar ENT Department, Royal Albert Edward Infirmary, Wigan, Wigan, UK

Wrightington, Wigan & Leigh Teaching NHS FT, Wigan, UK

Cristobal Langdon Department of Otorhinolaryngology, Rhinology and Skull Base Unit, Hospital Clinic, Universitat de Barcelona, Barcelona, Spain

Darlene Lubbe Division of Otolaryngology, Groote Schuur Hospital, University of Cape Town, Cape Town, South Africa

Sangeeta Maini Department of Otolaryngology, Grampian University Hospital, Aberdeen Royal Infirmary, Aberdeen, UK

Nick Makwana Department of Child Health, Sandwell and West Birmingham NHS Trust, Birmingham, UK

Lisha McClelland University Hospital Birmingham, Birmingham, UK

Ann-Louise McDermott Department of Otolaryngology, Birmingham Childrens Hospital, Birmingham Womens and Childrens Hospital NHS Foundation Trust, Birmingham, UK

Victoria McKay Liverpool Centre for Genomic Medicine, Liverpool Women's Hospital, Liverpool, UK

Jo-Lyn McKenzie Royal Brisbane and Womens Hospital, Brisbane, QLD, Australia

Claire Marie McLarnon Freeman & GNCH Hospitals, Newcastle upon Tyne, UK

Andrew S. McQueen Department of Radiology, Freeman Hospital, Newcastle upon Tyne Hospitals NHS Foundation Trust, Newcastle upon Tyne, UK

Cem Meco Department of Otorhinolaryngology—Head and Neck Surgery, Ankara University, Medical School, Ankara, Turkey

Department of Otorhinolaryngology—Head and Neck Surgery, Salzburg Paracelsus Medical University, Salzburg, Austria

Cara Morris Rhinology and Skull Base Research Group, St. Vincent's Centre for Applied Medical Research, University of New South Wales, Sydney, NSW, Australia

Department of Otolaryngology, Head, Neck and Skull Base Surgery, St. Vincent's Hospital, Sydney, NSW, Australia

Sydney ENT clinic, Darlinghurst, NSW, Australia

Stefan Müller Department for Otorhinolaryngology, Head and Neck Surgery, Asklepios Klinikum Harburg, Asklepios Campus Hamburg, Semmelweis University Budapest, Hamburg, Germany

Abdul Nassimizadeh University Hospital Birmingham, Birmingham, UK

Giancarlo Ottaviano Department of Neurosciences, Otolaryngology Section, University of Padua, Padua, Italy

Aishan Patil Specialist Registrar, Vascular Surgery, Dundee, UK

Anish Patil Royal Wolverhampton NHS Trust, Wolverhampton, UK

Carl Philpott The Norfolk Smell & Taste Clinic, Norfolk & Waveney ENT Service, Norwich, UK

Norwich Medical School, University of East Anglia, Norwich, UK

Yujay Ramakrishnan Queen's Medical Centre, Nottingham, UK

Bhaskar Ram Department of Otolaryngology, Grampian University Hospital, Aberdeen Royal Infirmary, Aberdeen, UK

Sietze Reitsma Department of Otorhinolaryngology and Head and Neck Surgery, Amsterdam University Medical Centres, AMC, Amsterdam, The Netherlands

Joanne Rimmer Department of Otolaryngology Head & Neck Surgery, Monash Health, Melbourne, Australia

Department of Otolaryngology Head & Neck Surgery, St Vincent's Hospital, Melbourne, Australia

Department of Surgery, Monash University, Melbourne, Australia

John Rocke ENT Department, Royal Albert Edward Infirmary, Wigan, UK

Wrightington, Wigan & Leigh Teaching NHS Foundation Trust, Wigan, UK

Alfonso Santamaría-Gadea Department of Otorhinolaryngology, Rhinology and Skull Base Surgery Unit, Ramón y Cajal University Hospital, Madrid, Spain

Daniel W. Scholfield Barts Health NHS Trust, London, UK

Giorgio Sileo Department of Biotechnology and Life Sciences, Head and Neck Surgery and Forensic Dissection Research Center (HNS and FDRc), University of Insubria, Varese, Italy

Marios Stavrakas University Hospitals Plymouth NHS Trust, Plymouth, UK

Andrew C. Swift Liverpool Head and Neck Centre, Liverpool University Hospitals Foundation Trust, Liverpool, UK

Neil Cheng-Wen Tan Royal Cornwall Hospitals NHS Trust, Truro, Cornwall, UK

University of Exeter Medical School, Exeter, UK

Vamsidhar Vallamkondu Department of Otolaryngology, Grampian University Hospital, Aberdeen Royal Infirmary, Aberdeen, UK

Laura Van Gerven Department of Otorhinolaryngology, University Hospitals Leuven, Leuven, Belgium

Department of Microbiology, Immunology and Transplantation, Allergy and Clinical Immunology Research Unit, KU Leuven, Leuven, Belgium

Department of Neurosciences, Experimental Otorhinolaryngology, KU Leuven, Leuven, Belgium

Thomas Verse Department for Otorhinolaryngology, Head and Neck Surgery, Asklepios Klinikum Harburg, Asklepios Campus Hamburg, Semmelweis University Budapest, Hamburg, Germany

Christian von Buchwald Department of Otorhinolaryngology-Head and Neck Surgery and Audiology, Copenhagen University Hospital, Copenhagen, Denmark

Sarah Vreugde Department of Surgery-Otolaryngology Head and Neck Surgery, Central Adelaide Local Health Network, Woodville South, Australia

The University of Adelaide, Adelaide, Australia

Rich Williams University Hospitals Plymouth NHS Trust, Derriford Hospital, Plymouth, UK

Stephen P. Williams Liverpool Head and Neck Centre, Liverpool University Hospitals NHS Foundation Trust, Liverpool, UK

Tim Woolford, MD, FRCS(ORL-HNS) Manchester Royal Infirmary, Manchester, UK

Edge Hill University, Ormskirk, UK

Peter-John Wormald Department of Surgery-Otolaryngology Head and Neck Surgery, Central Adelaide Local Health Network, Woodville South, Australia

The University of Adelaide, Adelaide, Australia

Michelle Wyatt Department of Paediatric Otolaryngology, Great Ormond Street Hospital for Children NHS Foundation Trust, London, UK

Tary Yin Department of Surgery, University of Auckland, Auckland, New Zealand

Section I

The Basic Science of Rhinology: Understanding the Nose and Sinuses

Embryology of the Nose and Paranasal Sinuses

1

Daniel W. Scholfield and Neil Cheng-Wen Tan

Nose Development

Early Development Three facial projections contribute to the formation of the nose—the frontonasal process, the maxillary process, and the mandibular process (Fig. 1.1). At the end of the third week of embryonic life, the forebrain enlarges and pushes overlying ectoderm forward to form the frontonasal process. The stomodeum forms inferior to the frontonasal process in the fourth week as an invagination with ectodermal covering.

The ectoderm over the stomodeum meets the endoderm of the developing foregut to form the oropharyngeal membrane, which breaks down in the fifth week to allow an external communication with the foregut (Tables 1.1 and 1.2).

Branchial Arches Mesenchymal growth of the first branchial arch forms the maxillary and mandibular processes bilaterally. The stomodeum is therefore surrounded by the maxillary processes either side, the mandibular processes below and frontonasal process above [1] (Fig. 1.1).

D. W. Scholfield
Barts Health NHS Trust, London, UK

N. C.-W. Tan (✉)
Royal Cornwall Hospitals NHS Trust,
Truro, Cornwall, UK

University of Exeter Medical School, Exeter, UK
e-mail: n.tan@exeter.ac.uk

Nasal Development Nasal development begins when a pair of thickened ectodermal nasal placodes, derived from the frontonasal process, becomes visible in the 4-week-old embryo. Pax-6 expression is essential in the development of the nasal placodes [2]. The forward growth of the lateral and medial aspects of the nasal placodes gives rise to the nasal pits, which are well developed at 32–34 days.

The nasomedial and nasolateral processes are mesenchymal elevations surrounding the nasal pits. This mesenchymal proliferation is stimulated by release of fibroblast growth factor 8 (FGF-8), expressed in the rim of invaginating nasal pits [3]. These swellings merge towards the midline during the sixth and seventh week. The nasolateral processes then form the alae of the nose, whilst the nasomedial processes form the tip and crest, with part of the nasal septum. The frontonasal process then recedes to contribute to the nasal bridge.

Olfactory Development The epithelium of the nasal pits develops neural processes under the influence of FGF-8 and sends axonal projects towards the olfactory bulb to form the olfactory neurons.

Choanal Development The nasal pits continue to deepen towards the oral cavity, and by 6.5 weeks, only a thin oronasal membrane separates the oral cavity from the nasal cavity. The rupture of the

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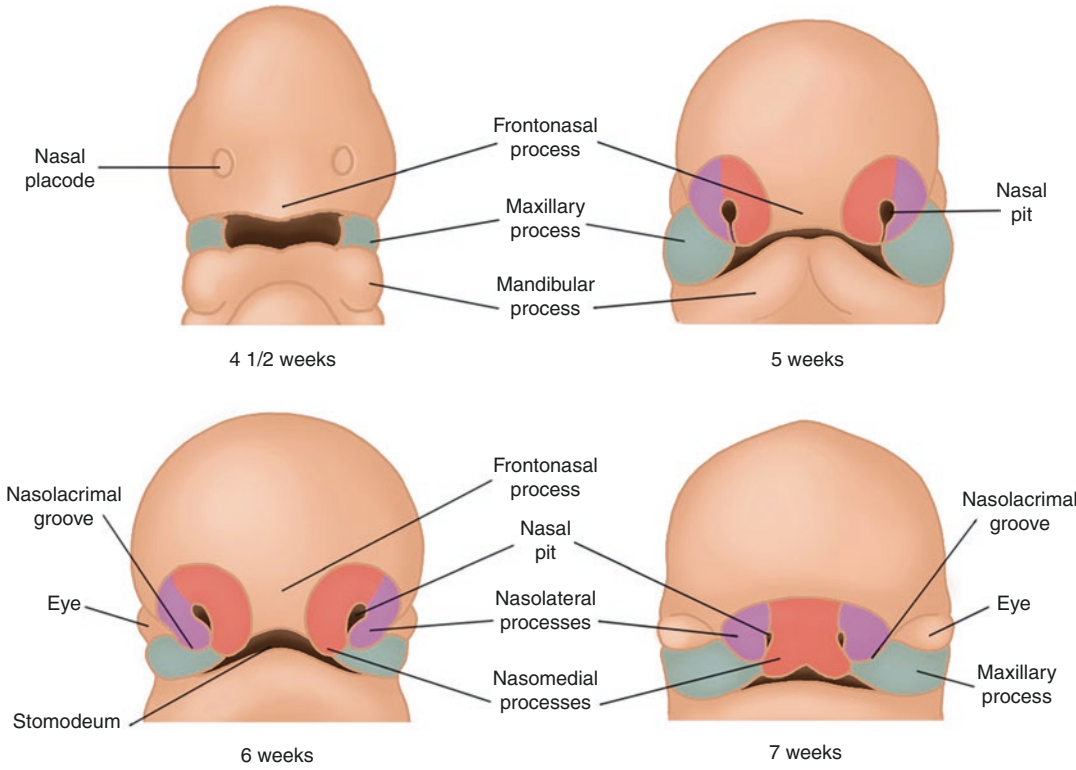

Fig. 1.1 Early naso-facial embryological development

Table 1.1 Timeline of foetal development

Week of gestation	Nasal development	Sinus development	Lacrimal development
3rd	Frontonasal process formation		
4th	Stomodeum and nasal placode formation	Ethmoid sinus development begins	
5th	Oropharyngeal membrane breakdown		Olfactory pit formation
6th	Oronasal membrane breakdown		Ectoderm extension from olfactory sac
7th	Turbinate development begins		
8th			Lacrimal pathway formation complete
9th			
10th		Maxillary sinus development begins	
11th			
12th	Chondrification of nasal capsule	Sphenoid sinus development begins	
13th		Tooth germs arise	
14th			
15th			
16th		Frontal sinus development begins	
17th	Apoptosis of epithelial plug		

Table 1.2 Timeline of early childhood

Age	Maxillary sinus	Ethmoid sinus	Frontal sinus	Sphenoid sinus
Birth	Lower border above nasal floor	3-4 air cells	Present as small pit	Rudimentary recess
1	1st rapid growth phase			
2			Present as small blind pocket	
3				Formation complete
4			Reaches mid-vertical height of orbit	
5				
6				
7	2nd rapid growth phase			
8			Reaches superior orbital rim	
9	Sinus floor level with nasal floor			
10			Extends into frontal squama	
11				
12			Adult size	
13				
14				Pneumatization complete
Adult		Up to 15 air cells		

oronasal membrane occurs between days 42 and 44, forming the primitive choanae—a communication between the primary oral and nasal cavities. The choanae lies behind the primary palate, which is formed by the fusion of the medial nasal processes. Choanal atresia results if the oronasal membrane fails to break down. The external nares are brought closer together as the frontonasal process, which separates them, reduces in size.

Palatal Development The maxillary processes arise from the first pharyngeal pouch and produce palatal shelves which are vertical mesenchymal tissue outgrowths. These re-orientate into the horizontal plane and continue growing until they meet at the midline. Secondary palate formation progresses from anterior to posterior, simultaneously forming the secondary nasal cavity. This results in the posterior choana being repositioned posteriorly. The nasopalatine canal remains as a persistent communication at the junction of the premaxilla and palate.

Nasal Vestibule A plug of epithelial cells blocks the anterior lumen of the nasal cavity by 7–8 weeks. By the 17th week, this epithelial plug undergoes apoptosis, resulting in the nasal passages reopening and becoming the nasal vestibule [4].

Internal Nose and Sinuses Nasal pit epithelium induces the surrounding neural crest mesenchyme to form the cartilaginous nasal capsule. This structure forms a boundary for paranasal sinus and nasal development while also combining with more centrally derived mesenchyme to form the nasal septum and later the ethmoid bones. Chondrification of the nasal capsule starts at the skull base adjacent to the sphenoid bone in the third month of development. Ossification of the nasal capsule originates in centres of ossification, the first of which is located at the anterior edge of the sphenoid bone. The second centre of ossification occurs in the lateral aspect of the nasal capsule, with multiple subsequent centres developing [5].

Nasal Septum The septum is initially entirely cartilaginous and develops from the medial wall of the lateral capsule during the second to third embryonic month. At birth, the maxillary crest, palatine crest and vomer will have ossified. The cartilaginous septum grows swiftly during the first 2 years of life. Ossification of the cranial and posterior part of the cartilaginous septum results in perpendicular plate formation [6].

Turbinate Development

During the seventh gestational week, the first projection into the nasal cavity occurs, namely, the maxilloturbinal, which is the precursor to the inferior turbinate.

The first ethmoturbinal originates at the superior junction of the lateral nasal wall and septum, developing into the middle turbinate. The middle nasal meatus forms between these two structures and within this the diverticulum of the embryonic infundibulum forms.

The second ethmoturbinal gives rise to the superior turbinate, and third ethmoturbinal forms the supreme turbinate, which can be identified in 50% of adults [7]. The furrow between these structures forms the supreme turbinate.

The first, second and third ethmoturbinals are considered ethmoid in origin. These structures grow from their origins in the lateral nasal wall to attach to the lamina papyracea and skull base.

Paranasal Sinus Development

The paranasal sinuses arise as outpouchings of the lateral nasal wall, except for the sphenoid sinus. They are generally established in the embryo but are rudimentary at birth, with the exception of the maxillary sinus. Their development influences facial structure during childhood and vocal resonance in adolescence, with highly variable growth patterns between sides and individuals.

Maxillary Sinus

The maxillary sinus begins as an outpouching of the lateral nasal capsule mucosa during the tenth week of gestation [8], occurring posterior to the primitive uncinate process within the primitive ethmoid infundibulum. At this stage, it can be considered as an extension of the infundibulum; therefore, both should be considered as part of the same anatomic and developmental unit. This is supported by the association of a poorly developed infundibulum with maxillary sinus hypoplasia [8]. The perichondrium of the nasal capsule prevents significant extension into the maxilla, and it is not until the nasal capsule undergoes ossification that the maxillary sinus pneumatizes into the maxilla.

Further growth of the maxillary sinus follows the descent of dentition. In the neonate, the lower border lies above the nasal floor; however, it begins to descend as the mid-third of the face develops and dentition erupts (Fig. 1.2). Between 9 and 12 years old, the floor of the maxillary sinus is at the level of the nasal floor [8]. The descent then continues as permanent teeth erupt, until it is 0.5–10 mm below the nasal cavity. The maxillary sinus has two period of rapid growth during childhood, one between birth and the 3rd year and the other between the 7th and the 12th year [9].

The maxillary sinus ostium is elliptical throughout prenatal development, with narrower proportions than the adult ostium. The foetal ostium is located in the anterior third of the ethmoid infundibulum, whereas the adult ostium is located between the middle and posterior third of the ethmoid infundibulum [8].

Tooth germs are identifiable as early as the 13th week of gestation [10]. It is important to note that until 8 years of age, the floor of the nose is still lower than the floor of the maxillary sinus,

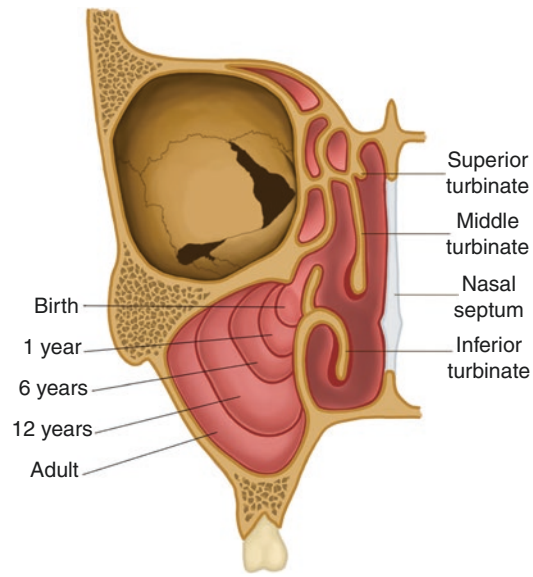

Fig. 1.2 Maxillary sinus development pattern

and the permanent teeth have not all erupted. Therefore, an inferior middle meatal antrostomy or Caldwell–Luc procedure in this age group could damage permanent tooth buds, leading to failure of tooth development [11, 12].

Ethmoid Sinus

Ethmoid sinus development begins in the fourth week of gestation. They are well developed at birth and comprises of 3–4 air cells, increasing to up to 15 by adulthood. Ethmoid sinus development can be divided into anterior and posterior cell groups, based on their initial sites of pneumatization. The anterior ethmoidal cell group develops in the middle meatus, and the posterior ethmoidal cell group originates in the superior meatus.

Five basal lamellae serve as attachments to the lateral nasal wall during development (Table 1.3). The first basal lamella is the lateral extension of the uncinate process; the second basal lamella is the lateral extension of the ethmoid bulla; the third basal lamella is the attachment of the middle turbinate; the fourth basal lamella is the attachment of the superior turbinate; and the fifth basal lamella is the attachment of the supreme turbinate when present. The ethmoidal sinus cells respect the boundaries of the lamella during development, and the lamella can be stretched but not broken. This is clinically relevant to the endoscopic sinus surgeon, who can make use of embryological knowledge to navigate safely through the full ethmoid labyrinth using a structured approach. Figure 1.3 highlights this concept of how the ethmoid lamellae act as doors and gateways to the ethmoid sinus chambers behind and the importance of identifying these lamellae to perform safe sinus surgery.

Depressions in the nasal mucosa of the nasal capsule deepen and become globular air cells during primary pneumatization. The sinuses are named by the bone in which they finally reside. However, they may have their origins in the ethmoid during foetal life. These are called extramural cells, an example being the frontal sinus which may be considered as a displaced anterior ethmoid cell. The extramural ethmoid air cells do not grow beyond the ethmoid bone until after birth. These cells include the agger nasi cells, which develop from the nasoturbinal prominence, anterior and superior to the middle meatus; the frontal sinus cells; infraorbital ethmoid cells and sphenoid bone cells.

Table 1.3 The basal lamellae

First basal lamella	The lateral extension of the uncinate process
Second basal lamella	The lateral extension of the ethmoid bulla
Third basal lamella	The lateral attachment of the middle turbinate
Fourth basal lamella	Attachment of the superior turbinate
Fifth basal lamella	Attachment of the supreme turbinate

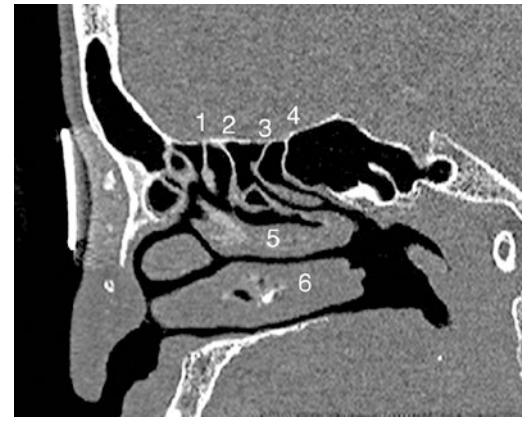

Fig. 1.3 Parasagittal slice of CT sinus demonstrating 1 uncinate process; 2 lamella of middle turbinate; 3 lamella of superior turbinate; 4 anterior face of sphenoid sinus; 5 middle turbinate; 6 inferior turbinate

Frontal Sinus

The frontal sinus begins to develop during the fourth month of gestation, by direct extension of the frontonasal recess or as a superior epithelial migration of the anterior ethmoidal cells that penetrate the inferior surface of the frontal bone [13]. The foetal frontal process is situated between the anterior attachment of the middle turbinate and the uncinate process.

The frontal sinus is not seen on imaging at birth but is present as a small pit. Underdevelopment means that frontal sinusitis cannot occur before 4 years of age. Primary pneumatization occurs in the first year after birth, and the frontal sinus remains a small blind pocket until 2 years after birth (Fig. 1.4). Secondary pneumatization begins between 6 months and 2 years and continues until adolescence. At 4 years of age, the superior edge of the frontal sinus reaches the mid-vertical height of the orbit. It then reaches the height of the superior orbital rim at 8 years and grows into the frontal squama at 10 years of age [4]. The adult appearance of the frontal sinus usually forms by 12 years. Supra-agger frontal cells, supra-bulla frontal cells or supra-orbital ethmoid cells may form if the anterior ethmoid cells pneumatize the frontal bone at a growth rate greater than the frontal sinus. This extensive variation in pneumatization of anterior ethmoid cells into the frontal recess and frontal sinus leads to the complex anatomical challenges when considering the surgical anatomy of the frontal sinus.

The left and right frontal sinuses may be asymmetrical due to their independent formation. A hypoplastic or absent frontal sinus is seen in about 5% of the population [14]; however, some populations such as Alaskan or Canadian Eskimos can have a much higher predisposition with up to 43% reported [15]. Excess pneumatization of the frontal sinus can also occur and is termed either sinus hyperpneumatization or pneumosinus dilatans with extension extending laterally to the orbital rim or even to the temporal bone.

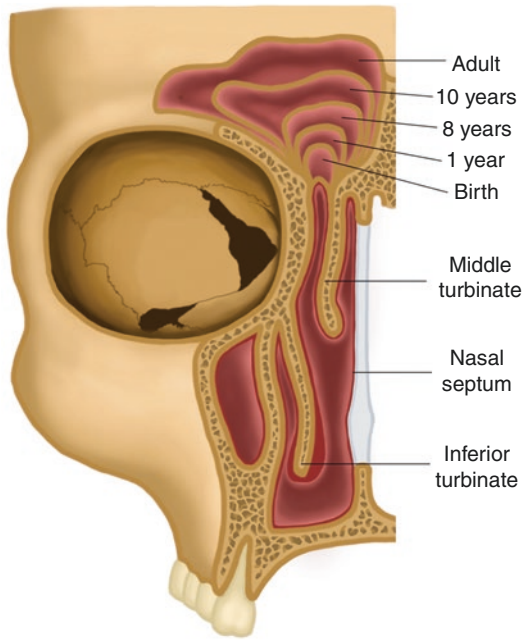

Fig. 1.4 Frontal sinus development pattern

Sphenoid Sinus

Sphenoid sinus development begins in the third month of gestation, when a small presphenoid recess forms by invagination of nasal mucosa into the posterior cartilaginous nasal septum. An inferiorly based nasal mucosal fold develops by the end of the fourth month, which partially separates the presphenoid recess from the nasal cavity. A cartilaginous sphenoid concha forms within this fold during chondrification of the nasal capsule, forming cartilaginous concavities which eventually enclose the presphenoid recess by the end of the fifth month. The surrounding cartilage wall ossifies towards the end of foetal development, and the presphenoid recess becomes the sinus ostium in adult life.

At birth, the sphenoid sinus is a rudimental recess. Magnetic resonance imaging shows the sphenoid sinus consists of red marrow (uniformly low signal intensity on T1-weighted images) in children less than 4 months old. Bone marrow conversion then commences at 4 months of age (signal intensity changes from hypointense to hyperintense) [16]. There is then extension inferiorly and posteriorly by the resorption of cartilage, forming the sphenoid sinus by 3 years of age. Unlike the other paranasal sinuses, primary pneumatization does not occur in sphenoid development. Pneumatization of the sphenoid sinus commences between 2 months and 3 years of age [17]. The sphenoid sinus pneumatizes by expanding into the presphenoid and then the basisphenoid, while the sphenoid concha remains as the anterior wall of the sinus. The sphenoethmoid recess is formed from the presphenoid recess. Pneumatization is complete by 14 years of age.

The sphenoid bone develops from the ossification of several independent cartilaginous precursors. The post-sphenoid and pre-sphenoid centres form the body of the sphenoid bone, and the alisphenoid forms the greater wings and orbitosphenoid contributes to the lesser wings. Union of these ossified components results in the formation of the sphenoid bone. The lateral craniopharyngeal or Sternberg's canal will form if there is incomplete fusion of the greater wings and sphenoid body. It exists with high incidence in 3-year-olds, but sinus pneumatization leads to obliteration of the canal, leaving a defect in less than 5% of adults [18]. Sternberg's canal is therefore infrequently associated with spontaneous cerebrospinal fluid (CSF) leak and congenital encephaloceles [19].

Prior to the development of the sphenoid sinus, the optic nerve, vidian nerve and carotid artery are present. As sinus formation progresses, these structures create irregularities in the walls of the sinus and subsequent canals. Vidian canal variants can be classified as type 1, within the sphenoid bony roof (55.6%); type 2, partially protruding into the sphenoid sinus (34.8%); and type 3, totally protruded into the sphenoid sinus with a stalk (9.6%) [20].

Nasolacrimal Duct Development

The lacrimal passageway arises from an epithelial cord embedded in the mesenchyme, as a thickening of the surface ectoderm in the rudimentary naso-optic fissure at 32 days of gestation.

This thickened ectoderm lies between the lateral nasal process and the maxillary process. At 37 days, the olfactory pit is well formed, and the surface ectoderm of the naso-optic fissure thickens and projects inferiorly. Caudal and cephalic branchings of the epithelial cord form the canaliculi and the duct.

By 44 days, the olfactory sac is well formed, and as the ectoderm extends downwards, it detaches itself from the surface and buries itself in the mesenchyme. This epithelial cord extends downwards towards the nasal cavity and is entirely buried between the inferior meatus of the nasal fossa and the inner canthus of the eye.

It later begins to canalize at the ocular end at 60 days and extends downwards to become the lacrimal pathway.

The distal end opens into the inferior meatus via the valve of Hasner, but the nasolacrimal duct is initially not patent in 73% of neonates [21]. In a small proportion of cases, this can lead to congenital epiphora, but about 95% of cases will undergo spontaneous resolution by the age of 13 months as canalization through the valve of Hasner occurs.

Sinonasal Vasculature Development

The vascular supply to the head, neck and sinonasal region arises from the aortic arches, which are formed sequentially within the pharyngeal arches. They initially appear symmetrically on both sides of the embryo but then regress or persist. The first pair of aortic arch arteries arises from the aortic sac, forming between day 22 and 24 of gestation. By day 26, the second arch artery arises in the second pharyngeal arch, and at the same time, the first pair of aortic arch arteries begins to regress. A first aortic arch remnant forms the maxillary artery and its subsequent branches, including the sphenopalatine artery. On day 28, the third and fourth aortic arch arteries form. The third arch arteries give rise to the common carotid arteries bilaterally and to the proximal portion of the right and left internal carotid arteries. The cranial extensions of the dorsal aorta give rise to the distal portion of the internal carotid artery, which gives rise to the ophthalmic artery and subsequently the anterior and posterior ethmoid arteries. The external carotid artery buds from the common carotid artery [22].

Areas of Uncertainty and Controversy

- The growth of the nasal septum has traditionally been described as occurring in a caudal direction, growing downward between the paired nasal cavities until it reaches the palatal shelves. However, scanning electron micro-

scope dissection suggests that the septum is derived from tissue between the primary choanae, which fuses with the palatal shelves as they elevate [23].

- Age of onset and completion of sinus pneumatization vary in the literature. However, it can generally be stated that initial signs of pneumatization are present at birth for the maxillary and ethmoid sinuses, at 9 months for sphenoid sinus, and after the age of 5 years for the frontal sinus [24].
- There are various theories on the embryology of choanal atresia, summarized by Hengerer et al. (2008) [25] as the following:
  - Persistence of the buccopharyngeal membrane from the foregut
  - Abnormal location or persistence of mesoderm, forming adhesions in the nasochoanal region
  - Abnormal persistence of the nasobuccal membrane of Hochstetter
  - Misdirection of neural crest cell migration

Key Learning Points

- Nasal development begins in the 4-week-old embryo, when a pair of thickened ectodermal nasal placodes becomes visible. These develop into the nasal pits.
- A plug of epithelial cells blocks the anterior lumen of the nasal cavity by 7–8 weeks. By the 17th week, this epithelial plug undergoes apoptosis, resulting in the nasal passages reopening and becoming the nasal vestibule.
- The septum is initially entirely cartilaginous. It develops from the medial wall of the lateral capsule during the second to third embryonic month. By birth, the maxillary crest, palatine crest and vomer will have ossified.
- The maxilloturbinal is the precursor to the inferior turbinate. The first ethmoturbinal originates at the superior junction of the lateral nasal wall and septum, developing into the middle turbinate. The second ethmoturbinal gives rise to the superior turbinate, and third ethmoturbinal forms the supreme turbinate, if present.
- The maxillary sinus begins as an invagination of the mucosa in the lateral wall of the nasal capsule during the tenth week of gestation. Further growth of the maxillary sinus follows the descent of dentition. The remaining sinuses are rudimentary at birth.
- Ethmoid sinus development begins in the fourth week of gestation and comprises of three to four air cells at birth. The extramural ethmoid air cells do not grow beyond the ethmoid bone until after birth.
- Five basal lamellae serve as attachments to the lateral nasal wall during development and are key for the endoscopic surgeon's understanding of surgical anatomy.
- The frontal sinus begins to develop during the fourth month of gestation, by direct extension of the frontonasal recess or as a superior epithelial migration of the anterior ethmoidal cells that penetrate the inferior surface of the frontal bone. The frontal sinus is not seen on imaging at birth but is present as a small pit.
- Sphenoid sinus development begins in the third month of gestation, when a small presphenoid recess forms, by invagination of nasal mucosa into the posterior cartilaginous nasal septum. At birth, the sphenoid sinus is a rudimental recess.
- The lower end of the lacrimal duct is not patent in most neonates.

Acknowledgements With thanks to Miss Livy Kenyon MRCS DOHNS for illustrations.

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2 Applied Anatomy of the Nose and Sinuses

Rajiv K. Bhalla

The Nose

Introduction

The nose is a complex anatomical structure, externally, a strong aesthetic component of the face and internally is responsible for humidifying, warming and cleansing inspired air before it reaches the lower airways, and as a gateway to the base of skull. The olfactory areas are also located in the roof of the nose bilaterally and are responsible for our sense of smell. Anatomy of the nose is considered cephalic, caudal, lateral or medial (Fig. 2.1).

External Structure

The external structure of the nose is best thought of in thirds in the horizontal plane (Fig. 2.2). The upper third consists of bones, the middle and lower thirds of cartilage. All of these structures are draped with skin and its underlying soft tissues of fat, muscles and fascia.

Bones of upper third of nose:
Two paired nasal bones
Paired frontal processes of maxilla
Paired nasal processes of frontal bone

R. K. Bhalla (✉)
Manchester Foundation Trust and Salford Royal Hospital, Manchester, UK

Sutures of upper third of nose (Fig. 2.3):
Fronto-nasal
Inter-nasal
Naso-maxillary
Fronto-maxillary

The middle third of the nose consists of the paired upper lateral cartilages, attached to the quadrangular cartilage of the nasal septum in the midline (Fig. 2.4). The cephalic borders of the upper lateral cartilages (ULCs) sit underneath the nasal bones (Fig. 2.5). The caudal edge of the ULCs curls back on themselves as a scroll.

The lower or tip third of the nose is comprised of the lower lateral cartilages (LLCs) and their association with the caudal end of the quadrangular septal cartilage (Fig. 2.6). The cephalic borders of the lateral crura of the lower lateral cartilages are in a scroll configuration with the caudal border of the upper lateral cartilages (Fig. 2.7).

Major tip support structures:
(1) The intrinsic integrity of the alar cartilages
(2) The medial crural footplates to the caudal septum
(3) The scroll junction between the upper lateral and lower lateral alar cartilages

Minor tip support structures:
Ligaments (interdomal, intercrural, Pitanguy's midline, pyriform, and a scroll ligament complex consisting of the longitudinal and vertical scroll ligaments)
Membranous septum
Anterior nasal spine
Attachment of alar cartilages to the overlying skin and musculature

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https://doi.org/10.1007/978-3-031-28690-2_2

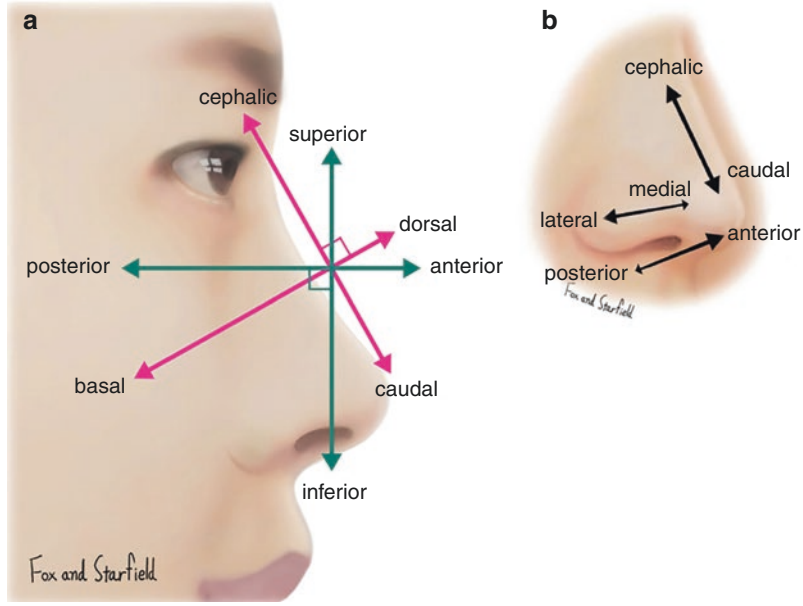

Fig. 2.1 Anatomical orientation when discussing the nose

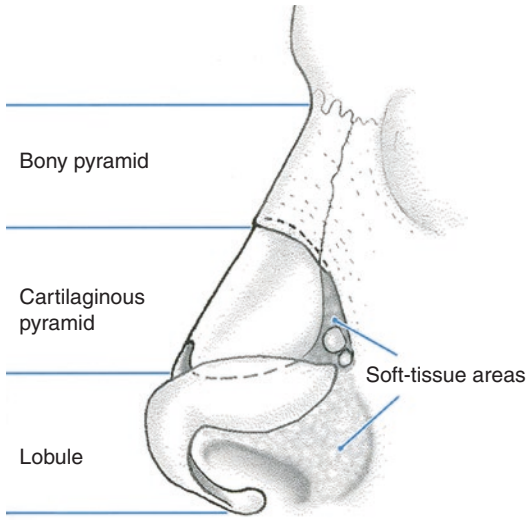

Fig. 2.2 The external structure of the nose in thirds

The Nasal Septum

The nasal septum separates the right nasal passage from the left and is cartilaginous anteriorly and bony posteriorly (Fig. 2.8). The bony septum is formed by the perpendicular plate of ethmoid above and vomer below. The septum sits in the crest of the maxilla in the midline and articulates with the rostrum of the sphenoid posteriorly. Superiorly, the cartilaginous septum forms the mid-third of the dorsum of the nose, and the perpendicular plate of the ethmoid attaches to the thin cribriform plate.

Key areas of the nasal septum (Fig. 2.9)**:**
Anterior septal angle
Posterior septal angle (attachment to anterior nasal spine)
K (keystone) area

The actual relationship between the cartilaginous septum, the bony perpendicular plate of the ethmoid (PPE), and the bony vomer, together with anatomical variants, is depicted in Fig. 2.10(10.1–10.3).

The Inferior Turbinate

The bone of the inferior turbinate is the inferior concha, articulating with the medial aspect of the maxilla and extending over the inferior maxillary hiatus like a bridge. Posteriorly, it articulates with the palatine bone and superiorly the uncinate process.

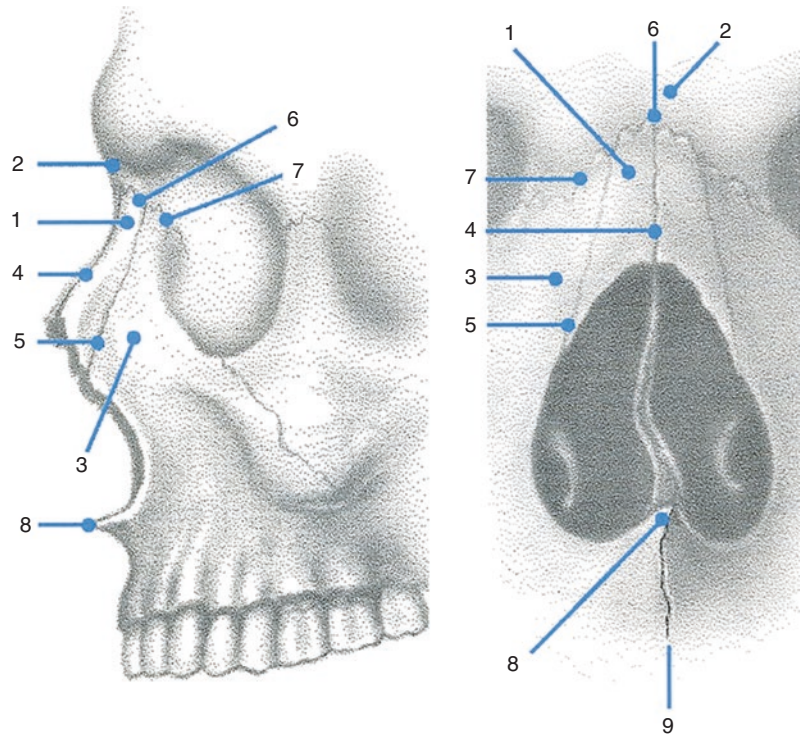

Fig. 2.3 Sutures of the nasal bones/upper third of nose:
Fronto-nasal suture 6
Inter-nasal suture 4
Naso-maxillary suture 5
Fronto-maxillary suture 7
Additional key numbers:
Nasal bone 1
Nasion 2
Frontal process of maxilla 3
Anterior nasal spine 8
Intermaxillary / median suture 9

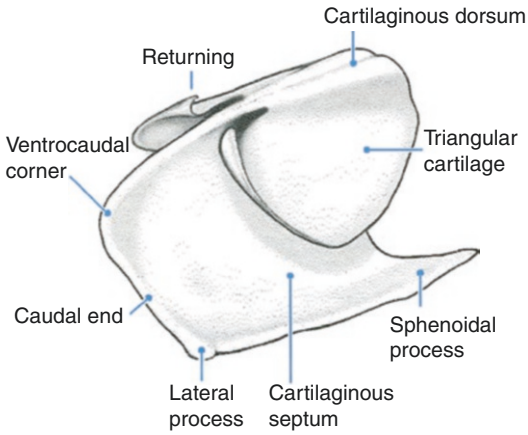

Fig. 2.4 The relationship of the upper lateral cartilages to the septal quadrangular cartilage

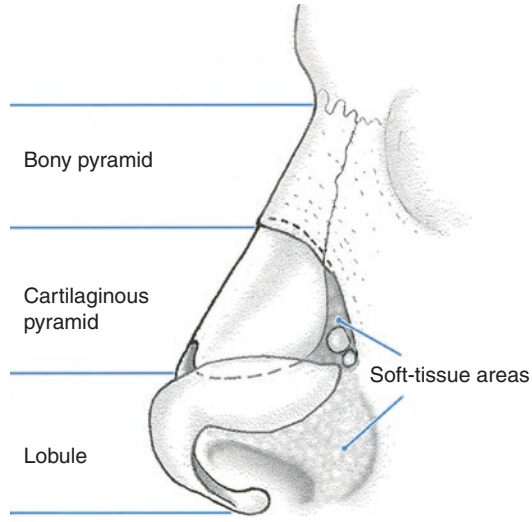

Fig. 2.5 The relationship of the upper lateral cartilages to the nasal bones

The scrolled bone of the inferior concha is covered by specialised erectile tissue and ciliated nasal mucosa. The erectile tissue contains vascular lakes that dilate (causing congestion) and constrict (causing decongestion) in response to the physiological nasal cycle.

The inferior turbinate is an extremely important structure and furnishes a sense of nasal health and well-being—it should be treated gen-

tly, with care, and mucosa should be preserved where possible. At its head it contributes to the internal nasal valve and awareness of nasal airflow. It should not be reduced excessively or aggressively as this may lead to the much feared 'empty nose syndrome'.

Allergens and irritants cause changes to both the mucosa of the inferior turbinate and to the functionality of the submucosal vascular lakes.

Inferolateral to the inferior concha is the inferior meatus.

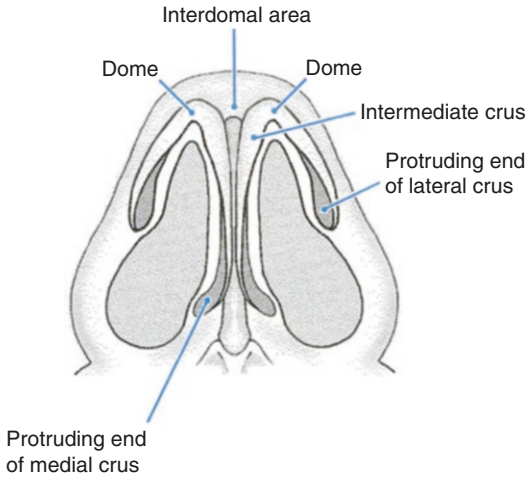

Fig. 2.6 The nasal tip cartilages and their association with the caudal end of the septal quadrangular cartilage

The nasolacrimal duct opens into the inferior meatus at the valve of Hasner, approximately 1 cm posterior to the head of the inferior turbinate (see below).

Sinonasal Mucosa

The mucosa of the nose and sinuses is of two types: largely a pseudostratified columnar ciliated respiratory variety, but with small areas of olfactory epithelium in the roof of the nose and adjacent nasal septum, middle and superior turbinates bilaterally.

Respiratory epithelium of the nose:

- Contains goblet cells that produce mucus
- Contains subepithelial vascular lakes that congest/decongest, warm and humidify inspired air
- Produces IgA that prevents microbes from attaching to and invading the mucosa
- Produces lysozyme which degrades pathogenic microbes

Olfaction

Olfactory neuroepithelium is located on the nasal surface of the cribriform plate and extends to the parts of the superior and middle turbinates and the superior nasal septum adjacent to the middle

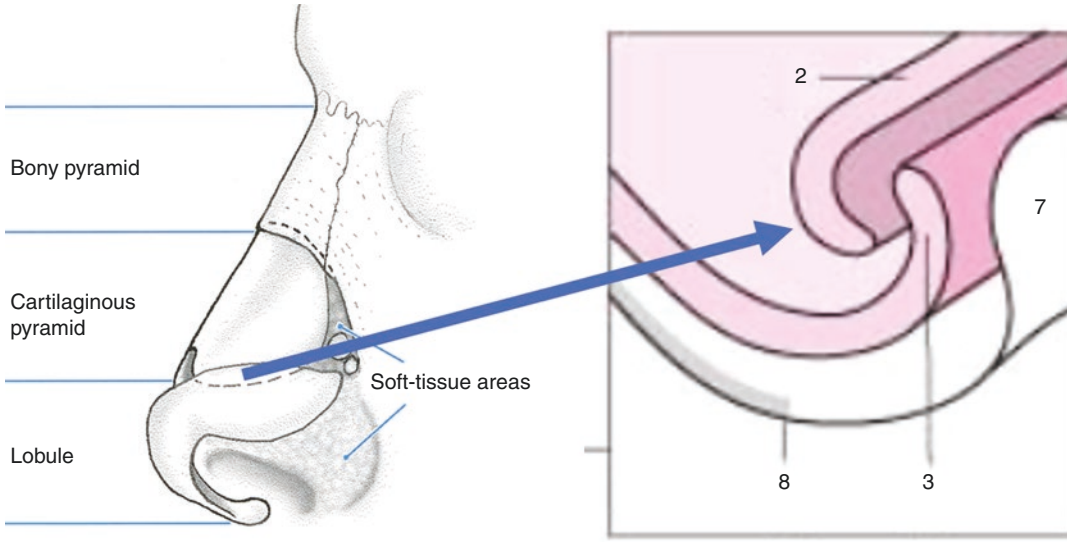

Fig. 2.7 The scroll configuration of the upper and lower lateral cartilages

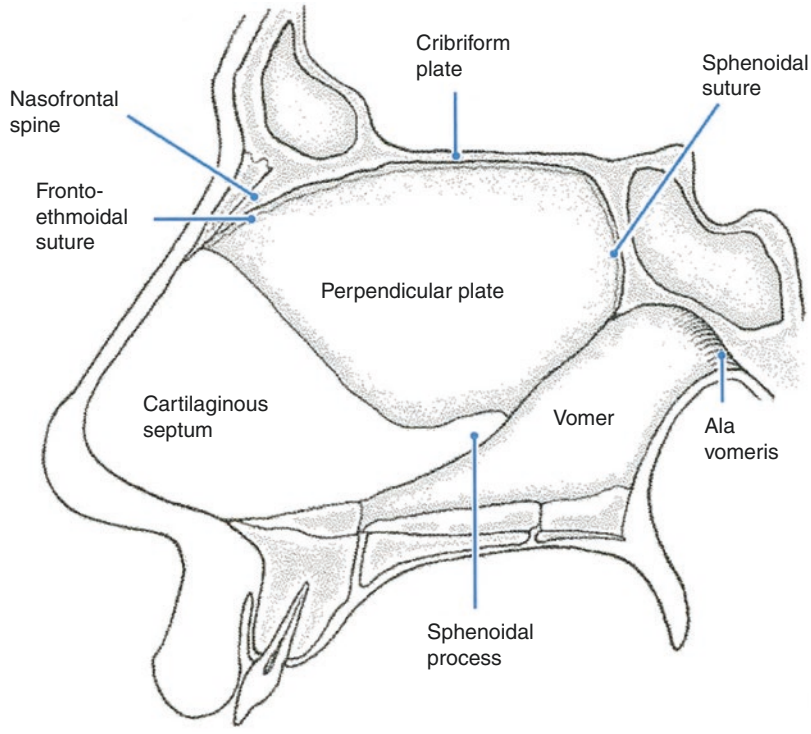

Fig. 2.8 The nasal septum

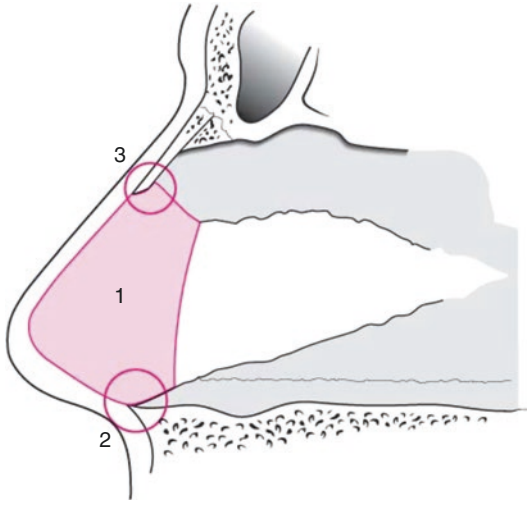

Fig. 2.9 Key areas of the nasal septum. 1 Septal quadrangular cartilage; 2 posterior septal angle; 3 K area

turbinate. Hence, turbinates should be preserved as far as possible.

Each olfactory cleft is 1–2 mm wide with 200–400 mm^2 of olfactory epithelium. The epithelium includes olfactory sensory neurones and supporting cells that include sustentacular, microvillar, globose basal, horizontal basal and duct cells, and Bowman's glands.

The olfactory sensory neurones give rise to fila that connect to the olfactory bulbs above the skull base. Within the olfactory bulbs, olfactory sensory neurones synapse with second order neurones (mitral and tufted cells). These project posteriorly as the olfactory tracts to various areas including the thalamus, the limbic system and the orbitofrontal neocortex (secondary olfactory cortex) (please refer to Chap. 41).

The primary olfactory cortex includes areas such as the anterior olfactory nucleus, the olfactory tubercle and the piriform cortex.

Projections of second-order neurones to the primary olfactory cortex are direct connections, with some neurones connecting in turn directly to the secondary olfactory cortex and some relaying via the thalamus between these two cortical areas.

Odour discrimination takes place in the secondary olfactory cortex, and affective responses are controlled by the limbic system.

After an odour passes into the nose, olfactory transduction relies on interaction between odour

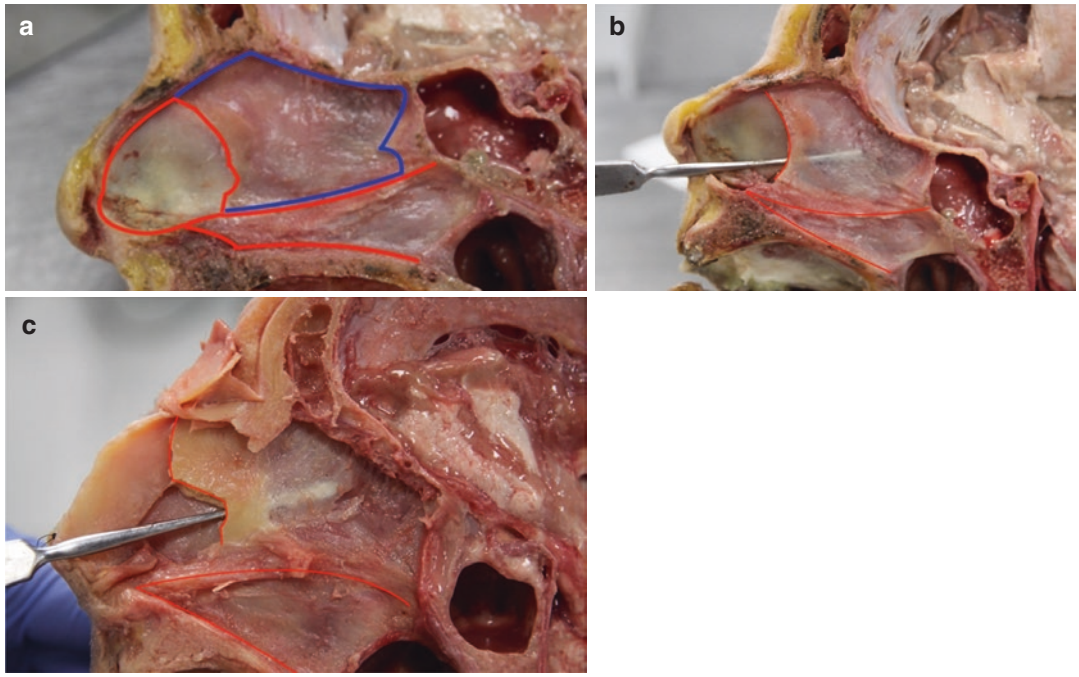

Fig. 2.10 Anatomy of the nasal septum. (Images of anatomical dissections prepared by Andrew C. Swift). (**a**) Sagittal cadaveric dissection of the nasal septum. The perpendicular plate of the ethmoid (PPE) is shown within the blue line. The quadrangular/quadrilateral cartilaginous septum is shown anterior to the PPE. The vomer is sited inferior to the PPE, outlined in red. (**b**) Cartilaginous septum separated from the PPE, demonstrating the junction between bone and cartilage and the thin, transparent area of the PPE. (**c**) Cartilaginous septum separated from the PPE, demonstrating the anatomical variant at the cartilaginous-osseous junction and the thick anterior bar of the PPE anterior to the paper-thin area of the PPE

molecules dissolved in the mucus layer and the transmembrane receptors of the cilia.

During *orthonasal* olfaction, up to 15% of an incoming air stream is directed towards the olfactory cleft during inhalation, facilitated by turbulence provided by the turbinates
Retronasal olfaction is the passage of food odours from the oral cavity whilst eating and accounts for approximately 80% of flavour perception

The Paranasal Sinuses

Introduction

There are four paired sinuses of unequal size: maxillary, ethmoid, sphenoid, and frontal. At birth, only the maxillary sinus and the ethmoid sinus are developed but not yet pneumatised. They are fully aerated by the age of 7. The sphenoid sinus appears at the age of 3. The frontal sinuses are the last to develop and may not be of significant size until adolescence.

The frontal sinuses may underdevelop or not develop at all. This should be noted during a preoperative appraisal of radiology.

The paranasal sinuses are thought to lighten the weight of the heavy skull and its contents, to provide resonance for voice, and to produce mucus. Mucus lubricates and protects the nose from pollutants, microorganisms, dust, and allergens.

Osteology

The nasal cavities are formed by the paired maxillary bones laterally and inferiorly and anteriorly with the paired nasal bones and the nasal process of the frontal bone.

The frontal bone is made up of two parts: the robust vertically oriented squamous part that forms

the forehead and the thinner horizontally oriented orbital part that forms the roof of the orbit.

The pyriform aperture is the triangular-shaped opening into the anterior aspect of the nasal cavity, with the floor of the aperture formed by the anterior nasal spine and pre-maxilla and the sides formed by the ascending processes of the maxillae.

The maxilla bone is a major bone of the midface making up the upper jaw, the floor of the orbit and along with its opposite number, the bony hard palate. It contains the upper alveolus with their dental roots, common sources of infection and inflammation of the maxillary sinus.

The roof of the nasal cavity from medial to lateral is formed by the cribriform plate, the lateral lamella of the cribriform plate and the fovea ethmoidalis of the frontal bone.

The cribriform plate, the honeycombed ethmoid air cells, the middle conchae, the roof of the ethmoid, perpendicular plate and the lamina papyracea are extremely important anatomical structures that make up the ethmoid bone.

The lamina papyracea makes up the majority of the medial wall of the orbit, with the lacrimal bone anteriorly, the optic canal in the lesser wing of the sphenoid bone posteriorly and the frontal bone superiorly.

The nasal cavities are divided into left and right by the bony nasal septum (see above).

The lateral wall of the nose, from front to back, is formed by the ascending process of the maxilla, the lacrimal bone, the lamina papyracea of the ethmoid bone, the palatine bone, and the medial pterygoid.

The sphenoid bone bounds the nasal cavity posteriorly along with the ala of the vomer posteromedially.

The sphenoid bone is perhaps the most complex bone of the sinonasal cavity. Made up of greater and lesser wings, it connects the sinonasal cavity to the anterior, middle and posterior cranial fossae. A thorough understanding of the sphenoid bone is essential for extended sinus and endoscopic skull base surgery.

There are various canals, ducts, foramina and notches that permit the passage of major structures into the sinonasal cavity (see below). Critical neurovascular structures pass into and through the sphenoid bone.

The Maxillary Sinus

This is the largest of the four sinuses, shaped like a pyramid with its base forming a large part of the lateral wall of the nose.

It is pneumatised at birth but through childhood largely contains unerupted teeth.

Anterosuperiorly on its medial wall is the infundibulum of the maxillary sinus, the conical-shaped communication with the nasal cavity.

When entering the maxillary sinus, it is important to angle instruments downwards and laterally to avoid inadvertent penetration of the orbit. This complication may cause ecchymosis at the medial canthus.

The bone is dehiscent over the medial wall forming the fontanelles that are often covered with mucosa and fibrous tissue. They are generally divided into anterior and posterior by the shape of the uncinate process. Dehiscences are seen as accessory ostia and must not be confused with the natural ostium.

The infundibulum and free posterior margin of the uncinate process make up the hiatus semilunaris inferioris, an area richly populated by ciliated pseudostratified columnar respiratory and vitally important for mucociliary clearance. A heavy hand surgically in this area can adversely affect the function of three sinuses: maxillary, frontal and anterior ethmoid.

A careful uncinectomy and gentle anatomical middle meatal antrostomy will successfully treat the majority of sinusitis affecting these three sinuses.

The infundibulum may be further narrowed by an infraorbital air cell (previous terminology: Haller cell). This anatomical variant can be identified on preoperative CT scanning. It is dealt with by carefully marsupialising at the time of the middle meatal antrostomy.

Maxillary atelectasis (silent sinus syndrome) is a particularly treacherous situation where the uncinate process is plastered to the inferomedial orbit. Failing to recognise the orientation of the uncinate process and difficulty of uncinectomy in these cases will invariably result in an orbital injury.

The Ethmoid Sinuses

The complex ethmoid sinus cells sit lateral to the middle turbinate. It is imperative to have a complete understanding of the anatomy of the middle turbinate (see Key concepts below).

Superiorly is the ethmoid roof; laterally the lamina papyracea of the orbit; medially the lateral surface of the middle turbinate; and inferiorly the horizontal attachment of the middle turbinate. It is important to carefully skeletonise these structures during sinus surgery to ensure that a complete ethmoidectomy has been performed. Otherwise, there is a risk of refractory disease and mucocele formation.

They are divided into anterior and posterior by the basal (or third) lamella (see Key concepts below).

The bulla ethmoidalis comprises the anterior ethmoid air cell(s). It may be a simple projection off the lamina orbitalis laterally or a more complex configuration of cells.

Its drainage is into the hiatus semilunaris superioris medially.

Its upper part may extend to the skull base or fall short, forming a suprabullar recess. The attachment of the bulla superiorly, either to the skull base or not, influences the drainage pathway of the frontal sinus.

The anterior ethmoidal artery sits between the second and third surgical lamellae (see Key concepts below).

When performing an anterior ethmoidectomy, instruments must be angled laterally and away from the lateral lamella of the cribriform plate to avoid an iatrogenic CSF leak. Powered instrumentation must also be used with care, particularly in the region of the anterior ethmoidal artery and on the lamina papyracea. If at all possible, the latter should be avoided outside of the most experienced hands.

The posterior ethmoidal air cells often comprise one to four air cells of varying sizes. They drain posteriorly into the superior meatus.

When entering the posterior ethmoid, this should be done low-and-medial on the basal lamella at the point where it turns to become horizontal (Fig. 2.11). High-and-lateral sits the optic canal and its nerve; high-and-medial sits the skull base and lateral lamella of the cribriform plate; and low-and-lateral sits the lamina papyracea of the orbit.

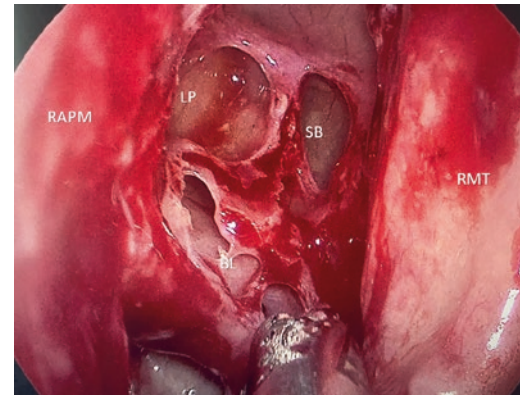

Fig. 2.11 Clinical image illustrating safe entry into the posterior ethmoid through the basal lamella. *RAPM* right ascending process maxilla, *LP* lamina papyracea, *SB* skull base, *RM* right middle turbinate, *BL* basal lamella

It is still possible to inadvertently penetrate the skull base when entering the posterior ethmoid from a low-and-medial point if the instrument being used is directed upwards rather than parallel to the hard palate.

With or without stereotactic navigation, it is sometimes difficult to identify the posterior ethmoid skull base and hence perform a complete clearance of air cells during an ethmoidectomy, especially with a low skull base. Here, identifying the level of the skull base in the sphenoid sinus and following forwards is extremely helpful.

The posterior ethmoid air cells should usually stop at the face of the sphenoid sinus and skull base above. Sometimes however, a posterior ethmoid air cell might extend beyond the face of the sphenoid sinus, forming a sphenoethmoidal (previous terminology: Onodi cell). These cells can be dangerous for a surgeon if unrecognised on preoperative CT imaging (please see Chap. 14).

An unrecognised sphenoethmoidal cell may lead to an iatrogenic injury of the optic nerve causing blindness.

It is not difficult to penetrate the ethmoid skull base at various sites to cause an iatrogenic CSF leak (see Table).

Weak points of the skull base:
- Cribriform plate/olfactory fossa
- Lateral lamella of the cribriform plate
- Fovea ethmoidalis
- Entry points into lateral lamella of anterior and posterior ethmoidal arteries

The Sphenoid Sinus

The sphenoid sinus is located in the sphenoid bone, with the left and right cells separated by the intersinus septum.

Superiorly is the planum sphenoidale and tuberculum sellae; posteriorly is the sella turcica and clivus; inferiorly is the rostrum of the sphenoid containing the vidian canal; and laterally is bone separating the sinus from Meckel's cave in the middle cranial fossa and containing the V_2 (maxillary division) of the trigeminal nerve, which exits the skull base through the foramen rotundum.

The sphenoid sinuses are often asymmetric in shape and size.

The sphenoid sinus may be variably pneumatised and is classified as conchal, pre-sella and sella varieties (Fig. 2.12).

In the conchal type, the area below the sella is solid bone without an air space extending below and behind into the clivus. This may give a very flat appearance to the sella, and neurovascular anatomical indentations may be impossible to discern. This is the commonest type in children but least common in adults.

In the pre-sella type, the sphenoid sinus has a moderate air space in front of the sella but without extension into the clivus below and posteriorly.

In the sella type, which is the commonest configuration in 85% of cases, the body of the sphenoid is well pneumatised, and so the sella and related neurovascular anatomy are well defined. Pneumatisation extends below and posteriorly into the clivus.

The most difficult for sella access during pituitary surgery is the conchal variety. Stereotactic navigation is almost mandatory in these cases.

The intersinus septum is positioned eccentrically and posterolaterally often attaches to the bony covering of the internal carotid artery (ICA). Vigorous manipulation of the intersinus septum may result in an iatrogenic injury to the ICA.

The sphenoid sinus drains into the nose through its natural ostium into the sphenoethmoidal recess. The sphenoid ostium is slit-like and is often obscured by the superior (or where present, supreme) turbinate.

The sphenoid ostium can usually be located 12–18 millimetres (mm) above the arch of the posterior choana (Fig. 2.13). Other reference points are very helpful and may prevent inadvertent penetration of the skull base (see Table).

Locating the sphenoid ostium using anatomical reference points:
12–18 mm above arch of posterior choana
Level with upper border of the maxillary ostium
Junction of mid- and lower thirds of the superior turbinate

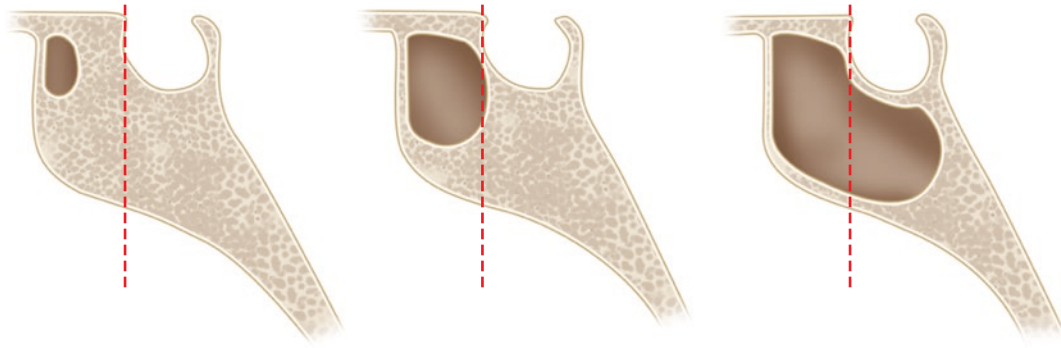

Fig. 2.12 Variations in sphenoid sinus pneumatisation. Sagittal view showing the types and degree of sphenoid sinus pneumatisation related to the anterior wall of sella turcica (red dashed line)

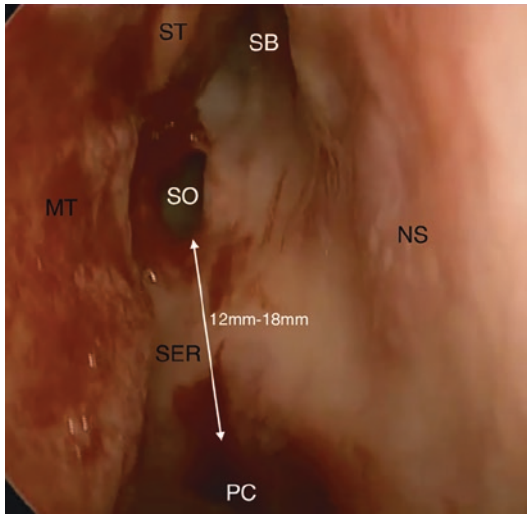

Fig. 2.13 Position of natural ostium of sphenoid sinus in the sphenoethmoidal recess. *SO* sphenoid ostium, *MT* middle turbinate, *ST* superior turbinate, *SB* skull base, *NS* nasal septum, *PC* posterior choana, *SER* sphenoethmoidal recess

If stereotactic navigation is not available, a diseased and contracted sphenoid sinus may be identified by opening into the normal side and traversing the intersinus septum or by following the vomer posteriorly as it becomes the intersinus septum. This latter technique will always ensure the sphenoid sinus is entered in the midline and away from critical neurovascular structures.

When entering the sphenoid sinus, instruments should be directed inferiorly, and the safest point of entry is via the natural ostium in the low and medial position on the face of the sinus. High-and-lateral is the optic canal and nerve; low-and-lateral is the ICA in its paraclinoid and cavernous segments; and high-and-medial is the skull base (planum sphenoidale).

The ICA may be dehiscent (absent of a bony covering) in 25–30% of cases. The optic canal may be dehiscent in 6% of cases. Both situations lend themselves to a high chance of an iatrogenic injury and should be recognised on careful appraisal of preoperative CT imaging.

The pituitary gland sits in the sella turcica, a midline structure in the posterosuperior sphenoid sinus. The optic chiasm sits above and behind the sella. The clivus sits below. Pituitary tumours, clival chordoma and chondrosarcoma, suprasellar pathologies such as craniopharyngioma and meningioma, and cavernous sinus and Meckel's cave pathologies can be accessed via a transsphenoidal corridor.

The Frontal Sinus

This is the sinus of the frontal bone. There are usually two frontal sinuses within the single frontal bone that is unique for humans. The frontal sinuses are often asymmetric in size and shape, and it is not unusual for there to be an overriding frontal sinus from one side.

Each frontal sinus is bounded anteriorly by its anterior table, posteriorly by its posterior table, medially by the intersinus septum, and inferiorly by the roof of the orbit.

The frontal sinus communicates with the nose via its hourglass-shaped infundibulum, through the frontal ostium and into the frontal recess. The infundibulum sits inferomedially in the frontal sinus. The opening into the nose is medial and anterior.

The frontal ostium is the narrowest part of this funnel-shaped communication, bounded anteriorly by the nasal process of the frontal bone (the frontal 'beak'), posteriorly by the frontal horn of the skull base, laterally by the orbit, and medially by the bony nasal septum (Fig. 2.14).

The frontal recess sits below the beak. It is an area bounded medially by the lateral surface of the middle turbinate, laterally by the orbit, anteriorly by the agger nasi, and posteriorly by either the bulla ethmoidalis or the suprabullar recess. Disease or scarring in this critical area may readily obstruct drainage and/or pneumatisation of the frontal sinus.

There may be massive pneumatisation into the frontal bone or very little pneumatisation at all. This is important to consider in patients that report a 'sinus headache' as an alternative cause for the headache should be sought in these cases.

It is imperative to accurately appraise preoperative CT imaging before contemplating surgery on either the frontal recess or the frontal ostium.

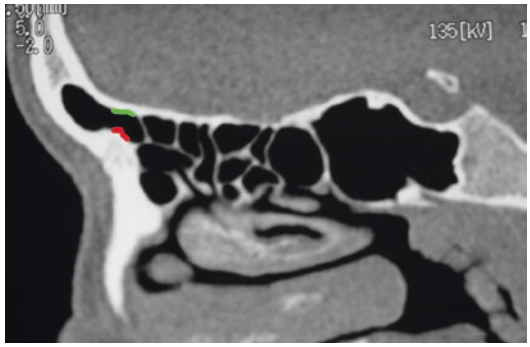

Fig. 2.14 Anatomical boundaries of the ostium of the frontal sinus. Posterior (green line), skull base; anterior (red line), nasal process frontal bone (frontal beak); inferior, agger nasi cell (or Kuhn 1 cell if present); lateral, lamina papyracea; medial, intraseptal cell

Failure to recognise frontal sinus agenesis or hypoplasia may lead to an iatrogenic CSF leak.

A supraorbital ethmoid air cell (SOEC) is pneumatisation into the orbital plate of the frontal bone. It may be confused for a frontal sinus. A SOEC opens posteriorly and laterally into the nose and may readily be confused for the natural ostium of the frontal sinus.

The frontal sinus should be managed carefully and by those with great experience. It is easy to cause more long-term harm than benefit if the drainage pathway is traumatised.

The mucosa of the natural ostium may be circumferentially damaged causing scarring and stenosis.

Fragments of the agger nasi or bulla ethmoidalis may be pushed upwards causing obstruction.

Inexperienced instrumentation may cause damage to the anterior ethmoidal artery, a CSF leak posteromedially, or orbital injury laterally with either exposure of orbital fat or dislocation of the trochlea and superior oblique extraocular muscle causing postoperative diplopia (please see Chap. 34).

It is often better to leave a frontal sinus and its drainage pathway untouched than to perform a partial, incomplete, or traumatic dissection. A significant volume of revision sinus surgery is a result iatrogenic obstruction of the frontal drainage pathway.

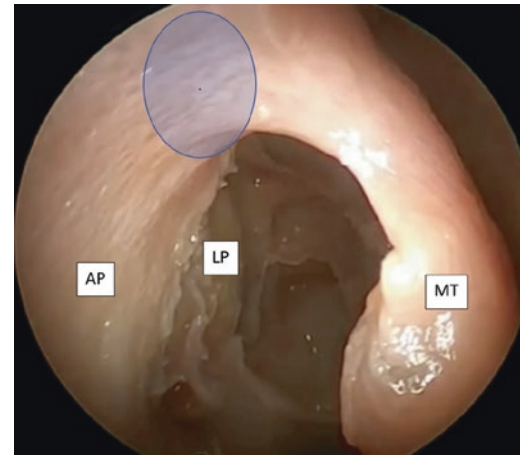

Fig. 2.15 Agger nasi 'bulge' in the axilla of the middle turbinate. *MT* middle turbinate, *LP* lamina papyracea, *AP* ascending process maxilla; shaded area—bulge of agger nasi cell

The Agger Nasi

This is the most anterior of ethmoid air cells and occurs in over 90% of individuals.

It sits at the upper aspect of the uncinate process and, when present, sits abutting the nasal process of the frontal bone. Its position causes a 'bulge' at the axilla of the middle turbinate (Fig. 2.15).

The degree of pneumatisation of the agger nasi and its relationship to the adjacent skull base and medial intraseptal pneumatisation may influence drainage from the frontal sinus and predispose to chronic frontal sinusitis.

The agger nasi and any associated frontal cells may be dissected with care and precision to aid ventilation and drainage of a diseased frontal sinus.

Frontal Cells and Classification

Several classification systems have been proposed for ethmoidal cells encroaching into the frontal sinus.

An effective frontal sinus cell classification system should:

- Aid clear and concise communication between clinicians
- Facilitate decisions regarding extent of surgery
- Be simple to apply
- Not be too complicated to remember
- Translate between countries

The most commonly in use are the Kuhn classification of frontoethmoidal cells and the International Frontal Sinus Anatomy Classification (IFAC) system (see Further reading).

The Kuhn classification has existed for some time now. Although it might not be considered to be perfect by all, it does permit decisions regarding interventions to be made easily. The classification does not, however, provide a direct link between anatomy and extent of surgery. The classification system talks of frontoethmoidal cells 1–4 (Fig. 2.16).

Type 1 Cell

A single air cell sits above the agger nasi. The degree of pneumatisation of this cell and of the agger nasi will push the frontal sinus drainage pathway posteriorly and medially. It can usually be accessed with an angled endoscope (70° or 45°) and a 90° frontal curette. Rarely, an axillary flap approach will be necessary if the pneumatisation is substantial.

Type 2 Cell

These are two or more (a tier) air cells sitting above the agger nasi. The frontal sinus drainage pathway is again pushed posteriorly and medially. The cap, uppermost part, of the topmost air cell is likely to be difficult to reach using a conventional uninarial frontal recess dissection with an angled endoscope and an angled curette. An axillary flap and rongeur excision of the axillary bone of the beak facilitates superb access to both the agger nasi and the type 2 cells.

Type 3 Cell

This is a much larger pneumatisation above the agger nasi, but it still only occupies less than 50%

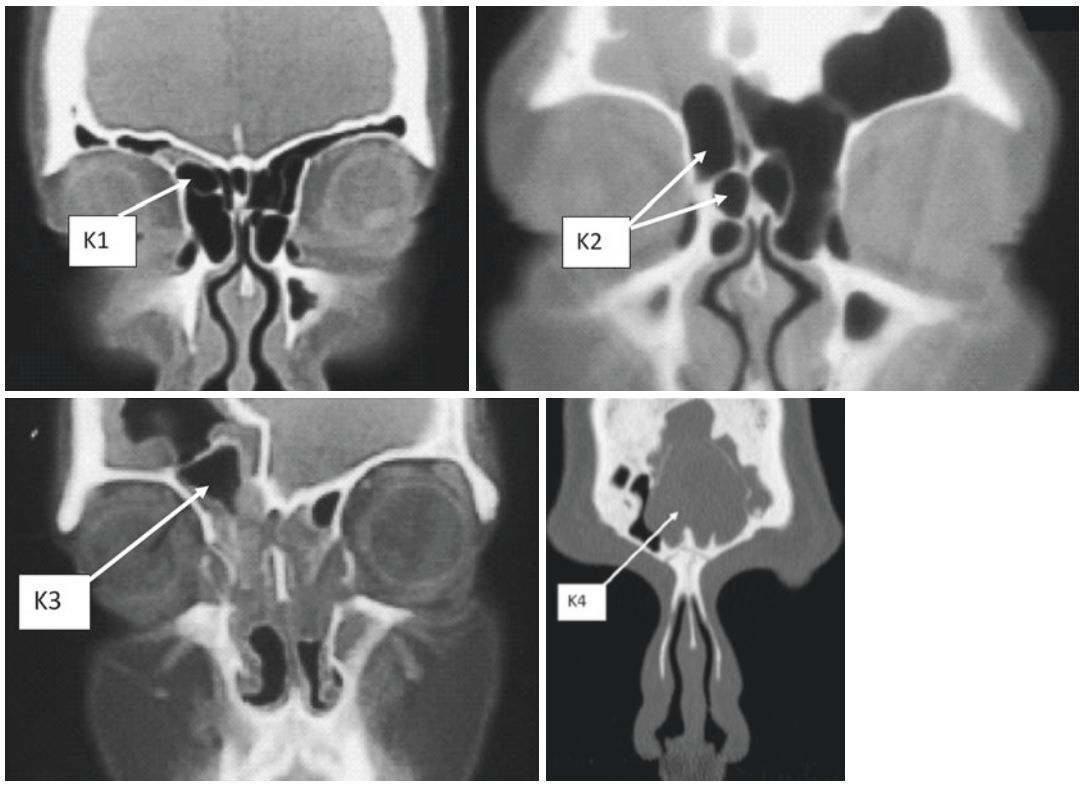

Fig. 2.16 Kuhn cells 1–4

of the height of the frontal sinus. In a uninarial approach, it is highly likely an axillary flap will be required to access the apex of the type 3 cell or alternatively, a more extensive frontal sinusotomy incorporating a degree of drill-out of the frontal beak. Occasionally, due to the restrictive anatomy of the nasal septum, the superomedial orbit and the skull base a bi-nostril approach (high-septal window and floor of frontal sinus drill-out) to a type 3 cell might be required, which facilitates a better 'cross-court' trajectory to the apex of the diseased cell and sinus.

Type 4 Cell

This is an exceptionally large pneumatisation above the agger nasi occupying more than 50% of the height of the frontal sinus. These cells are fortunately rare. Options to treat a diseased frontal sinus containing a type 4 cell are a frontal sinus drill-out or an osteoplastic flap, depending on the experience of the surgeon.

International Frontal Sinus Anatomy Classification (IFAC) system (Fig. 2.17).

Suprabullar Cell

This is a cell that sits above the bulla ethmoidalis and posterior to the frontal infundibulum upon which it impinges. They do not pass through the frontal ostium to enter the frontal sinus. A suprabullar cell pushes the frontal drainage pathway anteriorly. This is a complexity that should be identified on preoperative sagittal CT imaging. This cell or cells often must be addressed at the time of undertaking a frontal sinusotomy so as not to compromise the frontal outflow drainage pathway.

Frontal Bullar Cell

This is a cell arising above the bulla ethmoidalis which extends along the skull base to encroach on the frontal sinus by passing through the frontal ostium. It restricts the lumen of the frontal ostium from posteriorly and also pushes the frontal drainage pathway anteriorly. This is also a complexity that should be identified on preoperative sagittal CT imaging. This cell must also usually be addressed at the time of a frontal sinusotomy to optimise the frontal outflow drainage pathway.

Medial Intraseptal Cell

This is a pneumatisation at the upper aspect of the perpendicular plate of the ethmoid that constitutes the superior bony nasal septum. It pushes the frontal drainage pathway laterally. It is a cell that drains into one or other frontal recess—this should be identified on preoperative coronal CT imaging.

The IFAC system was developed to describe the extent of required surgery based on an anatomical classification of the frontal recess and sinus. In contrast to the Kuhn classification, the IFAC system proposed to reflect the different surgeries performed in a gradated manner in the frontal recess and frontal sinus during endoscopic sinus surgery.

Cells Defined in the IFAC

Anterior cells that push the drainage pathway of the frontal sinus medial, posterior, or posteromedially:

- Agger nasi cell
- Supra agger cell
- Supra agger frontal cell

Posterior cells that push the drainage pathway anteriorly:

- Supra bulla cell
- Supra bulla frontal cell
- Supraorbital ethmoid cell

Medial cells that push the drainage pathway laterally:

- Frontal septal cell

Grades 0–3 of IFAC extent of surgery relate to surgery of the frontal recess rather than surgery within the frontal sinus itself. These grades involve dilatation/fracture or removal of cells that obstruct the frontal ostium or frontal drainage pathway without enlargement of the bony frontal sinus ostium.

Grades 4–6 involve removal of bone to enlarge the bony frontal ostium.

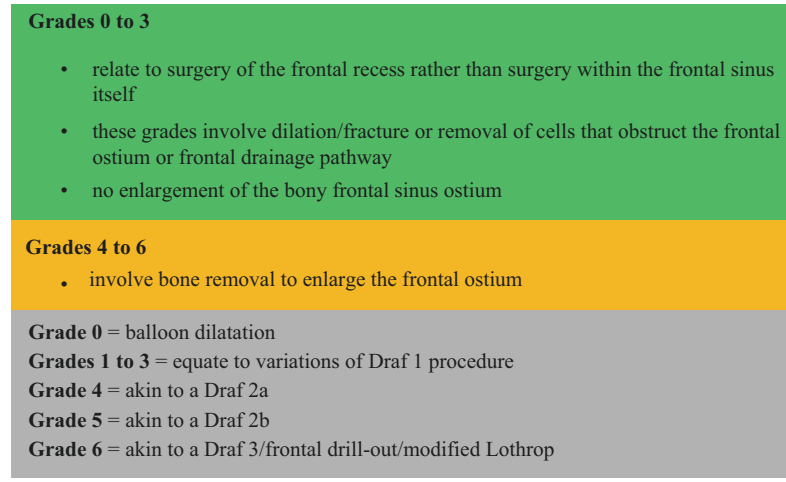

Fig. 2.17 Summary of IFAC system and relationship to Draf classification

IFAC extent of endoscopic frontal sinus surgery:
Grade 0: Balloon dilatation, no tissue removal
Grade 1: Clearance of cells in the frontal recess, below the frontal ostium (no bone removal aka. Draf 1)
Grade 2: Clearance of cells obstructing the frontal ostium (no bone removal aka. Draf 2a)
Grade 3: Clearance of cells pneumatising through the frontal ostium (no bone removal aka. Draf 2a)
Grade 4: Clearance of a cell pneumatising through the frontal ostium into the frontal sinus with removal of bone of the frontal beak (aka. Draf 2a)
Grade 5: Enlargement of the frontal ostium from the lamina papyracea to the nasal septum (a unilateral frontal drill out aka. Draf 2b)
Grade 6: Removal of the entire floor of the frontal sinus with joining of the left and right frontal ostia into a common ostium with a septal window (aka. Draf 3/modified Lothrop)

The Palatine Bone

The palatine bone forms a key area of the lateral nasal wall. It is a slender bone sitting between the maxilla and the pterygoid processes of the sphenoid bone.

It has a horizontal plate contributing to the floor of the nose, a perpendicular plate contributing to the lateral nasal wall, and three processes: pyramidal, orbital, and sphenoidal.

Superiorly, between the orbital and sphenoidal processes, there is a notch, which forms the large part of the sphenopalatine foramen. A groove halfway down the perpendicular plate articulates with the inferior concha.

The medial end of the horizontal plate articulates with its opposite number to form the posterior nasal spine. This facilitates attachment of the muscles of the uvula and is a key bony landmark to lower when performing surgery at the mid- and lower thirds of the clivus.

Two important foramina in the palatine bone transmit neurovascular structures: the greater and lesser palatine canals. The former transmits the greater palatine nerve and blood vessels; the latter transmits the lesser palatine nerve and blood vessels to the soft palate and palatine tonsils.

The Nasolacrimal Apparatus

Tears are produced by the lacrimal gland superolaterally and drain inferomedially into the superior and inferior puncta.

The drainage system comprises of the upper and lower canaliculi that join to form the common canaliculus, the lacrimal sac and the nasolacrimal duct. The common canaliculus enters the lacrimal sac approximately 5 mm below the fundus.

There are two one-way valves: the valve of Rosenmuller at the entrance of the lacrimal sac and the valve of Hasner at the distal end of the nasolacrimal duct as it opens into the inferior meatus.

The lacrimal sac and duct can be accessed endoscopically via dissection of bone of the lateral nasal wall in cases of low obstruction. Due to its ease of exposure from a nasal route, the duct might also easily be damaged through excessive anterograde bone removal during uncinectomy and creation of a middle meatal antrostomy.

Two-thirds of the lacrimal sac and duct sit lateral to the ascending process of the maxilla, a third lateral to the lacrimal bone. The anterior aspect of the sac is covered by bone of the beak which also overlies the agger nasi. It is not unusual to open the agger nasi when performing an endoscopic dacryocystorhinostomy [see Chap. 49].

The sac and its fundus extend up to 9 mm above the axilla of the middle turbinate. Hence, it is important to carefully carry bony removal above the axilla to ensure that the area around common canaliculus is exposed for optimal surgical results. Similarly, dissection and opening of the nasolacrimal duct should continue low enough to avoid the risks of both tear reflux and sumping.

The Blood Vessels of the Nose

The sinonasal cavity is incredibly well supplied by blood vessels (Fig. 2.18). Both the internal and external carotid arteries send branches to supply the nose. This is perhaps why epistaxis can sometimes be alarming and intraoperative bleeding difficult to control, particularly in cases of tumour resection.

Internal Carotid Artery System

The common carotid artery bifurcates in the neck into the internal and external carotid arteries. The internal carotid artery (ICA) enters the base of the skull without giving off any branches in the neck. It immediately turns medially and slightly posteriorly in its petrous segment before turning vertically in its paraclival segment. Off this first

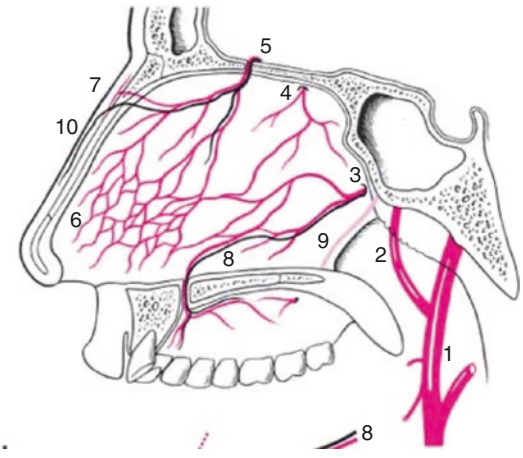

Fig. 2.18 Internal and external carotid artery supplies to the nose. External carotid artery 1 supply to the nose; 2 internal maxillary artery; 3 sphenopalatine artery; 8 greater palatine artery; 9 posterior septal artery. Internal carotid artery supply to the nose: 4 posterior ethmoidal artery; 5 anterior ethmoidal artery; 6 Kiesselbach's plexus; 7 dorsal nasal artery

genu comes the vidian artery. The vidian artery traverses anteriorly in its pterygoid canal with the vidian nerve to enter the pterygopalatine fossa posteriorly (see below). It is a key landmark to this first genu of the ICA during skull base surgery.

The paraclival ICA continues upwards to enter the cavernous sinus in its cavernous segment. It then moves to sit lateral to the sphenoid sinus before dipping medially and anteriorly in its paraclinoid segment. This forms the characteristic siphon, above which comes off the ophthalmic artery.

The ophthalmic artery passes through the superior orbital fissure into the orbit, giving off the posterior and anterior ethmoidal arteries. These arteries enter the roof of the ethmoid through their named foramina in the fronto-orbital suture of the medial orbital wall.

The posterior ethmoidal artery is most likely to sit in bone of the skull base. It may be absent in around 15% of individuals. The anterior ethmoidal artery may sit off the skull base in a bony mesentery. This can render it susceptible to injury during dissections of the frontal recess.

Both arteries traverse the roof of the ethmoid from lateral to medial to enter the lateral lamella of the cribriform plate. The arteries bifurcate to send a branch to the falx cerebri (falcine branch) and a branch into the nose (nasal branch).

A terminal branch of the ophthalmic artery is the angular artery of the nose. This vessel sits in the region of the nasal base line (medial canthus-alarfacial groove) and is often traumatised during external lateral osteotomies of the nose.

External Carotid Artery System

The external carotid system sends branches into the anterior and posterior nasal cavities from below and laterally. The superior labial artery is a branch off the facial artery. It supplies Kiesselbach's plexus in Little's area of the nasal septum.

The bulk of the blood supply to the nose comes via the **internal maxillary** (IMAX) branch of the external carotid system. The greater palatine artery comes off the IMAX in the retromaxillary space to enter its canal of the same name.

The IMAX becomes the **sphenopalatine artery** (SPA) once it crosses the sphenopalatine notch medially.

The SPA may divide into five or more branches in the lateral wall of the nose. Hence, in cases of intractable posterior epistaxis, it is important to seek out these additional vessels to give the best chance of control of bleeding.

A highly reliable surgical landmark to the SPA is the crista ethmoidalis of the palatine bone. The artery invariably sits within a few millimetres of the posterior edge of the crest. The crest may need to be excised to facilitate a better trajectory to the SPA.

The main external carotid supply to the nasal septum is the posterior septal branch, which crosses the face of the sphenoid from lateral to medial in the mucoperiosteum between the sphenoid ostium and the mucosal arch of the posterior choana. The posterior septal branch forms the basis of the pedicled nasoseptal flap used in reconstruction of skull base defects.

Vessels supplying Kiesselbach's plexus in Little's area of the nasal septum:

- Anterior ethmoidal artery
- Posterior ethmoidal artery
- Superior labial artery
- Greater palatine artery
- Sphenopalatine artery (via its nasal septal branch)

The Nerves of the Nose and Sinuses

The trigeminal nerve predominates in sensory innervation to the external and internal nose, whilst the facial nerve innervates the nasal musculature.

The olfactory nerve (CN 1) is responsible for the sense of smell. Olfactory fila from the olfactory bulbs pass through foramina in the cribriform plate into the roof of the nose. They supply the upper nasal septum and medial surfaces of the middle and superior turbinates.

The optic nerve (CN 2) passes out of the orbit via the optic canal in the lesser wing of the sphenoid bone and is responsible for vision. It is important to appreciate the anatomy of the optic canal during sinus surgery as unfamiliarity may

lead to an iatrogenic optic nerve injury. The orbital apex sits lateral to the face of the sphenoid sinus, and the optic canal sits in the superolateral aspect of the sphenoid sinus. A sphenoethmoidal (Onodi) cell may render the optic nerve susceptible to injury in the posterior ethmoid.

External Nose

Sensation of the external nose is derived from the ophthalmic (V_1) and maxillary (V_2) divisions of the trigeminal nerve. The lacrimal, frontal and nasociliary nerves are the three main branches of the ophthalmic division. The infratrochlear nerve arises from the nasociliary nerve and supplies the superior aspect of the external nose. Another branch of the nasociliary nerve is the external nasal nerve which, after exiting between the nasal bone and the upper lateral cartilage, provides sensation to the nasal tip skin, the medial aspect of the nasal alae, and the dorsum of the nose. The maxillary division provides sensory input to the lateral dorsum and the alae of the external nose.

Internal Nose

Both V_1 and V_2 also supply sensation to the nasal mucosa. The anterior ethmoidal nerve is a branch of the nasociliary nerve and provides sensation to the vault and anterior nasal septal mucosa. The nasopalatine nerve is a branch of V_2 and supplies the posterior nasal septum. The greater palatine nerve (V_2) and the anterior ethmoidal nerve (V_1) innervate the mucosa of the lateral wall of the internal nose.

Sinuses

The paranasal sinus mucosa is innervated by the V_1 and V_2 divisions of the trigeminal nerve.

The maxillary sinus is innervated by the V_2 division of the trigeminal nerve. The infraorbital nerve is the terminal branch of V_2. It runs in its canal in the roof of the maxillary sinus and exits the orbit at the infraorbital foramen. It supplies the skin of the lower eyelid, anterior cheek, side of the nose, moveable part of the nasal septum, and upper lip.

The frontal sinus is innervated by the V_1 division of the trigeminal nerve.

The ethmoid sinuses are also innervated by V_1 via the ophthalmic nerve and nasociliary nerve that branches into the ethmoidal nerves.

The sphenoid sinus is innervated by both the V_1 and V_2 divisions of the trigeminal nerve.

Autonomic Nerve Supply to the Nose

The nerve of the pterygoid canal (Vidian nerve: named after Vidus Vidius 1509–1569) contains axons of both sympathetic and parasympathetic nerves. It is formed by the greater petrosal (a branch of the facial nerve) and deep petrosal (a branch of the internal carotid plexus) nerves within the foramen lacerum. The vidian nerve travels to the pterygopalatine fossa through the pterygoid canal in the sphenoid bone.

The preganglionic parasympathetic axons synapse in the pterygopalatine ganglion which contains the postganglionic secretomotor fibres to the lacrimal gland and to the nasal and palatine goblet cells.

The postganglionic sympathetic axons travel on the branches of V_2 to provide sympathetic innervation to blood vessels. They do not synapse in the pterygopalatine ganglion.

Key Concepts

The Internal Valve

This is a critical area of the nose, the narrowest part of the nasal airway, and is responsible for sensing airflow. It is formed by the caudal border of the upper lateral cartilage superiorly, the nasal septum medially, the floor of the nose inferiorly, and the head of the inferior turbinate laterally. Hence, abnormalities of any of these structures at the internal valve may impede airflow and cause a sense of nasal airflow obstruction.

Septum Attachment Points

The nasal septum has critical attachment points at the k (keystone) area, at the anterior nasal spine, and at the anterior septal angle.

The k area is formed at the confluence of the nasal bones, the upper lateral cartilages, the quadrangular cartilage of the septum, and the perpendicular plate of the ethmoid bone. It is critical for support in the roof of the nose. Any septorhinoplastic surgery in this area should be performed cautiously as disruption may lead to cosmetic deformity.

The quadrangular cartilage of the nasal septum is firmly attached to the anterior nasal spine of the pre-maxilla. Disruption of these fibrous attachments during septoplasty surgery may lead to rotation of the quadrangular cartilage causing a supratip deformity. If disturbed, the quadrangular cartilage must be fixed firmly back to the anterior nasal spine.

The anterior septal angle plays an important role to the nasal tip support, length of the nose, and internal nasal valve anatomy. Surgery in this area must be conducted with care, with the complex configuration of the anterior septal angle and lower lateral cartilages restored at the completion of surgery.

The Middle Turbinate

Understanding the anatomy of the middle turbinate is key to successful sinus surgery. It is imperative to work lateral to the middle turbinate during sinus surgery to avoid inadvertent penetration of the skull base. It should be noted whether polyps are arising from lateral to or medial to the middle turbinate. Any polyps or polypoid mucosal change medial to the middle turbinate should be excised with extreme care as the cribriform plate is easily injured at this site. This is a particularly dangerous situation in revision sinus surgery.

The middle turbinate derives from the ethmoid bone. It has three parts: anterior, middle, and posterior thirds. The anterior third is oriented vertically and attaches to the lateral lamella of the cribriform plate. The middle third turns laterally and attaches to the lamina orbitalis. It is the junction of the anterior and posterior ethmoids. The posterior third is attached to the crista ethmoidalis of the maxilla on the lateral wall of the nose.

Careless instrumentation towards the frontal sinus in the anterior third of the middle turbinate may lead to an iatrogenic CSF leak if instruments are inadvertently turned medially.

The transition from anterior to posterior ethmoids happens at the basal lamella. This is otherwise known as the third surgical lamella and is described below.

The posterior attachment of the middle turbinate to the lateral nasal wall is a reliable landmark to identifying the sphenopalatine artery.

The middle turbinate should be respected during sinus surgery. It should be excised only as a very last resort. Excision can lead to lateral scarring, to loss of smell, and to confusion during revision surgery when trying to identify the frontal ostium. It should not be moved excessively during sinus surgery as this may lead to a ‘floppy’ turbinate that easily lateralises and causes sinus occlusion. Similarly, the horizontal attachment of the middle turbinate should be preserved when passing from the anterior to the posterior ethmoids as this will provide rigidity to the structure of the middle turbinate, again avoiding floppiness.

Often, the middle concha may contain a large air cell, called a concha bullosa. The lateral lamella only needs to be excised if sinus function is compromised. In the healthy state, a concha bullosa may be left intact.

Sometimes, a middle concha pneumatisation may occur further back producing an interlamellar cell. This type of pneumatisation may cause a variance of the frontal sinus drainage pathway and should be noted on the preoperative CT scan.

The middle turbinate may be curved laterally, called a paradoxic curvature. This is usually related to a deviation of the perpendicular plate of the nasal septum. A paradoxic curvature may be difficult to diagnose without decongestion of the nasal mucosa. It may certainly be missed by those less experienced in nasal endoscopy. A par-

adoxically curved middle turbinate may lead to disease of the maxillary and anterior ethmoid sinuses. For reasons alluded to above, the treatment of choice in these cases should relate to the septum, uncinate process, and bulla ethmoidalis rather than to excision of the middle turbinate.

The Ostiomeatal Complex

This is a key drainage area where disease might adversely impact the function of three sinuses: maxillary, ethmoid, and frontal sinuses. It is comprised of, from medial to lateral, the lateral surface of the middle turbinate, the frontal recess, the hiatus semilunaris superioris, the bulla ethmoidalis, the uncinate process, the hiatus semilunaris inferioris, the ethmoid infundibulum, and the maxillary ostium. Hence, a careful and complete uncinectomy with an anterior ethmoidectomy may successfully treat the large majority of cases of sinus disease involving the maxillary, anterior ethmoid and frontal sinuses without need for further, more complicated intervention.

The Surgical Lamellae

The complex ethmoidal labyrinth can be reduced into a series of obliquely oriented lamellae based on embryologic precursors. There are four in number and are broadly parallel to each other.

The 4 surgical lamellae:
1st: Uncinate process
2nd: Face of the ethmoid bulla
3rd: Third lamella (also known as the basal or ground lamella)
4th: Superior turbinate (some might refer to the face of the sphenoid as the fourth lamella)

It is imperative for dissection to proceed safely in primary sinus surgery that the surgical lamellae are dissected in sequence from 1 to 4. The only exception to this is in cases of isolated sphenoid sinus disease, where the middle turbinate may be gently lateralised to approach the sphenoid ostium directly via the sphenoethmoidal recess.

Pterygopalatine Fossa

This is a key area in the superomedial retromaxillary space, important for identifying the vidian nerve and the vidian canal in cases of infra- and suprapetrous dissection of the ICA. The boundaries are:

- Anterior: infratemporal surface of maxilla
- Posterior: root of the pterygoid and anterior surface of the greater wing of the sphenoid bone
- Medial: perpendicular plate of the palatine bone and its orbital and sphenoidal processes
- Lateral: pterygomaxillary suture
- Inferior: pyramidal process of the palatine bone

Contents of the pterygopalatine fossa:
IMAX (terminal third)
Maxillary nerve (V2)
Vidian nerve
Pterygopalatine ganglion suspended by nerve roots from V_2

The pterygopalatine fossa is readily accessed endoscopically by removal of bone in the region of the sphenopalatine notch (after ligating the SPA) and the adjacent medial pterygoid. The vidian nerve is a substantial nerve and should not be confused with the palatovaginal nerve, which is more readily identified but has a completely different, perpendicular course to the vidian nerve.

Infratemporal Fossa

This is another key area that sits in the superolateral retromaxillary space. It is where tumours, such as juvenile angiofibroma and meningioma, may extend to. Its boundaries are:

- Anterior: infratemporal surface of the maxilla
- Posterior: styloid and condylar processes
- Superior: greater wing of sphenoid containing the foramen ovale (which transmits the mandibular branch of the trigeminal nerve) and foramen spinosum (which transmits the middle meningeal artery)

- Inferior: medial pterygoid muscle
- Medial: lateral pterygoid plate
- Lateral: ramus of the mandible

Contents of the infratemporal fossa:

Muscles:
- Temporalis
- Lateral pterygoid
- Medial pterygoid

Vessels:
- IMAX
- Pterygoid venous plexus

Nerves:
- Mandibular (V3)
- Posterior superior alveolar
- Chorda tympani
- Lesser petrosal nerves
- Otic ganglion

The infratemporal fossa (ITF) is readily accessed endoscopically by first performing an endoscopic medial maxillectomy and then removing the posterior wall of the maxillary sinus to establish a corridor to the retromaxillary space—lateral is the ITF.

It is usually necessary to control the IMAX to avoid excessive bleeding. Fat in the ITF may also need to be excised to facilitate accurate identification of anatomical structures.

A trans-septal approach or canine fossa puncture may facilitate a better angle of approach to the ITF in either two- or four-handed surgery.

Essential Learning Points

- Understanding nasal and sinus anatomy is key to mastering surgery in these areas.
- Many surgical failures and complications happen due to a lack of understanding of critical anatomy.
- This chapter forms a basis for theoretical knowledge; this *must* be expanded upon by participating in dissection courses, observing experienced surgeons, recognising and learning from anatomical variants whenever seen, and being open to learning, irrespective of age or seniority.

Further Reading

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Physiology: Nasal Airflow

3

Giancarlo Ottaviano

Introduction

The nose has multiple functions. Among these, humidification, warming and cleaning of the air are the most important [1]. In physiological breathing, the nose is the gateway of the respiratory system that provides respiration as well as the ventilation of the paranasal sinuses [2]. Mouth breathing can sustain life, nevertheless exclusive oral breathing is rare. Nasal breathing can be supplemented by the oral airway in particular conditions, i.e., during physical exercise (see below) or severe nasal obstruction [3].

Neonates are obligate nasal breathers until the age of 2–3 months. Nasal occlusion in newborns causes impaired respiration leading to dyspnea [4]. Oral breathing in children can alter facial growth (children with chronic nasal obstruction tend to have longer and narrower faces) as well as cause dental malocclusion (especially posterior cross-bite), due to a lower dental-traverse maxillary dimensions [5].

The upper airway is responsible for up to 70% of the total airway resistance, helping the lungs to expand optimally while allowing venous return. During nasal inspiration, air enters the nasal cavities due to the pressure gradient existing between the ambient air and the alveoli. During nasal expiration, the opposite happens. Every day, more than 10,000 L of ambient air are inhaled and reach the lower respiratory airways for ventilation [6, 7]. Since proper gas exchange in the pulmonary region relies on clean air at a temperature of 37 °C with a relative humidity of 100%, the upper respiratory system, and particularly the nose, needs to filter, warm, and humidify the inhaled air before it reaches the lungs [1]. In order to be effectively filtered, heated, and humidified, the inhaled air benefits from maximal exposure to the nasal mucosa. While the nasal turbinates provide a large surface area of about 100 and 200 cm^2 [1], nasal airflow turbulence (see the following paragraph) guarantees a prolonged duration of air/mucosa contact time, allowing the nose to filter particles bigger than 10 μm as well as to warm and humidify the inhaled air before reaching the lungs [7, 8].

Nasal Breathing, Airflow Distribution, and Physiology

Nasal cavity airflow characteristics during breathing have been studied by means of simulations conducted on nasal models, such as those obtained as casts from human cadavers [3]. More recently, much more complex analyses of nasal cavity airflow patterns have been obtained by means of computational fluid dynamics (CFD). CFD are based on three-dimensional nasal mod-

G. Ottaviano (✉)
Department of Neurosciences, Otolaryngology Section, University of Padua, Padua, Italy
e-mail: giancarlo.ottaviano@unipd.it

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els generated from computed tomography or magnetic resonance imaging datasets. By means of CFD studies, airflow velocities, temperature, humidity, pressure, and distribution can be simulated and displayed as a function of multiple boundary conditions [8, 9].

Air entering the nostrils passes through the nasal vestibule and, just beyond this, converges into the nasal valve before entering the main nasal passages. The nasal valve has a dynamic character being bounded by compliant and mobile as well as rigid components [10]. At this level, the minimal cross-sectional (MCA) area (about 20–60 mm^2) has the greatest resistance (about 50%) of the entire respiratory airways [6, 11–13]. The airflow convergence promotes laminar flow through the narrow nasal valve. After this point, airflow enters to the much larger main nasal passages (cross-sectional area of 100–300 mm^2) and linear velocity decelerates from 12–18 to 2–4 m/s [10, 12]. The kinetic energy release generates inertial disturbances that promote mixing of the airstream. Hence the laminar airflow will be disrupted to become turbulent [3, 10]. Once in the main nasal passages, the airflow changes direction (with an angle of 60°–130°) and becomes parabolic [10] (Fig. 3.1). At the same instance, the airflow splits into three airstreams. The main one with a width of 1–3 mm proceeds between the inferior and the middle turbinates, horizontal to the middle meatus [3, 6, 12]. A second smaller airflow runs along the nasal floor. Finally, a minimal flow reaches the upper part of the nasal cavities where the olfactory mucosa is largely distributed. "Sniffing" [14] changes the airflow patterns enabling a greater amount of airflow to reach the nasal vault and as such the sites where olfactory mucosa is most predominant [15]. According to CFD findings on healthy human models, at a flow rate of 7.5 L/min, the percentage of the inhaled air passing through the middle meatus is about 36%, while the percentage of airflow that runs through the inferior meatus and the olfactory cleft is about 11% and 4%, respectively [16]. After reaching the choana, a reduction in the cross-sectional area (100–250 mm^2), leads to an increase in airflow speed (3–4 m/s) before entering the nasopharynx. At this level, the main airflow changes direction by almost 90° before entering the oropharynx and returning to laminar flow [12].

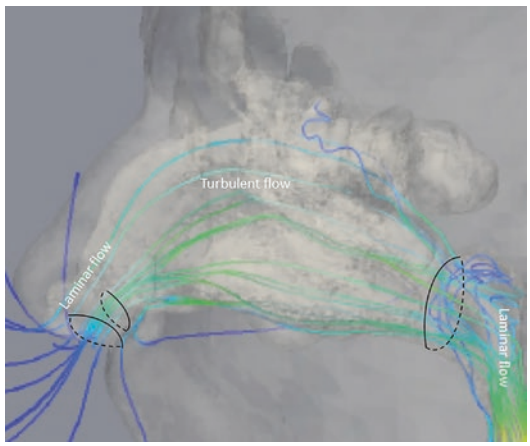

Fig. 3.1 A computational fluid dynamic (CFD) image showing the classic parabolic airflow during nasal inspiration in a normal subject. The areas where the airflow is laminar or turbulent during nasal respiration are indicated. The circles indicate the nasal vestibule, the nasal valve, and the choana

The division of the nasal airflow in different airstreams and the associated airflow turbulence allows maximal distribution of the inspired air throughout the nasal cavities [6]. In fact, under conditions of laminar flow, only the particles in the airstream close to the wall would come in contact with the mucosa [3]. Moreover, turbulence, leading to dehydration of the mucosa, increases the resistances to flow, thus helping to guarantee the contact between the inspiratory air and the nasal mucosa [1, 9]. Turbulence as well as the flow deceleration, prolonging the contact time between the inspiratory air and the mucosa, promotes adequate air heating, filtering, and humidification and prepares the air for gas exchange in the lungs [1, 3, 12, 17, 18]. Nasal airflow turbulence and deceleration are fundamental preconditions for proper respiratory function [1].

It has been estimated that the nose manages to humidify the inspired air to a humidity of over 80% before it enters the lungs [7]. CFD studies have shown that passing through the nose air temperature and humidity reach almost 98% of mucosal temperature and 94% of mucosal humid-

ity before the nasopharynx. The anterior part of the nasal cavity is characterized by high heat and moisture fluxes due to the larger temperature and humidity differences between ambient air and nasal surfaces. The contribution of the inferior and middle turbinates in heat and moisture transfer to the inhaled air is also significant (around 25.6% of total heat transfer), whereas heat transfer in the nasopharynx and olfactory area is barely perceptible. Interestingly, with increasing respiratory rate, heat flux increases more in the posterior than in the anterior part of the nose [16].

By contrast with the inspiratory airstream, during expiration, well-conditioned air coming from the lower airways is dispersed throughout the nasal cavities. Convective exchanges between the air and the cooled mucosa allow the partial recovery of heat and water. It has been estimated that during expiration, the nose is able to recover about 100 mL of water daily [6, 19]. Nevertheless, during nasal breathing at room temperature, the daily total loss of water is about 500 mL [6].

Airflow through the nasal passages is usually asymmetric [20] because of spontaneous congestion and decongestion of the nasal venous sinuses at the anterior end of the inferior turbinate and the nasal septum in the nasal valve region. This alternation of nasal airflow is usually referred to as the nasal cycle [11].

As mentioned above, normal upper airway function is essential for normal lower airway activity. A large body of evidence shows that there is a strict association between the upper and the lower airways and supports the concept of a unified airway in physiological as well as in pathological conditions [21]. Total nasal obstruction results in a significant decrease of total lung capacity, functional residual capacity, and residual volume [22].

Ventilation of Paranasal Sinuses and Physiology

The ventilation of the nose and paranasal sinuses includes the gas exchanges between these two areas, as well as the sinuses' mucosal gas exchanges [23, 24]. At resting ventilation, fluctuations of nasal respiratory airflow pressures approximate <±100 Pa (±1.0 cm H_2O). Such pressures are able to displace only 1/1000 [3] of the sinuses air volume through the patent ostia with each breath. Nevertheless, the gas exchange between the nose and the paranasal sinuses is faster due to passive processes of gas diffusion through the natural ostia. In normal conditions, a maxillary sinus undergoes a 90% air exchange within 5 min [25, 26].

In healthy conditions, the oxygen absorption by the mucosa of the maxillary sinus is about 0.1 mL per minute. The inflow of oxygen through an ostium with a functional size of 2.4 mm in diameter (corresponding to an ostium size of 5 mm^2) or more is enough to compensate for this absorption. Ostia patency is thus essential to guarantee normal gas exchange with a balance between inflow of gas through the ostium and local consumption. Interestingly, studies conducted on the maxillary sinus showed that the functional size of the ostium decreases when lying down, especially when passing from a 30° semi-recumbent position to the horizontal one [23, 25]. A pathological reduction of sinus patency causes gas pressures alterations within the sinus with pO_2 and pCO_2 alteration and, finally, mucosal exudation [25]. In some cases, the trapping of secretions into the maxillary sinus can lead to the absorption of gas and the creation of a subatmospheric pressure gradient finally leading to the sinus silent syndrome. The classical syndrome is characterized by bone absorption and remodeling of the orbital floor due to the bowing of the sinus walls and the inward displacement of them. Classically, it presents with ipsilateral maxillary sinus hypoplasia, hypoglobus, and otherwise asymptomatic maxillary sinus disease [27].

No conclusive theory on the function of paranasal sinuses has been accepted yet, and the physiological significance of the paranasal sinuses free from disease remains unclear. Many hypotheses have been proposed for their role. Some authors have suggested a functional role of the paranasal sinuses, such as helping nasal and olfactory functions as well as midface growth and phonetic and respiratory functions. Others

have argued that paranasal sinuses in humans do not play a significant role in processing respiratory air, being merely nonfunctional remnants of a common mammalian ancestor [6].

The Nasal Cycle

Nasal cycle is the spontaneous, reciprocal congestion and decongestion of the nasal mucosa during the day, where congestion of one side is often accompanied by reciprocal decongestion of the contralateral side. These changes result in asymmetrical airflow that alternates from one nasal passage to the other. The phase of decongestion is often called the "working phase," while the congested one is defined the "resting phase." This phenomenon is based on the dilation and constriction of the venous cavernous tissue in the mucosa of the turbinates and septum [28] and is present in almost 80% of people [29], but a true periodicity and reciprocity exists only in 21–39% of the population. The nasal cycle is considered an ultradian rhythm of side-to-side nasal mucosal engorgement. In most people, these cycles last around 2–4 h, but for some, the cycle can be irregular [30], shortened, elongated, or absent [31]. It is present in seated and standing position, as well as in the laterally and dorsally recumbent [32].

The functional role of the nasal cycle is not completely understood. It may be involved in the production of mucous nasal secretions [33], in the humidification of inspired air [34], and/or in respiratory defense [35]. In this regard, plasma is rich in immunoglobulins and proteins involved in the generation of inflammatory mediators, components important in the inflammatory response, and defense against infection. So, the contribution of the nasal cycle to the generation of plasma exudate may be seen as a contribution to respiratory defense. During nasal infection, the nasal cycle increases its amplitude and frequency, and this may enhance the generation of plasma exudate and so that of inflammatory components. White and colleagues [36] also suggested that the nasal cycle enables the upper airway to accommodate the contrasting roles of air-conditioning and the removal of entrapped contaminants through fluctuation in airflow. In particular, an efficient transport of entrapped inhaled pathogens and pollutants requires low air velocities and sustained airway surface liquid (ASL) hydration that is carried out by the congested side of the nose. Conversely, air-conditioning requires high air velocities to be effective, and this role is facilitated by the patent side. The presence of an alternation in nasal congestion and decongestion enables ASL layer to return to an uninterrupted state of hydration during the resting phase, thus supporting continuous and normal mucociliary clearance [36]. It has also been hypothesized that the nasal cycle allows local accumulation of nitric oxide, which normally has an important role in modulating epithelial function and antimicrobial features [37].

Recently, some authors [38] defined four types of nasal cycles

- Classic pattern, with reciprocal congestion/decongestion alterations and a constant total volume
- Parallel pattern, with congestion or decongestion appearing in both nasal cavities at the same time
- Irregular pattern, with mutual alteration in nasal volume without a defined pattern and a constant total nasal volume
- No pattern, in which total nasal volume and nasal volume in each nostril do not differ

Although in 2016 it was demonstrated that the majority of subjects exhibit reciprocal changes in unilateral airflow [39], more recently it was observed that in a group of 20 healthy subjects, half of them presented a parallel pattern, while the other half showed a reciprocal pattern [40] (Fig. 3.2).

Whatever the reason for cycling, it usually allows one nostril to be "at rest" relative to the other during normal breathing. The nasal cycle seems to be controlled mainly by the sympathetic nerve supply to the nose [41] under the direction of the central nervous system [42]. At present, the central regulation for the alternation of the sympathetic activity at the level of the nasal cavity is not completely understood.

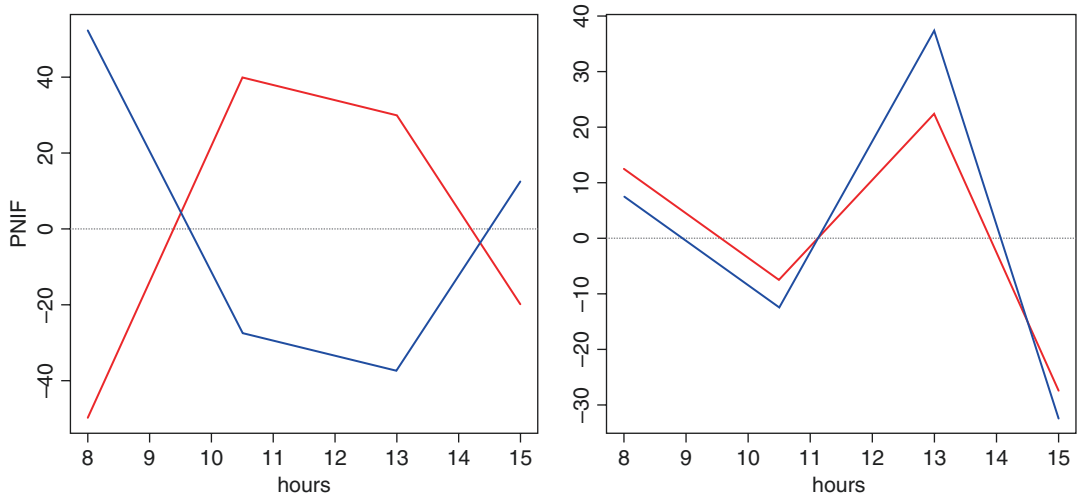

Fig. 3.2 Changes in unilateral nasal airflows measured by means of peak nasal inspiratory flow (PNIF) showing a classical nasal cycle type (left picture) in a healthy subject. Changes in unilateral nasal airflows measured by means of peak nasal inspiratory flow (PNIF) showing a parallel nasal cycle type (right picture) in a healthy subject. In red the left nostril, in blue the right nostril

A variety of external stimuli, such as arterial pCO_2, emotion, and skin temperature changes, are able to influence the activity of the nasal centers [32]. Airflow through the nose has been hypothesized as important in the control of the nasal vasomotor activity, although the presence of the nasal cycle has been demonstrated in laryngectomized patients, in the absence of nasal airflow [43, 44].

Effects of Physical Activity on Nasal Airflow

Since nasal function has historically been associated with performance in aerobic exercise, respiratory function during physical exercise has been extensively investigated [45, 46]. Exercise causes a decrease in nasal mucosa congestion similar to that seen with the application of a nasal decongestant such as oxymetazoline hydrochloride. Overall, exercise can produce a drop in total nasal resistances within 30 s that is maximal at 5 min and may persist for up to 30 min after completing the aerobic performance [47]. Many factors can be involved in the reduction of nasal resistance due to exercise: increase in the activity of alar nasal muscle, blood redistribution for muscles under exercise distant from nasal mucosa, increase in nasal airflow, hyperventilation, and nasal mucosal active vasoconstriction [48]. Vasoconstriction is believed to be a consequence of changes in arterial pCO_2 and is mediated by the autonomic innervation of the nasal vasculature [49]. Plasma concentrations of neuropeptide Y seem to correlate with postexercise nasal vasoconstriction suggesting that this neuropeptide might act as a modulator of nasal airways reactivity [50]. Interestingly, a rebound increase in nasal resistances after exercise has been observed [51, 52].

Some studies have evaluated the effects of the physical activity at high altitude. Globally, an increasing number of people living at low altitude enjoy sport and recreation at altitudes higher than 2000 m [53, 54]. During altitude exposure, the airways adapt by activating a number of mechanisms aimed at optimizing oxygen availability. In particular, high-altitude trips (defined as higher as 2700 m above sea level) [55] may cause, among others, nasal congestion and increased nasal resistances due to decreased partial oxygen pressure and dry air [56]. Nevertheless, a recent study, evaluating nasal function at rest in a group of subjects during a weeklong skiing vacation at high

altitude (3400 m) found a significant increase of nasal flows values at 3400 m with respect to the baseline values (measured at the base camp, 2000 m). Interestingly, similar results were observed in another study, which simulated the passage from the sea level to 8000 m in a hypobaric chamber [57]. The authors concluded that, when exposed to high altitude, the human body produces an increased amount of catecholamines, probably to enable a faster cell regeneration, ultimately producing nasal decongestion [58]. However, existing evidence is based on small sample sizes, and more studies on this fascinating topic are needed to confirm these findings.

Effects of Temperature and Air Humidity on Nasal Respiratory Function

The inhalation of cold/dry air and hot/humid air has an influence on nasal air-conditioning [59]. A study assessing the effects of air humidification on complaints of nasal obstruction and nasal patency measurement during 8–9 h of intercontinental flight noted that a 10% increase in the relative air humidity produced a significant reduction in symptomatic nasal obstruction [60]. In addition, it has been noted that application of a cooling face mask reducing facial skin temperature by 10 °C produced intranasal increases in humidity, mucosal temperature, and volumes, probably mediated by trigeminal nerve stimulation and necessary to guarantee a sufficient steady intranasal nasal air-conditioning [61].

Effects of Posture on Nasal Airflow

Although it is known that body position can influence pulmonary function [62], less is known about the influence of body position on nasal flows and patency [63].

In healthy subjects, changing from sitting to upright position (and vice versa) seems to have no effects on either nasal volumes [64] or on nasal flows [65]. On the contrary, as demonstrated by Roithmann and colleagues, change from sitting to supine position produces decreased nasal volumes in normal subjects [66]. In particular, in lateral recumbence, the nasal airflow of the side where one is lying on is reduced, while the other is mainly open for nasal airflow [11]. The nasal patency/airflow changes observed in the supine position could be explained by two different mechanisms: an increased central venous pressure when lying in the supine position and a reflex change in the nasal vasomotor tone due to the stimulation of receptors located in the area of the shoulder, lateral thorax, and hip, when laying laterally [1]. Although the effects of lateral recumbence can override the nasal cycle, in general, its periodic reciprocity begins again if the lateral posture is maintained [3].

Nasal Nitric Oxide

Nitric oxide (NO) is an endogenous mediator in the respiratory system. It is produced from arginine and oxygen by NO synthase (NOS) [67]. There are three NOS isoforms in the human airway mucosa: the neuronal-type NOS, the endothelial-type NOS, and the inducible-type NOS (iNOS). Whereas the first two are constitutively expressed and generate relatively low levels of NO, iNOS is primarily expressed in response to external stimuli, and it is raised in some pathologies [68, 69]. The role of NO in the airway is complex, possibly including pro-inflammatory effects, regulation of blood flow, stimulation of ciliary beat rate and bacteriostasis [70–72].

In the normal nose, high levels of NO are produced in remarkably large quantities from epithelial cells of the paranasal sinuses [70], especially the maxillary sinus [73], while less is produced by the nasal mucosa [74]. Nasal NO has a significant degree of interindividual variation (about 20–25%) and can be influenced by many internal and external factors [68, 75], so, although it has been suggested to be useful in the diagnosis of primary ciliary dyskinesia, cystic fibrosis, and nasal inflammation (i.e., rhinitis), its clinical value is limited [67].

Conclusions

Nonlaminar characteristics of inspiratory airflow are induced by the constricted lumen at the site of the nasal valve. Changes in nasal cavity diameter after this point produce a decrease in the linear velocity leading to the production of vortices and a turbulent airflow. These characteristics are of utmost importance as they promote cleansing and conditioning of ambient air and thereby protect smaller bronchioles and alveoli. The human nose is also able to recover heat and water from expiratory air (about 30% in temperate conditions). The paranasal sinuses do not have a significant role in the respiratory air processing that takes place in the nasal cavities.

When present and regular, the nasal cycle, a spontaneous congestion and decongestion of the nasal mucosa, has been described as alternating. It has been also demonstrated that in some subjects, the nasal cycle can exhibit in-phase changes. Very recently, it has been found that reciprocal and in-phase patterns of the nasal cycle can be equally distributed in adults.

Various physiological conditions can modify nasal airflow, such as physical exercise and body position. Exercise produces a significant nasal vasoconstriction with a drop of total nasal resistances. In lateral recumbence, the nasal airflow of the side where one is lying on is usually reduced, as consequence of the stimulation of some receptors located in the area of the shoulder, lateral thorax, and hip.

Key Learning Points

- The nasal valve is the most important area able to influence nasal respiration. At this level, the minimal cross-sectional area and the highest resistance of the entire upper respiratory system occur.
- During inspiration, the main nasal airstream is directed between the inferior and middle turbinates.
- The nasal turbinates create a large surface area and a uniform slit space between the septum and the lateral wall, which promotes warming, humidification, and cleansing of the inspired air.
- The nasal cycle allows the nose to alternate between working and resting phases to improve gradients of thermal energy and humidity.
- The paranasal sinuses do not play a significant role in processing respiratory air, and the net supply of humidity from all of the sinuses to the inspiratory air is small.
- In lateral recumbence, the nasal airflow of the side which one is lying on is usually reduced.

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4 Physiology of the Nose and Paranasal Sinuses: Mucociliary Clearance

Mikkel C. Alanin and Christian von Buchwald

Introduction

The conducting airways in the nose and sinuses are lined with a pseudostratified epithelium consisting of ciliated cells, secretory cells and goblet cells.

The epithelium in the sinonasal cavity is a main entry port for respiratory pathogens, allergens and pollutants, and it also plays an important role in the initial host responses against infection. Normal mucociliary clearance (MCC) is essential for the maintenance of an effective primary defence mechanism and healthy sinonasal cavities. Effective MCC necessitates appropriate mucus, and effective and synchronized ciliary beating accompanied with a proper periciliary fluid layer.

Cilia propel respiratory mucus. After inhalation of a pathogen, allergen, debris or a pollutant, the foreign material is trapped in the mucus and then phagocytised or removed by the process of MCC. The coordinated and continuous unidirectional beating of the cilia transports the mucus to the oropharynx, where it is cleared by ingestion, coughing and expectoration.

If MCC is compromised, the airways become vulnerable to infection and inflammation. This phenomenon is evident in patients with chronic rhinosinusitis who experience persistent cycles of infection and inflammation resulting in ciliary loss and a hyper-viscous mucus. Damage or disruption of mucociliary function due to viral infection is probably a major cause of secondary bacterial infection.

This chapter will review the essential components of the mucociliary apparatus and discusses important clinical examples of compromised MCC. Factors that can improve MCC will also be discussed.

Mucus

The normal mucosal lining of the nasal cavity is coated by a mucus layer up to 70 μm thick [1]. The periciliary fluid layer is approximately 5 μm thick [2].

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M. C. Alanin · C. von Buchwald (✉)
Department of Otorhinolaryngology-Head and Neck Surgery and Audiology, Copenhagen University Hospital, Copenhagen, Denmark
e-mail: christian.von.buchwald@regionh.dk

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Mucus is produced by goblet cells and by submucous glands in the mucosa [3]. In the nose, 100–200 mL of mucus is produced per day [2]. Mucus is a barrier to prevent water loss by diffusion and to remove inhaled foreign substances such as viruses, bacteria, allergens, inflammatory cells and pollutants. Upon infection of the nasal epithelium, secretory cells release anti-microbial surfactants and mucus to delay pathogen transmission in the airway [2]. Mucus is characterized by its volume, viscosity, elasticity and thread-forming capacity [4].

Mucus is a gel consisting of predominantly water (approximately 95%). The other key components are ions, proteins and macromolecules. The major macromolecular components of mucus are the mucin glycoproteins. These can be subdivided into:

1. Secreted mucins
2. Cell-associated mucins that are anchored at cell surfaces
3. Gel-forming mucins

This arrangement of cell-associated and gel-forming secreted mucins creates a two-layered airway surface mucus barrier with a periciliary liquid layer next to the cell surface and a gel-forming mucin layer. The most important cell-associated mucins are MUC1, MUC4, MUC16 and MUC20. The periciliary fluid, both in composition and volume, appears to be critical for proper mucociliary transport [1]. The cell-associated mucins attached to airway epithelial microvilli and cilia generate an osmotic barrier that preserves the periciliary layer [3].

The most important gel-forming secreted mucins are MUC5AC and MUC5B. These are responsible for the characteristic viscoelastic properties of the mucus gel layer. MUC5AC production from goblet cells increases following viral infection. It has been shown that rhinovirus infection induces temporary mucus hypersecretion which is evident during the common cold.

Mucins can also mediate inflammatory cascade pathways, and they contain innate immune proteins such as lactoferrin, lysozyme and s-IgA which aid in the local immune defences [5].

All of these rheologic and physical properties are influenced by the degree of hydration and the glycoprotein composition, factors that are host-regulated.

Mucus hyperproduction is also an important hallmark of type 2 inflammation via activation of Il-13 and Il-5; please see below.

Cilia

Ciliated cells are the major component of the pseudostratified epithelium. Cilia are hair-like organelles that are organized with microtubule, Fig. 4.1. There are 50–200 cilia per epithelial cell. The length of cilia is typically 6 μm, and they reach through the periciliary liquid layer and just into the mucus layer.

Cilia are coated with cell-associated mucins that exclude mucus from the periciliary space and promote the formation of a distinct mucus layer and a periciliary liquid layer as mentioned above [3].

Cilia are composed of structural proteins and motor proteins that drive their coordinated unidirectional beating of the cilia which are critical for MCC. Under normal conditions, the cilia beat at a frequency of 6–17 Hz [6, 7].

The normal ultrastructure of motile cilia contains nine outer doublets of microtubules and a central pair called the “9+2 axonemal appearance.” Outer and inner dynein arms are attached and contain enzymes for ATP hydrolysis producing power. Nexin links connect the doublets and stabilize the structure, whereas radial spokes interlock the outer doublet to the central pair. When activated, the dynein arms slide one microtubule-duplet relative to another, and since these are connected by the nexin links, the whole axoneme bends (Figs. 4.1 and 4.2).

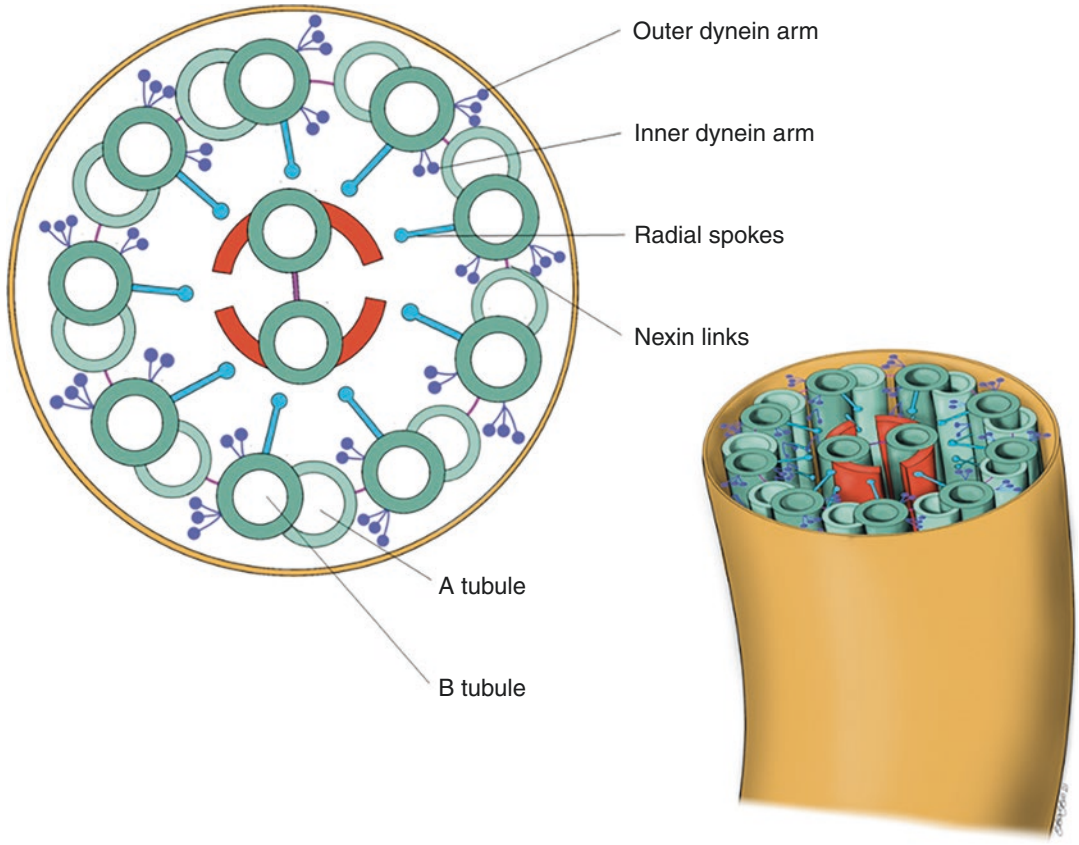

Fig. 4.1 Normal ultrastructure of cilia. Normal cilia have nine outer doublet (A + B tubule) and a central pair "9 + 2 appearance." Dynein arms are attached to the outer doublets. Nexin links connect the outer doublets, and radial spokes connect the outer doublets with the central pair

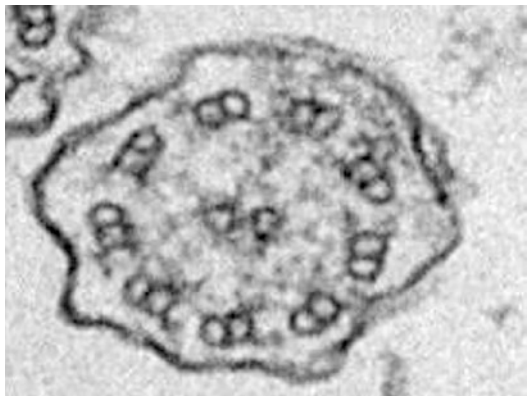

Fig. 4.2 Normal ultrastructure by TEM. The "9 + 2" axonemal appearance is evident

Assessment of Ciliary Ultrastructure and Ciliary Beat Function

Ciliary ultrastructure can be assessed by transmission electron microscopy (TEM). TEM is used for research purposes and in the clinical setting to aid in the diagnosis of primary ciliary dyskinesia (PCD); please see below. The required ciliated epithelial specimen can be obtained using a cytology brush on the inferior nasal turbinate [8].

Precise ciliary beat frequency and ciliary beat pattern can also be assessed from brush biopsies of the inferior turbinate using high-resolution, high-speed video microscopy with slow-motion

replay. Like TEM, it is used clinically to establish a diagnosis of PCD (Video 4.1).

Nasal Mucociliary Clearance Testing

The MCC time is the time taken for a molecule inserted into the nares to reach the oropharynx. Mucus moves at a speed of approximately 10 mm per minute in vivo under normal conditions, and normal values in adults are approximately 10–15 min. It can be assessed using different methods [6, 9].

Saccharin Test

A 5 mg particle of saccharin is placed on the inferior turbinate, 1.5 cm from the nares under direct visualization. A timer is started, and the transit time is reported as the elapsed time from the placement of the particle until the patient reports a sweet taste. Normal values reported for this assay are between 11 and 15 min and it has been recommended that further investigations are necessary in patients with a transit time of 60 min or more [9]. The saccharin particle can be dissolved with methylene blue. Thus, when the patient reports the taste sensation, the objective finding of blue dye in the oropharynx confirms the subjective taste report [10].

Scintigraphy with Technetium-99

A droplet of a suspension of colloid particles labelled with technetium-99 (usually 50 [mu]Ci diluted in 0.05 mL of saline) is placed 1 cm posterior to the mucocutaneous junction of the nasal cavity on the inferior turbinate or along the lateral floor. Movement of the radioactivity is recorded with a gamma camera with images obtained every 30 s during a 10-min period [7]. Most studies report an average velocity of 10.9 mm/min for control populations. To determine MCC in the lower airways, a turboinhaler may be used with labelled particles of different sizes. Larger particles typically deposit in the nose and pharynx, while smaller particles are deposited in the trachea, and minute particles remain suspended in inhaled air [4] (Video 4.2).

Examples of Compromised MCC

Impaired MCC leads to stagnant mucus in the respiratory tract, which predisposes to infection and inflammation.

Primary Ciliary Dyskinesia

PCD is an autosomal recessive genetic disease. Well-described mutations in more than 30 genes involved in ciliary structure and function are characterized, and genetic testing can identify approximately 60% of the phenotypically identified PCD patients. In PCD, MCC is impaired by genetic mutations resulting in non- or hypofunctional cilia.

The commonest ultrastructural defect in PCD is defects in one or both dynein arms. This is observed in >80% of patients with recognized structural defects (Fig. 4.3 [11]).

Initially, the composition of the mucus is presumably normal in the PCD airway; however, during prolonged or chronic infection and inflammation, DNA and actin released from neutrophils may increase the viscosity of the mucus.

PCD manifests primarily as an oto-sino-pulmonary disease comprising chronic otitis media with effusion, chronic rhinosinusitis with or without nasal polyps and recurrent or chronic lung infections leading to structural lung damage

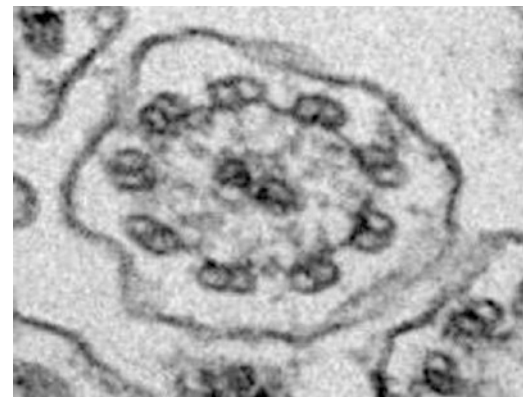

Fig. 4.3 Abnormal TEM in a patient with PCD. Transition electron microscopy displaying missing outer dynein arm, representing one of the most common findings in patients with PCD

such as bronchiectasis and declining lung function.

CRS and bacterial sinusitis are ubiquitous in patients with PCD affecting more than 70% of the patients. Sinus surgery can improve QoL in patients with PCD and may also be effective in eradicating Gram-negative bacteria from the global airways [12] (Video 4.3).

Cystic Fibrosis (CF)

Cystic fibrosis (CF) is a life-shortening genetic disease caused by a mutation in the CF transmembrane conductance regulator (CFTR) gene on chromosome 7. The gene encodes chloride channels, and the defect leads to abnormal transport of chloride and sodium across the cell. Loss of CFTR function results in deficient chloride and bicarbonate secretion and dysregulation of the epithelial sodium channel with excessive sodium absorption at the apical cell membrane. The resultant decrease in salt concentration in the airway secretion more than doubles the viscosity. This leads to a dehydrated and sticky mucus which reduces MCC by preventing normal ciliary movement and predisposes to infection. Recurrent or chronic lung infection with especially CF-pathogenic Gram-negative bacteria (GNB) including *Pseudomonas aeruginosa*, *Achromobacter xylosoxidans* and *Burkholderia cepacia* causes structural lung damage, declining lung function, premature death or lung transplantation. In CF, the cilia are apparently normal. However, a recent study demonstrated abnormal accumulation of an intracellular transport protein (IFT88) and disrupted intra-ciliary trafficking which suggest that disrupted ciliary function is also a feature of the CF phenotype, which might contribute to defective airway MCC [13].

Cough clearance is weakened in CF due to the depletion of the airway surface liquid which is not the case in PCD. Airway inflammation in both PCD and CF are dominated by neutrophilic infiltration compared to eosinophilic inflammation in patients with CRS with nasal polyps and asthma.

CRS with or without nasal polyposis is common in patients with CF, and radiographic evidence of CRS in CF is almost 100%. Nevertheless, <50% report symptoms, but they can have a substantial negative impact on QoL. Sinus surgery with adjuvant medical therapy can reduce pulmonary infections with CF-pathogenic GNB and improve QoL [14].

CFTR modulators serve as correctors or potentiators of the chloride channel, and there is substantial evidence that they can improve lung function, quality of life and slow the progression of lung disease. Emerging evidence support that CFTR modulators also may improve sinonasal symptoms, i.e. SNOT 22 in CF [15].

In contrast to PCD patient, OME is very rare in CF.

Secondary Ciliary Dyskinesia

Ciliary abnormalities detected after infection and inflammation are referred to as secondary ciliary dyskinesia. Mucostasis, hypoxia, microbial products and toxic inflammatory mediators can induce secondary ciliary changes, and ciliary impairment is a feature of both viral and bacterial rhinosinusitis.

Impairment of nasal MCC including a fall in the number of ciliated cells and a moderate and short-lasting change in beating frequency and synchrony has been observed in patients during the common cold. Other studies have further confirmed that impaired ciliogenesis is prominent following viral infections consistently leading to loss of cilia and ciliated cell ultrastructural abnormalities. Characteristically, influenza virus infection can be followed by apoptotic and necrotic cell death causing the loss of epithelium including ciliated cells, impacting ciliary function. During sinusitis, a study found a prolonged nasal MCC time of 18 min versus 10 min for matched controls [6]. Impairment of MCC following viral infection is probably a major cause of secondary bacterial infections.

Smoking

Ciliary impairment is associated with cigarette smoking. Smoking significantly prolongs nasal

MCC probably due to a reduced beat frequency, a reduction in number of cilia and changes in viscoelastic properties of mucus as a result of significantly increased goblet cell density and mucin volume density [3, 16]. It is also well known that smoking can contribute to the development of CRS [17].

Drugs

Several studies on the effect of nasal steroids have found no change on MCC in healthy subjects, but they may be effective in patients with perennial rhinitis; see below.

Studies on the imidazoline derivatives oxymetazoline and xylometazoline which are alpha adrenergic receptor agonists have found that they exhibit ciliotoxic effects and inhibit ciliary function and thus MCC [18]. Long-term use may also lead to rhinitis medicamentosa. It is believed that when the imidazoline derivatives are withdrawn, increased parasympathetic activity leads to rebound congestion as a consequence of vasodilation and mucosal swelling. Long-term use may also lead to goblet cell hyperplasia and destruction of nasal cilia which compromise MCC [19].

Gastroesophageal Reflux Disease (GERD)

Reflux of gastric acid into the pharynx and nasopharynx is thought to cause mucosal inflammation which may impair MCC.

Type 2 Inflammation

The immune system covers a wide variety of inflammatory cells with different functions and features. Inflammation is generally defined as a response to an invading pathogen or endogenous signals from, e.g. damaged cells. Toxic, non-allergic or allergen-induced inflammation of the nasal mucosa causes swelling resulting in reduced MCC.

Patients with asthma and CRS with nasal polyps usually present with type 2 helper T-cell (Th2) cytokine-mediated inflammation in the mucosa, which has similarities to allergic inflammation/hay fever. Controversially, neutrophilic Th1-dominated inflammation is seen in patients with COPD. Key Th1 cell cytokines are interferon (INF)-γ and tumour necrosis factor that trigger macrophages while inhibiting mast cells, eosinophils and IgE production.

Th2 cell-mediated production of interleukins is dominated by Il-4, Il-5 and Il-13. Il-5 production increases tissue eosinophilia. Il-13 hyperproduction leads to bronchial hyperreactivity, goblet cell metaplasia and vessel wall priming that allows eosinophils to extravasate, and they inhibit macrophages. Especially, mucus hyperproduction and bronchial smooth muscle proliferation are hallmarks of type 2 inflammation.

Mucus plugging of bronchi is seen in severe asthmatics and associated with airway eosinophilia. Similarly, mucus plugging in the sinus cavities is evident in severe Th2 cell-mediated inflammation. Activated eosinophils will release galectin-10 that will undergo a transition to a crystalline form as Charcot-Leyden crystals (Fig. 4.4 [20]). These crystals are sharp and act as a barbed wire infiltrating the mucus making it increasingly sticky—comparable to dried glue [21]. Mucus plugging in the nose and sinus cavities compromise MCC.

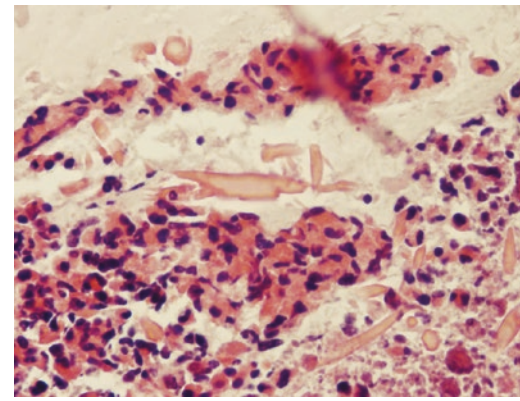

Fig. 4.4 Charcot-Leyden crystals formed in severe Th2 cell-mediated inflammation. Source: Original image kindly supplied by Andrew C. Swift

Improving Mucociliary Clearance (MCC)

Nasal Irrigation with Saline

Nasal irrigation with isotonic and hypertonic saline can improve the mucociliary transport function of the nasal mucosa [22]. Different kinds of nasal irrigation solutions, such as normal saline as well as various concentrations of hypertonic saline, have been used clinically. Saline solutions have been widely used in nasal irrigations for many years and are recommended for the treatment of various nasal diseases by several international expert groups including the EPOS 2020 [23]. Besides stimulating MCC, nasal irrigation may also be effective in reducing nasal congestion and secretions and moisturize the mucosa.

Drugs

Intranasally administered drugs can speed up or slow down MCC, which may be used in the clinical setting. For instance, a drug that increases MCC may lead to a faster clearance of pathogens or allergens from the mucosa. In contrast, drugs that prolong MCC may increase the bioavailability of topically administered drugs. However, many studies are conflicting, but it is an interesting area of future research [18].

Mucoactive drugs are regularly used as a therapeutic option for mucus alteration, including hypersecretion. The drugs can be divided into expectorants (e.g. hypertonic saline), mucoregulators that regulate mucous secretion (e.g. carbocisteine), mucolytics that decrease mucous viscosity (e.g. N-acetylcysteine and DNase) and mucokinetics that increase MCC by acting on the cilia (e.g. bronchodilators and surfactants). Long-term treatment of patients with perennial rhinitis with fluticasone propionate can increase nasal MCC, whereas treatment with xylometazoline may prolong it [9].

Endoscopic Sinus Surgery (ESS)

ESS can improve MCC by addressing the natural drainage pathways from the sinuses or by clearing polyps from the nasal cavity. ESS has also been found to significantly improve the number of cilia and can reduce the number of goblet cells in the mucosa which may facilitate MCC. In addition, ESS can facilitate nasal irrigation and subsequent topical treatment with steroids and antibiotics of the nose and sinuses [24].

Key Learning Points

- Effective mucociliary clearance necessitates proper mucus composition.
- Effective mucociliary clearance necessitates normal respiratory cilia.
- Mucociliary clearance can be tested but is primarily used for research purposes.
- Genetic diseases such as primary ciliary dyskinesia and cystic fibrosis lead to compromised mucociliary clearance.

Infection, inflammation, gastroesophageal reflux disease, smoking and various drugs can affect mucociliary clearance.

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5 Immunology of the Nose and Paranasal Sinuses

Stephen Ball and Richard Douglas

Allergy and Specific IgE

Allergic rhinitis is one of the commonest chronic diseases, with a prevalence in Western societies of around 20% [1]. In all countries in which there are reliable longitudinal data, the prevalence of this condition is increasing. It is characterised by specific IgE-mediated inflammation of the mucosa of the nasal cavity and is often associated with conjunctivitis, asthma and atopic dermatitis. The specific IgE that causes these conditions is usually directed towards proteins contained in aeroallergens such as grass pollen, house dust mite and cat dander. Approximately 40% of the population has an inherited predisposition to produce specific IgE in response to exposure to these aeroallergens, and about half of these develop symptoms as a result of this sensitisation (Fig. 5.1).

Allergic Rhinitis

Allergic rhinitis is characterised by nasal congestion, clear rhinorrhoea, sneezing and itch. If exposure to the allergen is seasonal (e.g. grass pollen) so will be the symptoms. A key feature in the diagnosis of allergic rhinitis is the age of onset of the symptoms. Atopic sensitisation to aeroallergens occurs in the first couple of years of life, and so allergic rhinitis generally has its onset in preschool years. This is in contrast to non-allergic rhinitis, which usually begins in early adulthood. Although histopathologically identical to allergic rhinitis, non-allergic rhinitis is pathogenetically distinct: it is not caused by exposure to aeroallergens, but rather the cause of the inflammatory response is unknown. As allergic rhinitis is associated with asthma, so is non-allergic rhinitis. Non-allergic rhinitis may also develop into chronic rhinosinusitis with nasal polyposis.

Specific IgE

Allergic rhinitis is diagnosed by features of the presenting history, the examination findings (enlarged inferior turbinates that often have a bluish tinge) and determination of the presence of specific IgE to aeroallergens. There are two techniques for detecting specific IgE: skin prick testing and radioallergosorbent (RAST) tests. In skin prick testing, a drop of allergen suspended in glycerol is placed on the volar surface of the forearm, and a lancet with a 1 mm point is placed through the allergen solution and into the dermis (Fig. 5.2). If there is pre-formed IgE specific to the aeroallergen on the mast cells within the dermis, this will trigger the release of

S. Ball (✉) · R. Douglas
Department of Surgery, The University of Auckland, Auckland, New Zealand
e-mail: stephen.ball@auckland.ac.nz; richard.douglas@auckland.ac.nz

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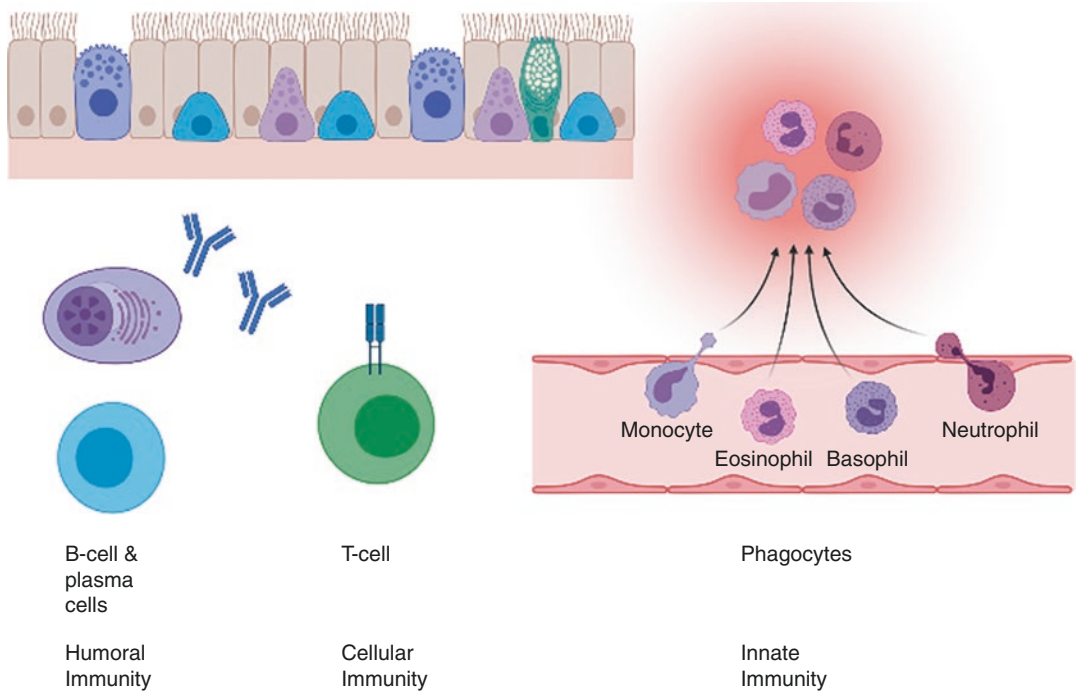

Fig. 5.1 Immunological defences in the nose. The pseudostratified respiratory epithelium provides a physical barrier, in combination with innate, cellular and humoral immune defence mechanisms. Deficiencies in any aspect of these systems predispose to sinonasal disease

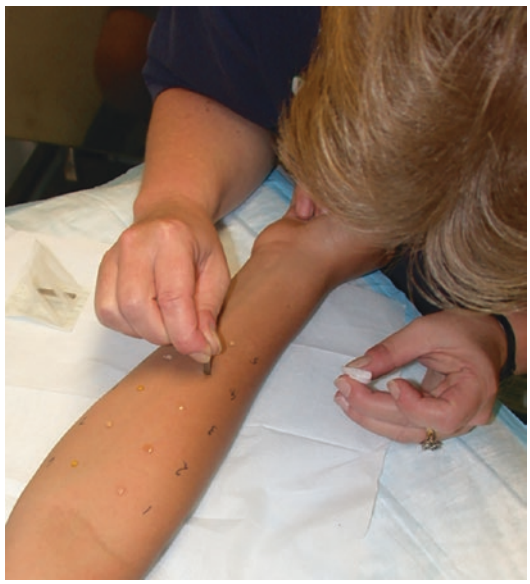

Fig. 5.2 Skin prick tests for specific IgE to the antigens tested. Clinical tests of specific IgE have a high sensitivity, but low specificity for allergic rhinitis due to the presence of atopy in up to 40% of the asymptomatic general population

histamine and other inflammatory mediators, and a wheal-and-flare reaction will ensue. A wheal of diameter greater than 3 mm is regarded as a positive result for that aeroallergen. RAST testing detects specific IgE circulating in the serum. The serum levels of specific IgE are generally much lower than the tissue levels, and for this reason, RAST tests are generally less sensitive. They also tend to be more expensive per allergen tested. However, RAST testing has a significant advantage in that the analysis of the serum sample can be performed remotely from the patient.

Positive skin prick and RAST tests to common aeroallergens define the atopic state. Although approximately 40% of the general population is atopic, only about half of the atopic population has symptoms of allergic conditions. Accordingly, the specificity of SPT or RAST tests is low (about 50%). The sensitivity, however, is high as allergic rhinitis is defined by rhinitis symptoms occurring in association with positive skin prick tests.

There are some subtleties in the interpretation of skin prick testing. One is the concept of entopy, in which there is local specific IgE production (in the nasal mucosa) but little systemic distribution of these antibodies, so both SPTs and RAST tests are negative. Testing for entopy has not been standardised, and it is not clear how prevalent or significant this local response is [2]. Another relatively recently described variation on the clinical manifestations of aeroallergen sensitivity is the central compartment syndrome, in which the mucosa of the inferior and middle turbinates is oedematous to the point where polyps form around the middle meatus [3]. Unlike most cases of CRSwNP, there is minimal involvement of the other regions of the paranasal sinuses. Whereas CRSwNP is generally not associated with an increased prevalence of atopy, central compartment syndrome is strongly related to atopy.

The pharmacological mainstays of treatment for allergic rhinitis are topical corticosteroid sprays and antihistamines. When combinations of these medications fail to provide adequate relief, surgery (turbinate reduction) or immunotherapy can be considered. Immunotherapy works on the poorly understood property of the immune system whereby exposure to small quantities of an allergen produces allergy, but exposure to large quantities induces anergy or immunological tolerance. Remarkably, once induced by repeated exposure to an aeroallergen, it can be very long lasting. Allergen immunotherapy has been historically administered by subcutaneous injections, but these are associated with a small risk of anaphylaxis so need to be given in a clinic setting. However, oral and sublingual preparations have been produced and have been shown to be effective and not associated with anaphylaxis and so can be taken at home, greatly reducing the overall cost and increasing the convenience of this type of treatment.

Chronic Rhinosinusitis

The overwhelming majority of patients with chronic rhinosinusitis have a normal immune system. However, there are two phenotypes of CRS that have specific immunological features: allergic fungal sinusitis and aspirin-exacerbated respiratory disease.

Allergic Fungal Rhinosinusitis

Allergic fungal rhinosinusitis is the sinonasal equivalent of allergic bronchopulmonary aspergillosis, in which there is a mucosal immune response mounted against colonising fungi. The condition shows marked geographic variations in prevalence, in part due to climate conditions and fungal diversity. It is characterised by nasal polyposis in association with fungal debris that can be identified by either their typical appearance, culture, microscopy or molecular methods [4]. There is an intense eosinophilic infiltration of the mucosa, an elevated total serum IgE and the presence of specific IgE to fungal antigens can be detected in many patients with this condition. Most patients respond to a combination of standard medical and surgical treatments. Antifungal agents are usually not required as the colonising fungi are not invasive.

Aspirin-Exacerbated Respiratory Disease (AERD) / N-ERD / Samter's Triad

Samter and Beers described a large cohort of patients with adult-onset asthma, nasal polyposis and aspirin hypersensitivity in a paper published in 1968 [5]. Aspirin-exacerbated respiratory disease (AERD) is the current preferred name and defines a triad of nasal polyposis, asthma and hypersensitivity to aspirin and similar cyclooxygenase inhibitors. It is of note that the terminology for this group of disorders has changed rapidly and whilst AERD is well-established for aspirin-sensitive patients, N-ERD (non-steroidal anti-inflammatory drug-exacerbated respiratory disease) is the most used term within EPOS2020. It is important to know whether asthmatic patients with nasal polyps have aspirin sensitivity because such patients can be desensitised to aspirin and subsequently take a daily dose of this medication. There is significant evidence that chronic aspirin

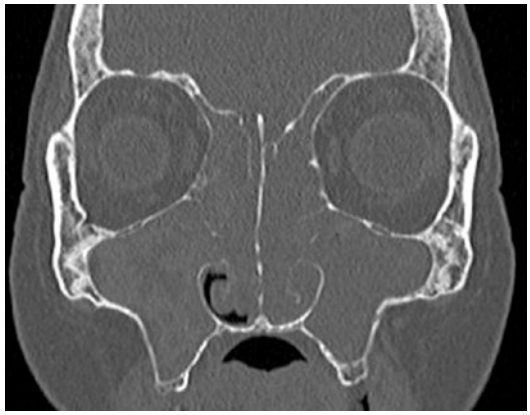

Fig. 5.3 Coronal CT scan image of a patient with AERD / Samter's triad and typical extent of sinonasal polyposis filling all paranasal sinuses and the nasal cavity

therapy post desensitisation improves treatment outcomes for such patients, who are at higher risk of early recurrence postoperatively (Fig. 5.3). The pathogenesis of this condition remains incompletely understood, but it reflects a disturbance of prostaglandin and leukotriene metabolism. Arachidonic acid is converted to prostaglandins by the action of cyclo-oxygenase or leukotrienes by the action of leukotriene synthase. Aspirin and other non-steroidal anti-inflammatory drugs act by inhibiting cyclo-oxygenase, which increases synthesis of leukotrienes. Leukotrienes are powerful bronchoconstrictors and enhance capillary permeability that increases rhinorrhoea and nasal obstruction. Patients with AERD / Samter's triad have higher basal levels of leukotrienes compared to healthy controls, which increase further after exposure to cyclo-oxygenase inhibitors. Higher tissue levels of prostaglandin receptors have been shown in the respiratory mucosa of patients with AERD / Samter's triad. All of these factors predispose these patients to the development of anaphylactoid responses after taking NSAIDs. Severe reactions associated with AERD are described as anaphylactoid rather than anaphylaxis as they are not IgE mediated.

The diagnosis of AERD / Samter's triad is typically made from the history alone. A patient with adult-onset asthma and rhinosinusitis ingests an NSAID (which have usually been previously well tolerated) and typically within an hour develops a hypersensitivity response of the upper and/or lower respiratory tract and the skin. There are no widely available confirmatory laboratory tests, but aspirin challenge can have a role to play in diagnosis. Patients with adult-onset asthma are typically warned against the potential dangers of taking NSAIDs, and many have had no indication to take NSAIDs since the time of developing their condition. These patients have not performed their own unintended aspirin challenge at home. In cases where no convincing history is evident, aspirin challenge can be considered. Many challenge protocols proceed directly into a desensitisation protocol, and so if a patient has a positive challenge, he or she can complete desensitisation. The optimal final dose has not been clearly defined; there are case series of successful desensitisations to doses of between 100 and 1200 mg. Higher doses are probably more effective but are associated with more side effects. Zileuton, a lipoxygenase inhibitor and montelukast, a leukotriene receptor antagonist, may both be useful drugs in the management of this condition [6]. There is rapidly increasing clinical experience with the use of biologics for patients with AERD / Samter's triad that proves recalcitrant to standard medical and surgical therapy. There are reports of excellent responses associated with dupilumab monoclonal antibody treatment [7].

Autoimmune Sinonasal Conditions

A small number of rare autoimmune conditions can either present with or be associated with sinonasal symptoms and pathology. These include two forms of vasculitis that are associated with anti-neutrophil cytoplasmic antibodies (ANCA) and sarcoidosis, which is characterised by non-caseating granulomas.

Granulomatosis with Polyangiitis

Granulomatosis with polyangiitis (GPA, formerly known as Wegener's granulomatosis) is a vasculitic condition that affects the upper and lower respiratory system and the kidneys. The condition's commonest sinonasal manifestations

are crusting and sinusitis, and it may cause septal perforation and a saddle deformity. It may also result in subglottic stenosis, pulmonary lesions and glomerulonephritis. The diagnosis of GPA is usually secured by a combination of radiological investigations, biopsies and serological tests. The cytoplasmic or classical cANCA immunofluorescent test is sensitive for generalised GPA but less so for localised disease. Specificity of serology testing is improved by using ELISA test for PR-3 antibodies. Proteinase 3 (PR-3) is the antigen towards which most cANCA antibodies are directed [8].

GPA is treated with immunosuppressants. A combination of cyclophosphamide and corticosteroids is used to induce remission, after which less toxic agents than cyclophosphamide (such as mycophenolate) are used for maintenance as the corticosteroid dose is reduced. Biologic agents such as rituximab have been used successfully in recalcitrant cases [9].

If patients with GPA have symptomatic sinusitis despite medical treatment, it is reasonable to consider performing FESS. Reconstructive surgery can be offered for nasal deformities once remission has been very well established.

Eosinophilic Granulomatosis with Polyangiitis

Eosinophilic granulomatosis with polyangiitis (eGPA) was formerly known as Churg-Strauss disease. It occurs in a very small percentage of patients with adult-onset asthma. The condition is characterised by eosinophilia of the peripheral blood and eosinophilic infiltration of many tissues associated with a small vessel vasculitis. Nasal polyposis is the commonest sinonasal manifestation of eGPA. Pulmonary infiltrates may be seen on chest radiographs. The tissues of the heart, skin and peripheral nerves can be involved. The diagnosis is suspected in asthmatic patients who develop pronounced peripheral blood eosinophilia. ANCA immunofluorescent tests are usually positive and demonstrate a perinuclear rather than a classical pattern. ELISA tests may be positive for either PR-3 or MPO antibodies [10].

Sarcoidosis

Sarcoidosis is a chronic non-caseating granulomatous condition whose origin is unknown. It is a multisystem disease which predominantly affects the lungs but can affect any organ [11]. Up to a third of patients with sarcoidosis may have head and neck involvement, though sinonasal disease is rarer with a 6% prevalence reported [12]. The aetiology remains elusive, with immune, genetic, environmental and infectious events possible triggers of disease. Clinical manifestations of sinonasal sarcoidosis are similar to the symptoms of idiopathic CRS, but there is often poorer response to standard CRS treatment regimens. Non-specific symptoms are often present and include respiratory symptoms of haemoptysis, dyspnoea, fatigue, weight loss and fever. Diagnosis is made by a combination of serology for serum angiotensin-converting enzyme (ACE), radiology with high-resolution chest CT and biopsy. Pathological examination of sinonasal sarcoid biopsies shows granulomatous disease with Langerhans giant cells and epithelioid cells. It is not uncommon for sinonasal sarcoidosis to be identified in biopsies without prior clinical suspicion. Symptomatic sinonasal sarcoid is generally treated with a combination of topical and systemic immunosuppressive medications.

Immunodeficiencies and Sinonasal Conditions

Conditions associated with immunodeficiency are of clinical importance to rhinologists as some patients who present with CRS are predisposed to their condition by an underlying immunodeficient state. Immunodeficiency conditions may cause patients with CRS to respond less well to standard therapies, and some patients may require specific treatment for their immunodeficiency for their CRS to be optimally managed.

Immunodeficiency states can be primary or secondary to other diagnoses or to immunosuppressive medication. Primary immunodeficiency conditions may be categorised according to whether the deficiency affects B cells

(humoral immunity), T cells (cellular immunity), phagocytes or the complement system (both innate immunity) [13]. In some cases, there are multiple defects.

CRS is mainly associated with conditions causing humoral deficiency, and in this section, the discussion of primary immunodeficiency will be mostly confined to hypogammaglobulinaemia.

Immune deficiencies are more common in patients with CRS. A meta-analysis including 1418 patients with CRS from 13 studies found 23% of patients with difficult-to-treat CRS and 13% of individuals with recurrent CRS had immunoglobulin deficiencies [14]. However, many of the patients diagnosed in the meta-analysis had subclass or specific antibody deficiency. Laboratory criteria for diagnosing these conditions and their clinical implications are not uniformly accepted. Many studies contributing to the meta-analysis were performed in larger tertiary referral centres, potentially biasing patient populations towards having underlying immune defects. It is likely the prevalence of hypogammaglobulinaemia in CRS patients is higher than in the general population, even though the great majority of cases of CRS occur in patients with normal immune systems.

Most cases of primary hypogammaglobulinaemia are caused by genetic mutations. The majority of these are sporadic, although family history of hypogammaglobulinaemia would increase diagnostic suspicion (Table 5.1. Causes of primary hypogammaglobulinaemia). Immunoglobulins act by opsonising encapsulated bacteria, so patients with hypogammaglobulinaemia tend to be more susceptible to infections with streptococcal species, *Haemophilus influenzae* and *Moraxella catarrhalis* [15]. Patients with hypogammaglobulinaemia are as a result at a greater risk of developing sinusitis, pneumonia, bronchiectasis and otitis media.

Table 5.1 Causes of primary hypogammaglobulinaemia

X-linked agammaglobulinaemia
Common variable immunodeficiency (CVID)
Selective IgA deficiency
IgG subclass deficiency
Selective antibody deficiency

Other rare causes include Good's syndrome, which is CVID associated with thymoma and hyper-IgE syndrome, in which patients have eczema and staphylococcal furuncles. The number of causes of primary hypogammaglobulinaemia keeps increasing as the genotypes of these conditions are identified [16].

X-linked agammaglobulinaemia presents in infant boys with recurrent respiratory tract infections. Symptoms typically commence after 6 months of age when passive protection from maternal immunoglobulins is lost.

Common variable immunodeficiency (CVID) is more likely than X-linked agammaglobulinaemia to present to rhinologists because its onset is usually in adulthood. It is diagnosed by low immunoglobulin levels and by a poor response to vaccinations. In 2015, the International Consensus Document on CVID was published identifying six diagnostic criteria for this condition, clarifying the clinical and laboratory diagnosis [17]. Patients with CVID are unfortunately predisposed to other autoimmune conditions and malignancies such as gastric lymphoma.

IgA deficiency is the most frequent immunoglobulin deficiency. Its prevalence is reported between 1:173 and 1:3024 [18]. Most patients are asymptomatic, though IgA deficiency predisposes patients to sinusitis and allergies [13].

IgG has four subclasses, each of which has subtly different functions. Subclass deficiencies are diagnosed when serum IgG level is normal, but one or more of the subclasses are deficient. IgG subclass deficiency is a controversial diagnosis, and there is ongoing debate about the clinical significance of this finding [19]. The overdiagnosis of IgG subclass deficiency as a cause of immunodeficiency may not be uncommon and can potentially result in unnecessary long-term treatment.

Selective antibody deficiency (SAD) is diagnosed when patients have normal serum immunoglobulin levels but impaired responses to polysaccharide antigens such as *Pneumovax* [20].

Table 5.2 Clinical features that suggest Immunodeficiency

Recalcitrance to standard treatments
Rapid recurrence of symptoms after stopping antibiotics
Association of upper and lower respiratory tract infections

However, diagnostic criteria are not universally accepted.

CRS secondary to hypogammaglobulinaemia may present to a rhinologist in a manner identical to idiopathic CRS, explaining why there is often a delay between initial presentation and diagnosis of underlying immunodeficiency (Table 5.2). Clinical features that may raise suspicion include recalcitrance to standard treatments, especially the rapid recurrence of symptoms after stopping antibiotics, and association with lower respiratory tract infections. Measuring serum antibody levels in all patients presenting with CRS is not advised as primary immunoglobulin deficiencies are so rare. It is recommended the above clinical features are used to select patients for immune function testing.

Where CRS patients are clinically suspected of having humoral immunodeficiency because of their presentation or response to treatment, the key investigation is measuring serum immunoglobulin levels. If levels are normal, but there is high suspicion of humoral immunodeficiency remaining, referring to a clinical immunologist is suggested. Antibody tests are the next step in confirming whether a relative immunoglobulin isotype is clinically significant, but we suggest that ORL surgeons to refer to clinical immunologists for further testing as the interpretation of these more sophisticated tests of immune function are better interpreted by experts in the field.

If low serum antibody levels are detected, the next step is to determine the patient's ability to respond to specific antigens. To do this, the patient is immunised with protein antigens (such as tetanus toxoid) and polysaccharide antigens (*Pneumovax*) and pre- and post-immunisation antibody levels are compared [21].

The main treatment of hypogammaglobulinaemia is immunoglobulin replacement therapy, in which the immunoglobulin fraction is extracted from the plasma of a large number of pooled donors so that passive immunity to a large number of antigens can be transferred. Immunoglobulin replacement can be given intravenously or subcutaneously [22]. Decisions about initiating intravenous immunoglobulin therapy and its subsequent oversight are usually made by a clinical immunologist.

Long-term antibiotic treatment has improved outcomes in some primary immunodeficiency syndromes, although the numbers of controlled trials are few [23]. In one observational study of CVID, patients treated with prophylactic antibiotics continued to have infections despite immunoglobulin therapy, and no reduction in frequency of infections was observed [24].

Various types of antibiotics and treatment regimens have been trialled, often at half the usual dose. Switching antibiotics either monthly or every 6 months has been suggested to minimise chances of antibiotic resistance. However, there are no studies to evaluate the efficacy of this practice [23].

It has been found that some patients with low antibody levels to pneumococcal serotypes may respond well to conjugated pneumococcal vaccinations, subsequently reducing antibiotic requirements [25].

The relative benefit of sinus surgery for patients with hypogammaglobulinaemia compared to idiopathic CRS has not been extensively reported. A nested case control study comparing FESS in patients with immunodeficiency (mostly secondary) and those with idiopathic CRS found immunodeficient patients responded as well as their controls [26].

Chronic Rhinosinusitis (CRS) and Secondary Immune Deficiencies

The prevalence of secondary immune deficiency is rising due to the increased administration of biologics and other novel immunosuppressants [27]. Rituximab is a monoclonal antibody targeting CD20, which acts by causing B-cell depletion. As indications for rituximab are increasing

so is the incidence of rituximab-induced hypogammaglobulinaemia. A recent study of patients receiving rituximab for systemic autoimmune disorders reported moderate-to-severe hypogammaglobulinaemia in 26% of patients, although 50% of cases resolved spontaneously while still on the medication [28]. Additionally, immunoglobulin replacement was started in only 4.2% of patients for recurrent infections.

Recent reviews on HIV-associated presentations in otolaryngology highlight the prevalence of CRS in patients with HIV [29]. Rhinologists need to consider this condition, especially when atypical pathogens are identified.

Chronic Rhinosinusitis (CRS) and Secondary Fungal Sinusitis

The detection of fungal-specific IgE was one of Bent and Kuhn's original criteria for diagnosing allergic fungal sinusitis [30]. However, the interpretation of positive or negative results may not be straightforward in suspected cases of allergic fungal sinusitis. There is variable sensitivity of the allergen used in the actual skin prick tests or RAST tests. Fungi can change their antigenic expression depending on the environment they grow, so antigens being tested may not be the same as those from fungi in the patients' sinuses. It is also very common for patients with allergic rhinitis to produce fungal specific IgE. The link between fungal specific IgE and polyp formation is not clear.

Should we treat allergic fungal sinusitis differently to idiopathic CRS? Surgically, complete removal of fungal debris is required, as are postoperative short-term systemic and long-term topical corticosteroids and saline lavage. Accordingly, this management protocol is identical to that of patients with idiopathic nasal polyposis. Establishing a fungal specific diagnosis is important if it offers patients additional specific treatments. Evidence supporting efficacy of topical or systemic antifungals for the treatment of non-invasive fungal sinusitis is not convincing [31, 32]. Studies supporting the efficacy of subcutaneous immunotherapy for fungal CRS are few [33]. It is not common practice to prescribe systemic antifungal agents for non-invasive fungal sinusitis.

Conclusion

Perturbations of the immune system can result in a range of sinonasal conditions, by far the most common of which are allergic rhinitis and CRS. The great majority of cases of CRS are idiopathic and do not have a recognisable underlying immune deficiency. Features that may suggest coexisting immune dysfunction include an early age of onset, coexistence of lower airways disease or otitis media, being refractory to conventional treatments and rapid recurrence on cessation of antibiotic therapy. Measurement of serum immunoglobulins is the key initial investigation, though normal levels do not exclude immunocompromised and where clinical suspicion exists referral to a clinical immunologist is warranted.

Key Points

- Sinonasal conditions can be caused by dysfunction of the immune system. The most common are allergy, autoimmunity, immunodeficiency and neoplasia.
- The overwhelming majority of CRS patients do not have underlying immunodeficiency.
- Clinical features that raise suspicion of immunodeficiency in CRS include recalcitrance to standard treatments, especially the rapid recurrence of symptoms after stopping antibiotics, and association with lower respiratory tract infections.
- Where CRS patients are clinically suspected of having humoral immunodeficiency because of their presentation or response to treatment, the key investigation is measuring serum immunoglobulin levels.
- If immunoglobulin levels are normal, but high suspicion of humoral immunodeficiency remains, referral to a clinical immunologist is suggested.

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Allergy and the Nose

6

Cecilia Ahlström Emanuelsson and Nick Makwana

Introduction

Normal Function The main function of the nose is breathing. The nasal mucosa lining carries out the necessary conditioning by cleaning, warming and moistening the inhaled air. Nasal conchae/turbinates play a major part in this process, and nasal hair/vibrissae in the nostrils filter the air to prevent large particles from entering the lungs. Sneezing is a reflex to expel unwanted particles from the nose that irritate the mucosal lining.

Inflammatory Rhinitis The symptoms of rhinitis including rhinorrhoea, nasal obstruction or blockage, nasal itching, sneezing and postnasal drip are common. Many patients do not recognize rhinitis as a disease, and the prevalence of allergic rhinitis is probably underestimated. Although allergic rhinitis is not usually a severe disease, it affects patients' social life, school performance and work productivity.

Allergic Rhinitis Allergy affecting the nose represents a global health problem affecting 10–30% of the population. About 15–40% of patients with allergic rhinitis also have asthma [1–3], and the presence of nasal symptoms in patients with asthma varies widely from 6 to 85% depending on the study [1, 4–7].

Allergy: Terminology

Atopy Atopy refers to the genetic predisposition of developing allergy-related diseases such as eczema, food allergy, asthma or allergic rhinitis (AR) [8]. The characteristics of these diseases are an exaggerated immune response to environmental allergens and are associated with the production of allergen-specific immunoglobulin E (IgE). Both environmental and genetic factors influence the risk of development of allergen-specific IgE sensitization [9]. Atopic disorders are well known to have physical symptoms but, in addition, can have psychological effects and can be life-threatening [10, 11]. It is worth noting that being atopic does not guarantee an allergy will develop but makes this more likely. Atopic family members will often have different kinds of allergies to each other, although identical twins are more likely to have the same allergies [12].

C. A. Emanuelsson (✉)
ENT-Department, Skane University Hospital, Lund, Sweden
e-mail: Cecilia.ahlstrom-emanuelsson@med.lu.se

N. Makwana
Department of Child Health, Sandwell and West Birmingham NHS Trust, Birmingham, UK
e-mail: nmakwana@nhs.net

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Allergic Sensitization Sensitization is induced by the exposure to exogenous allergenic molecules, which are generally specific proteins. There is a complex interaction between the intrinsic properties of the proteins, environmental co-factors and host immune responses that explains why every individual exposed to an allergen does not develop an allergy. During the sensitization phase, allergens are taken up by dendritic cells which induce a series of events leading to the generation of plasma cells that produce allergen-specific IgE. This IgE binds to mast cells and basophils [13]. Some, but not all, individuals who are sensitized will develop an allergic reaction on re-exposure to the antigen. It is possible for an individual to go through their whole life carrying allergen-specific IgE bound mast cells without ever experiencing an allergic reaction. In those that do develop an allergic response, subsequent allergen exposure activates basophils and mast cells, for example, in the nasal mucosa, which triggers the release of allergic mediators (including histamine, leukotrienes and prostaglandins) leading to the acute symptoms of allergic rhinitis [14].

Types of Allergic Reaction

Allergy is an abnormal response to an antigen. Hypersensitivity is the immunological process that leads to the clinical features of an allergy. Hypersensitivity reactions are divided into four types by the Gell and Coombs classification. Many hypersensitivity disorders involve more than one type.

Type I

Type I reaction is the most well-known type of reaction and is the basis of IgE-mediated allergy, and the symptoms are of rapid onset. The physiological changes of Type I allergy result in the acute symptoms of allergic rhinitis; the most severe form of Type I allergy is anaphylaxis. The mediator release, as noted above, leads to vasodilation, increased capillary permeability, mucus hypersecretion, smooth muscle spasm and tissue infiltration with inflammatory cells, including eosinophils.

Type II

Type II hypersensitivity reactions are due to the abnormal binding of antibodies to normal host targets. These are autoimmune reactions and involve immunoglobulin G and M antibodies that activate the complement cascade. Examples would include blood transfusion reactions and drug-induced haemolytic anaemia.

Type III

Type III hypersensitivity involves immunoglobulin G antibodies bound to foreign antigens in the blood. These antibody–antigen complexes can precipitate and deposit in the blood vessels of the skin, kidneys and joints where they activate the complement cascade and cause local damage. Examples would include systemic lupus erythematosus and Henoch–Schoenlein purpura.

Type IV

Type IV hypersensitivity, or delayed hypersensitivity, occurs 48–72 h after exposure to an allergen. This reaction does not involve antibodies but rather the activation of T cells. The helper CD4+ T cells initially recognize the antigen and release cytokines that activate killer CD8+ T cells, which have direct cytotoxic effects. Three types of Type IV reaction are identified: contact dermatitis, tuberculin-type hypersensitivity and granulomatous-type hypersensitivity.

Allergy, Intolerance and Hypersensitivity

The terms allergy, intolerance and hypersensitivity are often used interchangeably, but this is incorrect. An overview of hypersensitivity is noted above. Intolerance refers to an individual's ability to handle different types of food or drink. Food intolerance is not an allergy as there is no clearly defined immune mechanism, and the symptoms are often specific to the gastrointestinal tract. An intolerance is normally found in the context of a deficiency of enzymes that aid digestion. The absence of these enzymes results in abnormal by-products that produce symptoms. An example would be lactose intolerance which

is due to a deficiency in the enzyme lactase, which breaks down lactose. The absence of this enzyme results in increased lactose entering the colon and fermenting. This leads to symptoms such as bloating, cramps (related to production of hydrogen, carbon dioxide and methane) and osmotic diarrhoea. Whilst uncomfortable, continued ingestion of lactose is not life-threatening. With a true food allergy, the individual is required to avoid that food for life in view of the potential risk of anaphylaxis.

Allergens

As we have noted, allergies arise in response to certain proteins, termed allergens, capable of triggering immediate (Type I) hypersensitivity reactions. The question naturally arises as to why certain foreign proteins act as allergens whilst other foreign proteins present in the same allergenic material do not.

Allergens are foreign proteins, or glycoproteins, with a molecular mass usually ranging between 5000 and 70,000 kDa that must be present in substantial amounts, and over prolonged periods, in the patients' environment or food, in order to become an allergen. In addition, the allergenic potential of a protein is also determined by the ease with which the proteins reach the mucosa. For example, the lack of allergy to pine pollen in Scandinavian countries is related to the structure of the pollen grain. The pine pollen proteins are encased in a tough cellulose layer which is resistant to the enzymes of the respiratory tract, and therefore no antigenic material comes into contact with the mucosa [15].

As well as the mode and degree of exposure, structural characteristics are also important in determining the capacity of foreign proteins to modulate the immune response. Allergenic proteins cannot be recognized by T cells per se but require processing and presentation by antigen-presenting cells (APC). An allergenic protein will therefore contain epitopes with the potential to induce Th2 responses. Identification and purification of allergens have been essential for structural and immunological studies necessary to understand how these proteins stimulate IgE antibody formation [7].

There are two categories of IgE-binding epitopes, linear and conformational, that occur in allergens. Linear epitopes only require the primary amino acid sequence of the allergen for IgE to bind, whilst conformational epitopes occur when either the secondary or tertiary structure of the allergen is required before IgE will bind [16]. Despite the importance of conformational epitopes for efficient IgE binding, the knowledge of structural characteristics of conformational IgE-binding sites is limited, and currently it is not possible to identify any structural motif or conformational sequence common to all allergenic proteins.

Resistance to denaturation and digestion is thought to be an important characteristic of food allergens, because the longer a significant portion of the protein remains intact, the more likely it is to encounter cells of the immune system. Although allergen stability has been demonstrated for a variety of food allergens, there is little known about why these proteins have the ability to resist degradation, and indeed some labile proteins can still cause symptoms (e.g. pollen, fruit and vegetable proteins associated with pollen-food/oral allergy syndrome).

Proteins with enzymatic activity have a propensity for inducing allergic reactions. Allergens possess a wide range of biologic activities, and some mechanisms have been identified whereby the activity could contribute to the efficacy of the allergen. The house dust mite allergen Der p 1 is known to have proteolytic activity which has been shown to increase the permeability of the bronchial epithelium which may contribute to the uptake of the allergen and production of inflammatory cytokines [17]. In addition, Der p 1 cleaves the low-affinity receptor for IgE on B cells and monocytes and thereby increasing IgE production [18, 19] and decreases proliferation of Th1 cells which creates bias of the immune response to Th2 cells [20]. Whilst these observations do not explain how and why patients develop an allergic response to Der p 1, they demonstrate the ability of this allergen to facilitate its penetration of the bronchial epithelium

and to shift the immune response towards IgE production.

As we can see, a protein that is abundant, resistant to processing, has some specific structural characteristics, with some biological activity that has the potential to become an allergen. However, not all proteins with these properties become allergens as the development of an allergic reaction is a complex process involving a receptive immune system (genetic predisposition), the protein being presented with the correct inducers (signals that elicit a Th2 response) and a protein with appropriate biological characteristics.

The Concept of the 'United Airways'

Interactions between the lower and the upper airways in both health and disease are well known and have been extensively studied since 1990.

In normal subjects, the structure of the airway mucosa shows similarities between the nose and the bronchi. Both nasal and bronchial mucosae are characterized by a pseudostratified epithelium with columnar, ciliated cells resting on a basement membrane. In the submucosa, vessels, mucous glands, structural cells, some inflammatory cells (e.g. lymphocytes and mast cells) [21, 22] and nerves are present.

Specific inflammatory cells appear to be the same in the nasal and bronchial mucosa [23] with similar inflammatory infiltrate, comprising eosinophils, mast cells, T lymphocytes, cells of the monocytic lineage [23–26] and the same pro-inflammatory mediators (histamine and leukotrienes) and Th2 cytokines (IL-4, IL-5, IL-13, GM-CSF) [23, 27–29].

Differences Between the Nose and the Bronchi

The nose is richly supplied with a subepithelial capillary and arterial system and venous cavernous sinusoids. This rich vascularization is a key feature of the nasal mucosa, and changes in the vasculature may lead to severe nasal obstruction [30].

In contrast, the bronchi are characterized by the presence of smooth muscle from the trachea to the bronchioles, accounting for the bronchoconstriction of asthma [31].

The intensity of the inflammation may not be identical in the upper and the lower airways. In patients with moderate–severe asthma, eosinophilic inflammation is more pronounced in the bronchi than in the nasal mucosa [32]. The remodelling of the airways that can be found in the bronchial mucosa appears to feature less extensively in the nasal mucosa.

Allergy in the Nose

Allergic rhinitis is a symptomatic IgE-driven inflammation of the nasal mucosa resulting from allergen introduction in a sensitized individual.

Allergic Rhinitis

Allergic rhinitis (AR) is clinically defined as a symptomatic disorder induced by allergen exposure and IgE-mediated inflammation of the nasal mucous membranes.

Typically, there is a clear pattern of nasal symptoms that include rhinorrhoea (anterior or posterior), congestion, intra-nasal itching and sneezing. Additional symptoms often include itchy, watery and red eyes from allergic conjunctivitis, throat symptoms such as itching, throat clearing, sore throat or itching in the roof of the mouth.

Trigger factors for allergic rhinitis are environmental allergens such as pollen, pet hair, house dust mite or mould. The symptoms are reversible spontaneously or with treatment.

Entopy or Local Allergic Rhinitis (LAR)

Some patients previously diagnosed with non-allergic rhinitis (NAR) or idiopathic rhinitis will actually have local allergic rhinitis. These patients display a phenotype of allergic rhinitis that is characterized by a localized nasal allergic response; skin prick testing to inhalant allergen is

negative; serum-specific IgE antibodies are non-detectable.

Local allergic rhinitis (LAR) is characterized by

- Local production of sIgE [33, 34]
- Nasal cellular Th2 immune response during natural exposure to aeroallergens [33, 34, 35]

The diagnosis is confirmed by a positive response to nasal allergen provocation (NAPT) [33, 34, 35, 36], increased levels of local sIgE, tryptase and eosinophil cationic protein (ECP) in fluid from nasal lavage [37, 38].

Classification of Allergic Rhinitis

The traditional classification of allergic rhinitis into seasonal, perennial and occupational rhinitis is based on the time of exposure to allergen. Whilst this classification has now been revised, the terms will still be utilized to facilitate interpretation of published studies.

The most recent classification was instigated by the ARIA (Allergic Rhinitis and its Impact on Asthma) in 2001, based on duration and severity of symptoms (see Table 6.1) [39] intermittent allergic rhinitis (IAR) and persistent allergic rhinitis (PER) are not synonymous with 'seasonal' and 'perennial' (Fig. 6.1).

Perennial Allergic Rhinitis (PAR) This is most frequently, although not necessarily, caused by indoor allergens such as house dust mites, moulds, cockroaches and animal dander.

Table 6.1 ARIA classification of allergic rhinitis

Duration
• Intermittent—symptoms are present less than 4 days a week or for less than 4 weeks
• Persistent—symptoms are present at least 4 days a week and for at least 4 weeks
Severity
• Mild—none of the following is present
• Moderate–severe—at least one of the following is present
Sleep disturbance
Impairment of daily activities, leisure and/or sport or impairment of school or work
Troublesome symptoms

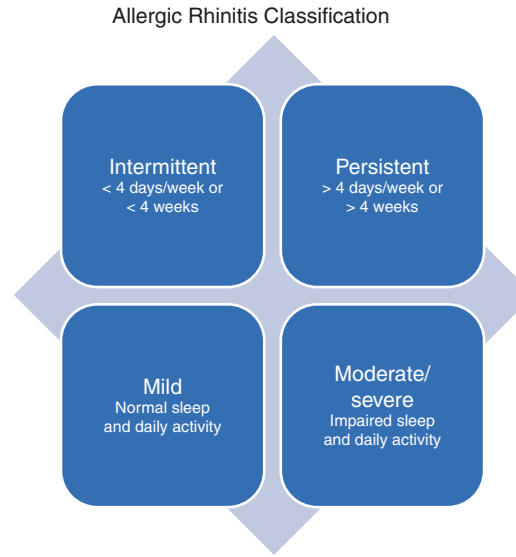

Fig. 6.1 Current classification of allergic rhinitis

Seasonal Allergic Rhinitis (SAR) This is most often caused by outdoor allergens such as pollens or moulds.

Occupational Rhinitis This refers to work-related exposure to allergens and must be differentiated from non-allergic rhinitis due to exposure to irritants at work.

Immunological Aspects of Allergy

Allergic inflammation results from exaggerated immune responses to external factors known as allergens [40]. The components of the allergic reaction are both humoral and cellular.

The humoral component includes a number of cytokines that include interleukins, interferons and growth factor. Cytokines are peptides or small proteins, secreted by immunological cells, and have an effect on the function of other cells.

The cellular component of the immune reaction includes a variety of cell types but primarily lymphocytes of the T-cell variety. Reactions are

now subdivided into two main groups, namely, T1 and T2 subtypes.

An important part of the response includes the interaction between antigen-presenting dendritic cells and Th2 lymphocytes. As a result of this cellular crosstalk, specific cytokines are produced, e.g. IL-3, IL-4, IL-5 and GM-CSF. These cytokines regulate the inflammatory response and are involved in IgE synthesis and in eosinophil recruitment and survival (Fig. 6.2).

Mast Cell Activity

One of the immediate allergic features is the interaction between allergen and specific IgE on the surface of mast cells. This triggers mast cell activation and induces release of histamine, tryptase and other potent mediators (e.g. leukotrienes, prostaglandins). Whilst histamine is a key mediator of the acute response to allergen, others may have more sustained effects [41] (Fig. 6.3).

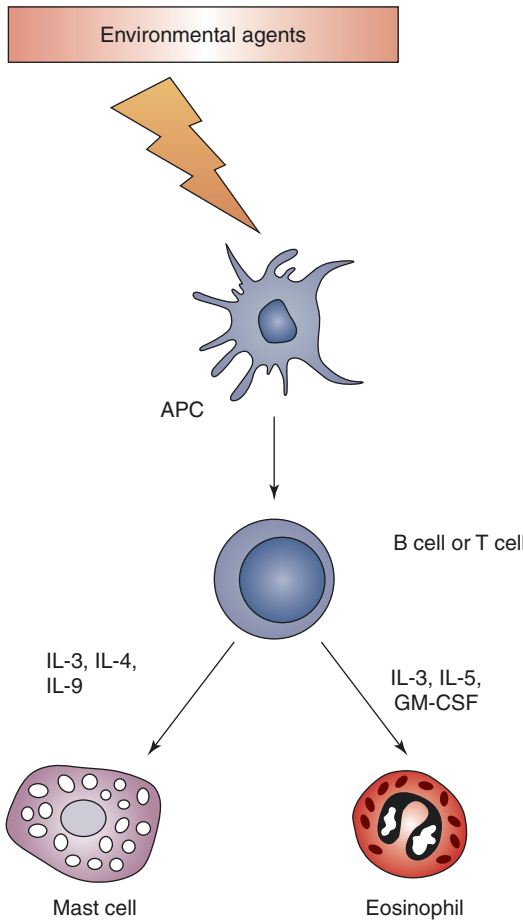

Fig. 6.2 Cellular response to exposure to an allergen

Granulocyte Activity

Tissue infiltration of activated eosinophils is a hallmark of allergic inflammation [42]. Increased numbers of eosinophils in the nasal mucosa and increased levels of eosinophil products including ECP characterize allergic rhinitis [43]. Acute allergen exposure will recruit neutrophils in allergic rhinitis [44], but major release of neutrophil mediators may not occur on seasonal allergen exposure.

End-Organ Responses

In allergic rhinitis, end organs of the nasal mucosa, i.e. microvasculature, glands and nerves, react to the inflammatory activity produced by allergen exposure. The microvasculature responds with vasodilatation, increased blood flow and plasma exudation. Glands respond with increased secretion and nerves with increased signalling [45].

Plasma exudation is reflected by increased levels of plasma proteins on the mucosal surface, including α2-macroglobulin (molecular weight, 725 kDa) [46].

Plasma exudation implies a dramatic change to the molecular environment during an inflammatory response. The extravasation and flux of plasma into the nasal lumen affect the luminal entry of cellular products from the tissue compartment.

Airway end organs are often hyper-responsive in allergic rhinitis and asthma. The response to cholinergic agonists and sensory nerve stimuli may be increased [47]. Also, the ability of histamine to produce plasma exudation is heightened in ongoing allergic rhinitis, i.e. an exudative hyper-responsiveness (Fig. 6.4).

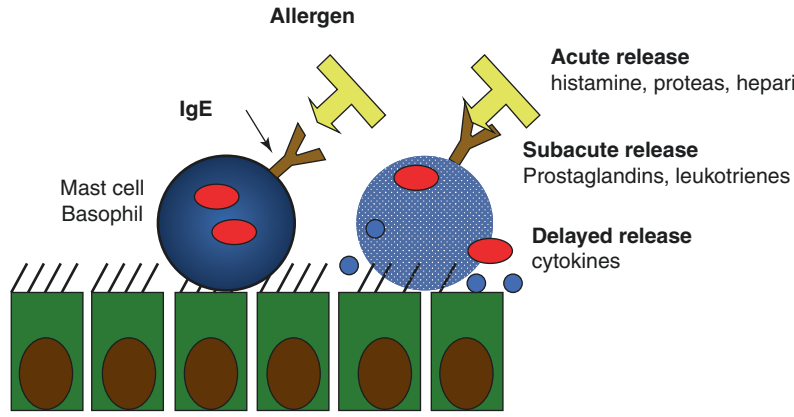

Fig. 6.3 Mechanism of mast cell activation

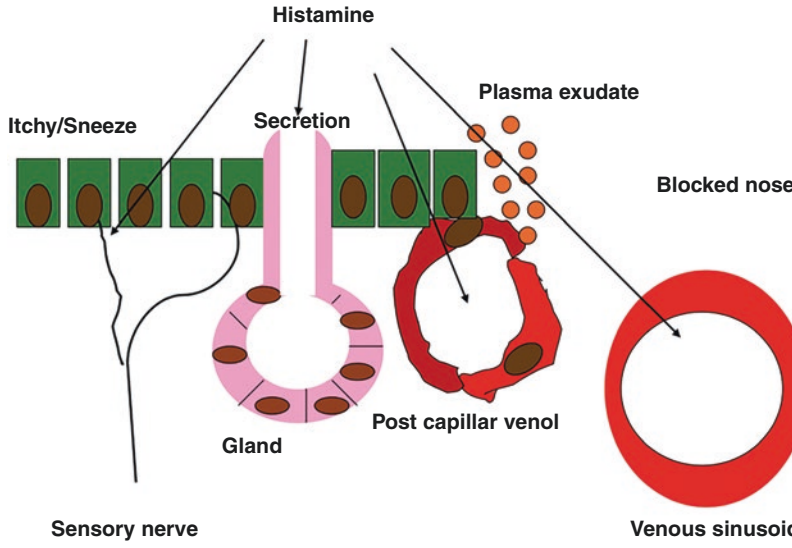

Fig. 6.4 End-organ response and activity of histamine

Remodelling

Airway remodelling in asthma constitutes cellular and extracellular matrix changes in the large and small airways, epithelial cell apoptosis, airway smooth muscle cell proliferation and fibroblast activation [48].

Remodelling in AR is poorly understood [49]. The inflammation in AR and asthma is similar, but the pathologic extent of nasal remodelling may differ from the bronchi. The epithelial damage is only minimal in the nasal mucosa [50–52], and the reticular basement membrane does not display pseudo-thickening [53].

Maybe some of the differences in remodelling between the nasal and the bronchial mucosa are related to the smooth muscle cells interacting with the epithelium and other mesenchymal cells [54–56]. The nose and the bronchi have different embryologic origins, and it might be proposed that the persistence of foetal genes is involved in the difference in remodelling.

Clinical Assessment for Suspected Allergy

Medical History (Anamneses)

As always, the clinical history and association of symptom exacerbation with various situations are very important. Suspected allergic rhinitis

can often be confirmed or rejected with an adequate history.

An appropriate review of the history would include

- Family situation
- Living situation—house/flat, city/countryside
- Pets—in home, relatives, friends, at work
- Work—kind of work, how is the environment/surrounding
- Hobbies
- Presence of other atopic diseases
- Heredity
- When do the allergy/symptoms occur?
  - Time of year
  - Time of season
  - Time of day
  - Specific location
- What are the symptoms?
  - Nose—blocked/runny/itchy/sneezing
  - Eyes—itchy/red/runny/swollen
  - Itchy throat/ears
  - Exacerbations of asthma

Nasal Endoscopy

Endoscopic examination of the nose after decongestion is of paramount diagnostic importance and may be crucial in identifying other pathologies that may either be associated with allergy or mimic allergic symptoms.

The differentiation between AR, NAR and CRS may be a challenge, as significant overlap may occur. The combination of careful clinical history, nasal endoscopy and, in some cases, a CT sinus scan will all contribute to an accurate diagnosis and thus more precise individualized treatment.

Spirometry

Spirometry is the most common pulmonary function test to diagnose asthma. This measures the volume of air that an individual can inspire and expire with maximal effort. An important part of spirometry is the reversibility test. This determines whether there is obstruction that is reversible (decreases) after inhalation of bronchodilators. First, spirometry is performed with measurement of FEV1 (forced expiratory volume) with the patient unmedicated. The patient then inhales bronchodilators, for example, four puffs (4 × 100 μg) of salbutamol (Ventolin®, Buventol®, Airomir®). The examination is then repeated after 15 min. An increase in FEV1 of more than 12% and at least 0.2 L from baseline would be interpreted as a significant pharmacological effect and possible asthma (Global Initiative for Asthma, 2021: www.ginasthma.org). Other tests to assist asthma diagnosis include methacholine challenge, nitric oxide test and sputum eosinophils.

Allergy Testing

Allergen sensitization is confirmed by detecting the presence of sIgE. Allergen-specific IgE can be detected with skin prick tests (SPTs) or by serum immunoassay [57].

Skin Prick Testing

SPT is the simplest in vivo method to assess the presence of IgE sensitization. A specific allergen is introduced through a lancet into the skin of allergic individuals. This leads to dermal mast cells degranulating, mainly due to the cross-linking of allergen-specific IgE bound to their membrane receptors. Degranulation leads to the immediate release of histamine and other mediators, inducing a cutaneous response, clinically characterized by a wheal and surrounding erythema (flare) that can be measured in order to assess the degree of cutaneous sensitivity. SPT therefore represents a surrogate indicator of systemic allergic sensitization through the presence of cutaneous reactivity to specific allergens.

SPT should only be performed after an appropriate medical history and physical examination. SPTs provide an objective and reliable confirmation of allergic sensitization, but the clinical relevance of IgE-mediated sensitizations should always be carefully considered since,

sometimes, positive SPTs do not directly imply allergic manifestations.

The presence of allergic sensitization (a positive SPT with no correlative allergic disease) is a common finding, occurring in 8–30% of the population when using a local standard panel of aeroallergens. Standard allergen panels can include various grass, tree and weed pollen mixes and, in addition, can also have house dust mite and mould mixes, depending on which panel is requested.

There are also panels that include food and animal allergens. If the clinical information suggests Type I (immediate-type) allergy, SPTs are indicated to detect the presence of specific IgE to relevant causative allergens (e.g. inhalant in rhinitis/rhinosinusitis/rhino-conjunctivitis).

The number of skin tests and the selection of allergens for skin testing should be determined based on specific clinical history, allergen exposure pattern (seasonal versus perennial, or sporadic), distribution of allergenic sources in the local environment, as well as living conditions, occupation, hobbies or recreational activities. When indicated, SPTs are convenient, simple, biologically relevant, reproducible, time- and cost-effective and highly sensitive.

Since the interpretation of skin tests can have significant impact on daily life, in terms of avoidance measures and therapies, individuals must be aware that:

- Positive tests may occur in the absence of clinically relevant symptoms (sensitization).
- Negative skin prick test results can miss the presence of IgE-mediated sensitization (e.g. due to lack of major allergens in commercial extracts).
- Negative SPT results in children do not exclude the possibility of development of allergic diseases in the future.

Specific IgE (sIgE) Testing

As a general rule, SPTs are more sensitive than in vitro tests, whereas serum sIgE detection is more quantitative than SPT. The amount of total IgE was considered in early studies as the simplest way to identify allergic subjects; however, it soon became evident that total IgE levels could not be considered a reliable marker of allergy status [58] and low or normal values do not exclude the presence of IgE-mediated diseases. Serum IgE concentration is largely age dependent. Very low levels of IgE are found in cord serum (<4.8 ng/mL) with a progressive increase observed up to the age of 15 years, similar to serum IgA. Total serum IgE then declines from the second through the eighth decades of life [59].

The measurement of specific IgE recognizing allergenic epitopes can be achieved both through the usage of single reagents (singleplex) or with a pre-defined panel of a number of molecules to be tested simultaneously (multiplex) [60]. Allergens used for sIgE can be raw extract allergens or single molecules. Most specific IgE blood tests are immunoassays that include enzyme-linked immunosorbent assays (ELISAs), fluorescent enzyme immunoassays (FEIAs), chemiluminescent assays or radioallergosorbent assays (RASTs). Since 2010, the National Institute of Allergy and Infectious Diseases (NIAID)/National Institutes of Health (NIH) have recommended discontinuation of the RAST as a diagnostic tool for allergy in favour of more sensitive fluorescence enzyme-labelled assays, in which a fluorescent antibody binds to the patient's sIgE and the amount of IgE present is calculated from the amount of fluorescence.

There are two distinct types of molecules used in assays for sIgE. The first one is represented by the so-called 'genuine' markers of exposure, such as Phl p 1 from timothy grass pollen. These allergenic molecules belong to a specific biological source and are able to not only identify IgE sensitization but also point towards the presence of the related allergenic sources in the environment [61]. The second group of molecules is represented by the so-called 'cross-reactive molecules' or 'pan-allergens' [62]. They are families of strictly related proteins that are widely distributed amongst different species because they are involved in crucial cellular processes. Several panels of pan-allergens families are now identified and facilitate the diagnosis of sensitiza-

tion in individual patients and also enhance the accuracy of epidemiologic research. In recent years, the availability of molecular components (identifying both genuine and cross-reacting molecules) has substantially improved the single-plexed strategy by allowing mixing of whole allergen extracts and selected components in order to have a clear description of the IgE profile of the patient. Whilst traditional extract-based IgE blood tests measure the sum of the sensitization to all protein components in whole allergens, e.g. peanut, molecular allergology makes it possible to investigate important individual proteins within a peanut for sIgE sensitization. IgE antibody profiles to these proteins vary significantly from patient to patient, and they also differ geographically due to local differences of exposure. Molecular diagnostics therefore reveals more specific information about what a patient is allergic to, as individual proteins and profiles can indicate different clinical characteristics [63].

From a practical point of view, allergists use the single-plexed diagnostics in two different ways. The first is related to the results of SPT performed in the patient, in order to verify whether a positive or a negative result is confirmed by the presence of IgE to that allergen, or if a SPT solution to that specific allergen is not available. Using this approach, the allergist would focus on a very select (and small) number of allergens. Secondly, more focused on primary care is related to the use of allergen panels. It is evident that panels for adults are different from panels for children, panels for a respiratory allergy are different from panels for a food allergy, panels for northern countries are different from panels of southern countries, etc. As with SPT, however, the presence of antibody only proves sensitization, not allergy, the latter being sensitization in the context of clinical symptoms, and the use of panels is often discouraged unless being used in specific circumstances as evidenced by clinical history.

Multiplex assays are now commercially available that can detect multiple allergen-specific IgE (between 112 and 284) on a very small sample of blood [64]. The assays correlate well overall with singleplex assays and are highly reproducible and accurate. These assays can be used to risk stratify food allergic reactivity and selection of patients for allergen-specific immunotherapy; determine true allergy when there are multiple sensitizations on singleplex assays; understand cross-reactions between species, e.g. in oral allergy (pollen food) syndrome; and determine possible underlying cause of idiopathic anaphylaxis. An advantage of multiplex analysis, however, is also one of its main pitfalls: the generation of an extensive IgE sensitization profile, detecting IgE to unexpected allergens, which may sometimes lead to confusion if there is no suggestive pretest clinical history.

The sensitivity of specific serum IgE antibody measurements could be considered as comparable to that obtained with skin prick testing for respiratory and food allergy. Serum IgE testing entails no risk to the patient other than a blood drawn and is preferable if the patient has an unstable or uncontrolled medical condition, is at high risk of anaphylaxis, is taking essential medication that interferes with testing, is very young such that the procedure would be unduly stressful or has a skin condition that limits available skin for testing (e.g. severe atopic dermatitis).

Occasionally, skin prick testing to inhalant allergens is negative, and serum-specific IgE antibodies are not detected, but history is typical for allergic rhinitis. This condition is likely to be localized nasal allergy (LAR) (see above).

Commercial Allergy Tests (Outside of Hospital Practice)

Food allergy is a frequent allergic disorder, as 6–8% of children and 2–3% of adults are affected. The public perception of food allergy/intolerance however is higher, as one in three people believe they are allergic or intolerant to one or more foods. This perception is at least in part based on the results of unproven diagnostic approaches. SPT and sIgE are the only clinically valid tests available as they test a direct response to an allergen.

Numerous tests claiming to diagnose allergies can be found internationally on the high street and online. There is no evidence that any of the

below can accurately and reliably diagnose allergies:

- *Applied kinesiology* looks for muscle weakness after test substances are placed in the patient's mouth or hands. Muscle weakness has no relationship to whether the patient is allergic to the substance. In fact, results of kinesiology tests are heavily influenced by the tester.
- *Cytotoxic tests (ALCAT, FACT, Bryan's test)* expose a person's blood sample to test substances. The reaction of the white blood cells is observed. But the reaction of blood cells is the same in people with and without allergies.
- *Food-specific IgG testing (food intolerance test, York Test, Hemocode)* looks for specific IgG antibodies against food stuffs in the blood. Medical evidence has shown elevated IgG levels do not suggest an allergy. Results are frequently positive in individuals who do not have an allergy or a food intolerance.
- *Hair testing*, in most cases, uses electroacupuncture to look at the electromagnetic resonance of a lock of hair. Hair is not involved in allergic reactions, so testing hair samples cannot provide any useful information on allergic status.
- *Nambudripad's Allergy Elimination Techniques (NAET)* are based on the idea that allergies are caused by 'energy blockage' and can be diagnosed by muscle testing and cured by acupuncture. There is no credible evidence that this technique can diagnose or treat allergy.
- *Vega test* combines acupuncture and homeopathy theory and measures electronic resistance across the skin at various points. The measurements have no relation to allergic status, and the test cannot distinguish between people who have an allergy and those who don't.

Therefore, these unreliable diagnostic approaches may be costly for patients, delaying appropriate diagnosis and therapy.

Other Aspects of Allergic Rhinitis in Clinical Practice

Children with Allergic Rhinitis

Allergic rhinitis affects 3% of 4 year olds, increasing to 27% of 18 year olds [65]. Allergic rhinitis in early childhood is a risk factor for developing asthma in later childhood and adulthood [66, 67]. It has a significant impact on a child's quality of life and can have negative effects on sleep, behaviour, school performance and family dynamics [68]. It often presents alongside other atopic disorders—asthma, eczema and food allergy. Its presentation may be influenced by comorbidities, such as conjunctivitis, impaired hearing, rhinosinusitis, sleep problems and oral allergy (pollen-food) syndrome (PFS/OAS) [69]. Entopy (local allergic rhinitis), diagnosed by nasal allergen challenge, is found in children [70].

The incidence of allergic sensitization and allergic (mostly seasonal) rhinitis is very low in the first 2 years. Anecdotal information suggests that very few infants and toddlers develop allergic-type symptoms during any pollen season before the third year of life. In general, 2 years (seasons) of environmental allergen exposure seem to be needed before allergic sensitization can be observed by specific serum IgE measurement. The percentage of new cases with seasonal allergic rhinitis increases between the ages of 3 and 12 years at a constant rate of ~2% per year. A positive family history (father or mother with allergic rhinitis) is the best predictor of allergic rhinitis.

Early in life, IgE responses to indoor or outdoor allergen sources may only be directed to a minority of allergens, but the 12-month prevalence of sensitization rises from year to year in the first decade of life. A systematic evaluation of the process of sensitization was performed in grass and birch pollen allergies: The analysis of sequential blood samples for IgE antibodies against grass and birch pollen, including individual allergen molecules, demonstrated the process of sensitization, which precedes the initiation of symptoms by several years. IgE responses to individual pollen allergens increase with time (molecular allergen spreading), and IgE serum concentrations

increase during pre-symptomatic years. Once sensitization to pollen is established, the probability for symptoms within the next 3 years strongly increases (odds ratio 13.6). Simple detection of preclinical allergic sensitization may therefore allow prediction of the onset of allergic rhinitis in an allergen-specific manner [71].

The key points of the approach to the diagnosis and management of allergic rhinitis in children are as follows [71, 72]:

- The approach to diagnosis in children is similar to that in adults: history, skin prick test and anterior rhinoscopy (Fig. 6.5).
- Entopy (local allergic rhinitis), diagnosed by nasal allergen challenge, is found in this age group.
- Therapy of rhinitis in children is based on the same principles as in adults; however, it should take into account specific paediatric needs, such as acceptability, practicality for both children and parents and concern for potential side effects. Nasal saline irrigation is effective in the treatment of AR in children (Fig. 6.6).
- Brief concomitant use (3 days) of topical decongestants can be helpful in children with significant nasal blockage to aid introduction of topical nasal steroid therapy.
- Recommendation for continuous use of intranasal steroids can often create anxiety in parents; intranasal steroids with low bioavailability (mometasone, fluticasone) have a better safety profile at recommended doses and should be used in preference.
- It is advisable to monitor growth in children, especially if they are receiving steroids by multiple routes.
- A short course (3–7 days) of oral corticosteroids may be required in severe cases. Intramuscular steroids have no role in the treatment of AR.
- Immunotherapy is recommended in subjects who have not adequately responded to maximal pharmacotherapy; the potential added

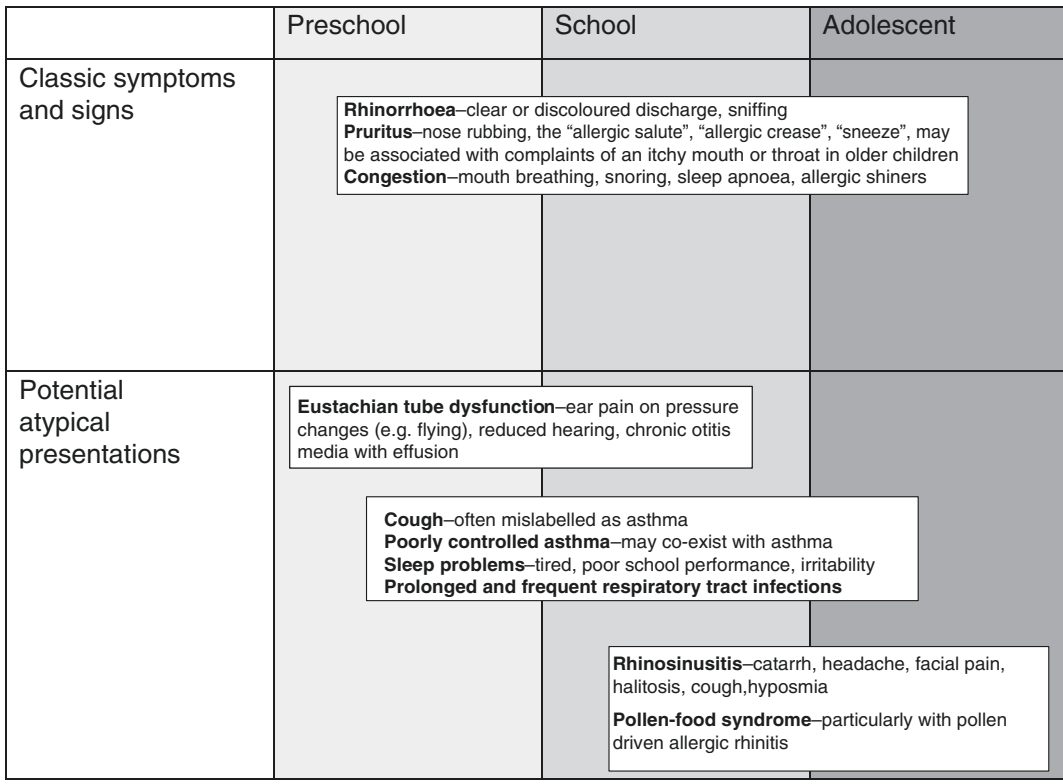

Fig. 6.5 Adapted from paediatric rhinitis: position paper of the European Academy of Allergy and Clinical Immunology [73]

benefit in disease prevention (e.g. asthma) should be considered when treating children.
- Education on therapy plays an important role on treatment outcome. Both children and carers should be provided with the relevant information and appropriate training.
- Otitis media with effusion and/or adenoidal hypertrophy may be associated with AR; the mechanistic link is unknown. Some studies suggest benefit to these common paediatric conditions from rhinitis treatment.
- Red flag features that would prompt specialist referral would include children with unilateral symptoms, severe nasal obstruction +/− sleep apnoea, children under 2 years old and those with a history of rhinitis symptoms present continuously from birth, children with nasal polyps and those children refractory to medical management.

There are no high-quality data to formulate treatment recommendations in children with non-allergic and non-infectious rhinitis. Management should be directed by the underlying cause. Where this is not obvious, saline douches and/or topical corticosteroids should be tried first. If symptoms continue, further investigation should be undertaken to exclude possible differential diagnoses. For persistent obstruction, topical antihistamine and then short-term topical decongestants may be considered. For watery rhinorrhoea, ipratropium may help.

Food Allergy, Sensitivity and Intolerance

Food allergy is an adverse immune response to a food. It is included here as patients may suspect food allergy or associate exacerbation of their nasal symptoms with certain foods.

Food allergy can be classified into IgE-mediated (acute onset after ingestion of food and usually within 2 h) and non-IgE-mediated reactions (delayed onset and can occur 2–72 h after food ingestion). Many non-IgE reactions, which are poorly defined both clinically and scientifically, are believed to be T-cell-mediated. Some reactions involve a mixture of both IgE and non-IgE responses and are classified as mixed IgE and non-IgE allergic reactions.

Food allergy may be confused with food intolerance, which is a non-immunological reaction that can be caused by enzyme deficiencies, pharmacological agents and naturally occurring substances. Hypersensitivity has been discussed elsewhere. In view of genetic predisposition and

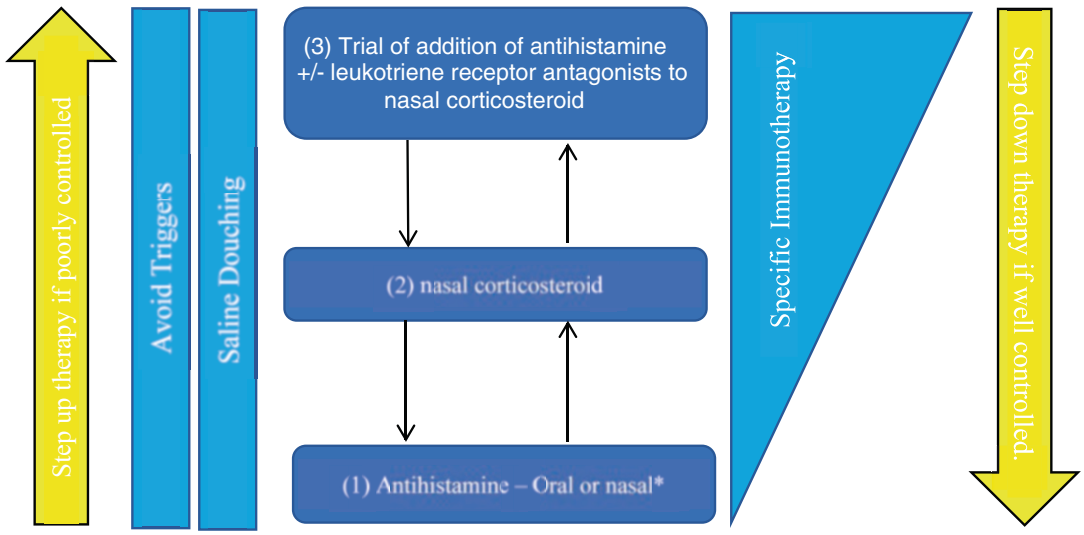

Fig. 6.6 Approach to therapy for paediatric allergic rhinitis. 1, 2 and 3 are potential entry points into therapeutic approach depending on the severity of the rhinitis symptoms. For seasonal disease, regular therapy should be commenced 2 weeks before the anticipated start of symptoms. *Oral antihistamines may be better tolerated, whilst intranasal antihistamines have a more rapid onset [73]

the atopic march, food allergy may be seen in patients with allergic rhinitis.

The common mechanism leading to various food allergies is the breakdown of immunologic and clinical tolerance to an ingested food, which results in both IgE and non-IgE-mediated reactions. Sensitization to food allergens can occur through the gastrointestinal tract, the skin and, less commonly, the respiratory tract, presumably in conjunction with impaired and/or inflamed barrier function. Induction and maintenance of tolerance to food antigens require active generation of food antigen-specific regulatory T (Treg) cells, which are likely influenced by the resident microbiome. This mucosal barrier might be less efficient or 'immature' in infants and young children. This would explain the increased prevalence of both gastrointestinal tract infections and food allergy in the first years of life. The skin is also more recently felt be a route of sensitization, as exemplified in several mouse models [74] and in epidemiologic studies suggesting that environmental exposure to peanut might promote sensitization and allergy [75, 76]. Thus, the role of the skin barrier has attracted increasing attention. Constitutive alterations in the skin, for example, such as a defect in the filaggrin gene, might also lead to a great risk of sensitization [77].

There are extensive data to suggest that food allergies are common (up to 10% affected), [78] have been increasing in prevalence in the last 2–3 decades, appear to disproportionately affect persons in industrialized/westernized regions and are more common in children compared with adults and that a shortlist of foods accounts for most of the more serious disease burden, namely, peanut, tree nuts, fish, shellfish, egg, milk, wheat, soy and seeds [79–81].

The key to diagnosis and onwards referral is an allergy focused history with identification of relevant symptoms as noted in the Table 6.2 (adapted from the NICE Food Allergy in under 19s: assessment and diagnosis [CG116] guideline).

If a food allergy is suspected, then referral for a specialist opinion should be organized promptly for confirmation of the diagnosis.

Allergic rhinitis can be associated with the **pollen-food syndrome** (PFS). Symptoms of oral pruritus and swelling occur due to cross-reactivity between aeroallergens, such as birch pollen, and fruits and vegetables such as apple. The reactions usually occur to the raw foods and some nuts. The close homology of the food proteins to pollen proteins leads to the symptoms, which often abate if the food is cooked, leading to denaturing of the proteins. In patients with PFS, sensitization occurs via the respiratory route. Following this sensitization, the oral pruritus of allergic patients when eating, for example, raw apples, originates from the cross-reactivity of the apple protein Mal d 1 to a homologous birch pollen protein Bet v 1. There are limited paediatric data although one study suggests that a quarter of 8 year olds with allergic rhinitis are affected [82].

Table 6.2 Relevant symptoms of note in an Allergy-focused history

IgE mediated	Non-IgE mediated
The skin	
Pruritus	Pruritus
Erythema	Erythema
Acute urticaria	Atopic eczema
Acute angioedema	
The gastrointestinal system	
Angioedema of lips, tongue and palate	Gastroesophageal reflux disease
Oral pruritus	Loose or frequent stools
Nausea	Blood and/or mucus in stools
Colicky abdominal pain	Abdominal pain
Vomiting	Infantile colic
Diarrhoea	Food refusal
	Constipation
	Perianal redness
	Pallor and tiredness
	Faltering growth in conjunction with at least one or more gastrointestinal symptoms above (with or without significant atopic eczema)
The respiratory system (usually in combination with one or more of the above symptoms and signs)	
Upper respiratory tract symptoms (nasal itching, sneezing, rhinorrhoea or congestion [with or without conjunctivitis])	
Lower respiratory tract symptoms (cough, chest tightness, wheezing or shortness of breath)	
Other	
Signs or symptoms of anaphylaxis or other systemic allergic reactions	

The natural course of childhood food allergy depends on the food protein causing symptoms. Some food allergies have a high rate of resolution in childhood, such as milk (>50% by age 5–10 years), egg (approximately 50% by ages 2–9 years), wheat (50% by age 7 years) and soy (45% by age 6 years), with continued resolution into adolescence. Other food allergies typically persist or have low rates of childhood resolution: peanut allergy (approximately 20% by age 4 years), tree nut allergy (approximately 10%) and allergy to seeds, fish and shellfish are also considered persistent, but studies are lacking to define the course.

Alcoholic Drinks and the Nose

Alcoholic beverages, notably red and white wines, are known to produce bronchial symptoms in certain individuals [83–85]. Alcohol-induced nasal symptoms (ANS) can also occur after wine intake [83, 86]. ANS are about twice as common in women than in men [87].

Nasal blockage is the dominating symptom of ANS, but sneezing and nasal discharge can also occur. Alcohoic drinks I can trigger migraine and induce acute onset symptoms of nasal congestion, clear watery rhinorrhoea, and pressure over the forehead and cheeks.

Red wine is the most frequently described cause of acute-onset symptoms compared to other alcoholic beverages. Red wine is also associated with rhinorrhoea and a corresponding increase of fucose, a carbohydrate present in mucin glycoproteins, that can be measured in nasal lavage fluid [86], and reflects altered mucinous secretion [88]. Sulphite and histamine are constituents of wine and both have been suggested to induce airway symptoms [84, 85, 89].

Patients with Aspirin-exacerbated respiratory disease (AERD) have a predilection for alcohol intolerance and respiratory reactions. Reactions are most likely to occur with red wine, beer and sometimes white wine. It has been suggested that the reaction is induced by polyphenols that inhibit the COX-1 enzyme. Polyphenols occur in red wine grape skin, barley and hops used in brewing beer and oak barrels used to age white wine.

Patients should be advised to limit or avoid alcohol, or try clear liquor such as vodka that is free from polyphenols. In patients with AERD, aspirin desensitisation has been shown to improve alcohol intolerance. Loratidine has been shown to reduce nasal blockage after drinking red wine [86]. Wine produced with ecological methods has been suggested to give less nasal blockage than wine not labelled as ecologically produced [90].

The Principles of Management

Allergic diseases are chronic and often variable in degree of severity. Environmental factors often play a major role in the development of allergic disorders and in the symptom profile. Once allergy is recognized, symptom control is dependent on identifying allergens, minimizing exposure and appropriate medication. Patient information leaflets and web links, adjusting the environmental exposure and clinical review to assess impact of treatment, are all important components to consider.

Allergen Avoidance Allergen avoidance is the first line in management but is not always practically possible or sufficient.

Medication The drug treatment for allergic rhinitis (and conjunctivitis) is based on local treatment for the nose and/or oral treatment with antihistamines and/or local nasal corticosteroids, depending on the degree of discomfort and patient preference. Many recommended preparations can be bought without a prescription (OTC) and can be used for self-care in case of temporary or mild symptoms. The combination of treatments may achieve additive effects. Pronounced symptoms in adolescents and adults may require a short course of oral steroids to allow more rapid symptomatic relief.

Immunotherapy In cases of poor symptom control despite allergen avoidance, optimal medi-

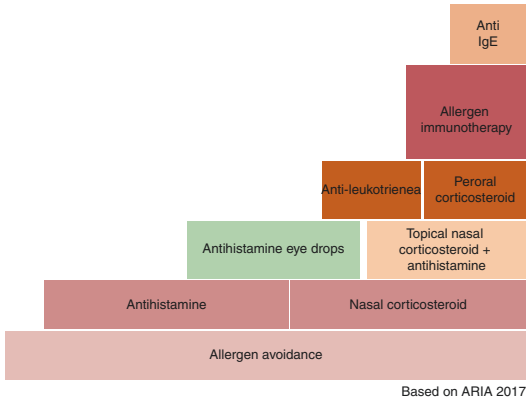

Fig. 6.7 Treatment of allergic rhinitis

cal treatment and good compliance, the patient should be considered for allergen immunotherapy (AIT) (see Chap. 20) (Fig. 6.7).

Key Learning Points

- Symptoms of rhinitis including rhinorrhoea, nasal obstruction or blockage, nasal itching, sneezing and postnasal drip exclude allergic rhinitis.
- Histamine is acute released by the allergic reaction and gives rise to the symptoms of rhinorrhoea, nasal obstruction and sneezing.
- The inspection in the nose, after decongestion, with endoscope is obligated by patient with rhinitis.
- Many people with allergic rhinitis also have asthma.
- A majority of people with asthma also have rhinitis.

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Genetics and Disorders of the Nose and Sinuses

7

Emily Anderson and Victoria McKay

Introduction

Humans have 46 chromosomes in almost every cell, arranged into 23 pairs. One homologue, or copy, of each pair is paternally inherited (from the father), and the other is maternally inherited (from the mother). Chromosomes are numbered from pair 1 to 22; chromosome 1 is the largest chromosome, and 22 is the smallest. The 23rd pair forms the sex chromosomes: XX in females and XY in males.

Within the chromosomes sit around 20,000 individual genes. Some have been extensively studied, and their role in human development and disease is well-understood; others remain poorly characterised with no clearly defined links to human disease. Each gene is comprised of **exons**, the coding sections of the gene. Between the exons are the **introns**, or non-coding sections of deoxyribonucleic acid (DNA). The joining regions between introns and exons are called **splice sites**.

The basic structure of DNA is the double-stranded helix, first identified back in the 1950s. The DNA itself consists of a series of bases, known as adenine (A), guanine (G), cytosine (C) and thymine (T). Adenine on one strand pairs with guanine on the complementary strand and cytosine with guanine.

E. Anderson (✉) · V. McKay
Liverpool Centre for Genomic Medicine, Liverpool Women's Hospital, Liverpool, UK
e-mail: Emily.anderson@lwh.nhs.uk

When referring to the DNA sequence, it is the order of these four bases, A, C, T and G, that is important. When a cell requires the production of a specific protein, a process called transcription occurs. This is the 'reading' of the DNA sequence to produce ribonucleic acid (RNA), a single-strand replica of the DNA sequence for that gene, as shown in Fig. 7.1. An important step following transcription is called splicing, whereby the introns (non-coding sections) are removed, so that the final, mature RNA only contains the code of the exons, as shown in Fig. 7.2.

The mRNA is then transported out of the nucleus to the cytoplasm, where it interacts with a ribosome. This allows for translation, the process by which the genetic code is read, three bases at a time. Small molecules known as transfer RNAs align to the mRNA. The transfer RNAs are each attached to an amino acid, and the combination of these amino acids leads to the formation of the final protein product, as shown in Fig. 7.3.

Changes to the original (or germline) DNA sequence can result in changes to the mRNA and subsequent amino acid and protein structure. There are many ways that the DNA sequence can be disrupted including:

- Substitution of a base
- Deletion of one or more bases, or one or more exons
- Insertion of one or more bases, or one or more exons

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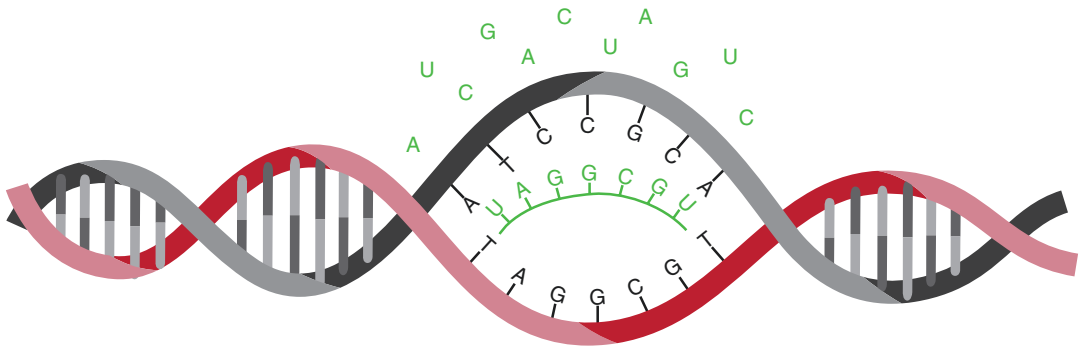

Fig. 7.1 Gene transcription. The double-helix DNA unwinds in the region to be transcribed. The two complementary strands separate, and free-floating nucleotides (shown in green) align to the coding strand (shown in black). Note that adenine (A), cytosine (C) and guanine (G) exist as in DNA; thymine (T) is replaced by uracil (U). An enzyme called RNA polymerase causes the free-floating nucleotides to form a strand of RNA

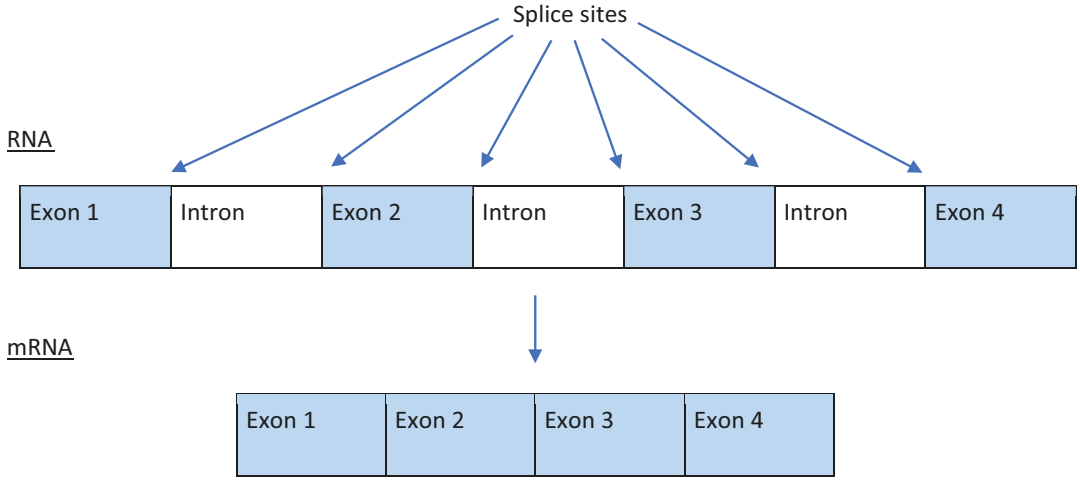

Fig. 7.2 Splicing. Introns are spliced out, forming mature messenger RNA (mRNA) containing only the coding sequence

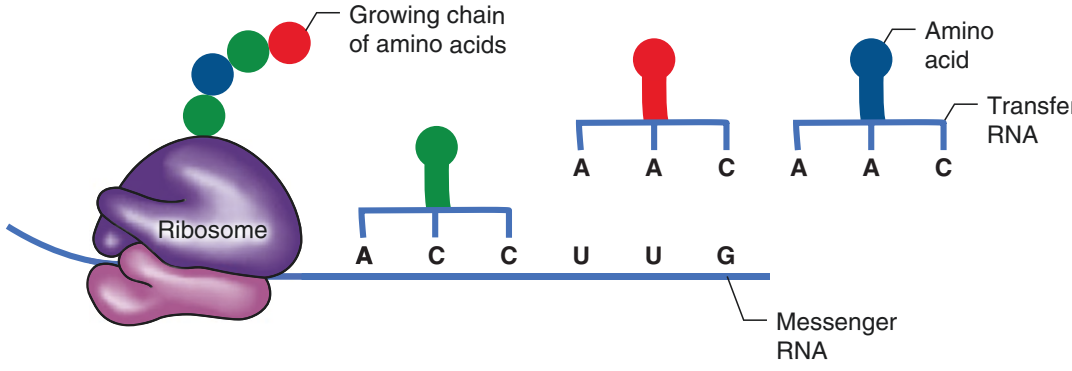

Fig. 7.3 Gene translation. The mature messenger RNA (mRNA) is transported out of the nucleus to the cell cytoplasm, where it interacts with a ribosome. The mRNA is 'read' three bases at a time. Transfer RNA molecules (shown in blue) align to the mRNA, attached to specific amino acids. The amino acids then link to form the final protein product

- Substitution, deletion or insertion of the splice site bases
- Whole gene deletion or insertion
- Contiguous gene deletion, where multiple adjacent genes are deleted

In addition, there are other factors that can affect the function of a gene and can result in human disease. These include disruption or alteration of gene regulators and epigenetic factors such as imprinting, although these will not be discussed in detail here.

Genetic Testing

Genetic testing is constantly evolving. It is helpful to understand the basis of some of the more commonly requested tests.

General Sample Information

Most genetic tests are carried out on germline DNA, i.e. the constitutional DNA created at conception and present in almost every cell of the body. Germline DNA is usually obtained from a blood sample, although in some circumstances it may be necessary to consider alternate sources such as saliva, buccal swab or skin biopsy.

In certain types of cancer, it may be appropriate to offer testing on tumour tissue, i.e. the DNA contained within the tumour itself. During the process of tumorigenesis, the tumour DNA will accumulate many new variants and chromosomal changes. Genetic changes present in a tumour may not be present in the germline DNA, and therefore the results need to be interpreted with caution by an experienced clinician.

Karyotype

A karyotype is an assessment of the number and structure of the chromosomes. It will detect any whole extra or missing chromosomes, e.g. trisomy 21 (Down syndrome), and will also detect large structural changes such as deletions, duplications and translocations, where material from one chromosome becomes attached to a different chromosome. Karyotyping is rarely used as a routine clinical test and has largely been superseded by new technologies such as microarray (see below).

Microarray

A microarray is a more detailed analysis of the chromosomes, specifically looking for any deletions or duplications. It will detect missing or additional genetic material much more sensitively than a karyotype. Microarray is usually used as the first-line genetic test for individuals with learning difficulties, developmental delay and/or multiple congenital anomalies.

Single Gene Testing

Historically, most genetic testing involved analysis of a single gene at a time. Nowadays, this is far less commonly requested, as it is more cost-effective and efficient to analyse large groups of genes simultaneously. Single gene testing is still appropriate in some circumstances, usually when the patient's phenotype is highly suggestive of a single disorder. For example, a baby with meconium ileus, failure to thrive and recurrent respiratory infections may undergo single gene testing of the *CFTR* gene for cystic fibrosis.

Gene Panels

A gene panel involves simultaneous analysis of multiple genes linked to a given disorder or phenotype (clinical feature or collection of features). Panels may be small, with only a handful of genes linked to that condition, e.g. hereditary haemorrhagic telangiectasia. Other panels may be very large, with hundreds or thousands of genes linked to a particular characteristic, e.g. hearing loss.

The advantages and disadvantages of using a panel-based approach are outlined in Table 7.1.

Table 7.1 Advantages and disadvantages of gene panels

Advantages	Disadvantages
More efficient and cost-effective than testing a single gene at a time	Generally takes longer for a result than a single gene test
Useful when there is no obvious clinical diagnosis but a high suspicion of an underlying genetic cause	Increased chance of receiving uncertain or incidental findings, due to the large number of genes being analysed
Increased chance of finding a clinically relevant variant compared to single gene testing	

Whole Exome/Genome Sequencing

Recent advances in genetic technology have enabled the advent of whole exome sequencing (WES) and whole genome sequencing (WGS). These approaches involve sequencing either the exome (the coding sections of all genes) or the genome (all of the DNA). By analysing a much larger proportion of the DNA, new variants and even new genes are being discovered, and the diagnostic rate for individuals with rare diseases is going up. The cost of WES/WGS approaches is falling rapidly, and results are now able to be reported in a clinically relevant timeframe. This means these technologies are becoming more accessible in every day clinical practice.

However, the number of variants generated from these approaches can be vast, and it can be challenging to classify their pathogenicity (see variant interpretation below). This can be particularly relevant in WGS when variants are found outside the coding region of a gene. With the increase of WES and WGS, it is likely that many more patients will be found to have uncertain genetic results, which may increase anxiety and may not always be clinically helpful.

Ethics of Genetic Testing

Diagnostic genetic testing, where a patient with symptoms of a genetic disorder undergoes testing to try to confirm a diagnosis, is usually fairly straightforward from an ethical viewpoint. A diagnostic test can be offered to a child or adult, if it is felt that this would contribute to their clinical care. Some genetic tests can be requested by clinicians outside of Clinical Genetics; others can only be requested following consultation with a Clinical Geneticist.

Predictive genetic testing, where an asymptomatic person is offered a test for a genetic condition known about in the wider family, is ethically more complex. Predictive testing is often not carried out in children, unless there is a specific reason why this result would change clinical care in childhood. Undergoing a predictive test can have insurance implications for the patients and, in almost all circumstances, can only be requested by clinicians working within the field of Clinical Genetics.

Variant Interpretation

Current nomenclature states that any change to the genetic code is described as a 'variant'. Historically, genetic changes were called 'mutations', but this term is no longer preferred for two reasons: firstly, the term mutation or mutant may have negative connotations for patients, and secondly, it implies that the genetic change is disease-causing. The human genome is subject to a wide range of variation between individuals, but most of these variants will not be associated with disease.

Variants can be classified using a five-point scale of pathogenicity (as summarised in Table 7.2), according to published guidelines [1]:

The key message is that not every variant identified on genetic testing is causative of disease.

When the result of a genetic test is reported, the clinical scientist will classify any variants identified using standard criteria. The variant classification is usually clearly stated on the report.

If a pathogenic or likely pathogenic variant is identified in a gene linked to the patient's phenotype, this can be regarded as a molecular confirmation that the patient has the disease with which the gene is associated. If there is uncertainty about the phenotype, e.g. the patient has a likely pathogenic variant found on a panel but the phenotype does not entirely fit, then this should

Table 7.2 Summary of variant classification (adapted from ACMG guidelines) [1]

Class 1	Benign	Not clinically relevant
Class 2	Likely benign	
Class 3	Uncertain significance	Not clinically actionable but may be appropriate to discuss with a clinical geneticist
Class 4	Likely pathogenic	Clinically actionable, i.e. likely to be causative of disease
Class 5	Pathogenic	

be discussed with the reporting laboratory or the patient should be referred to a Clinical Geneticist.

In most circumstances, the laboratory will not report variants classified as benign or likely benign, as these are regarded as part of the normal variation between individuals and are not clinically relevant.

Where a variant is classed as being of uncertain significance, the decision on whether or not to report the variant will lie with the reporting laboratory, often in conjunction with input from Clinical Geneticists. If a patient is reported to have a variant of uncertain significance, it is sometimes appropriate to discuss with the local Clinical Genetics service for further evaluation. In some scenarios, it would be appropriate to test other family members for the variant; this may glean further information to reclassify the variant as likely benign or likely pathogenic. Family studies are usually only requested from within the Clinical Genetics service.

Inheritance Patterns

There are different patterns of inheritance for genetic disorders. It is important to correctly identify the inheritance pattern within a family in order to understand the risk of other family members being affected by the condition. Table 7.3 summarises some of the key findings in a family to help identify the inheritance pattern.

Autosomal Dominant

An autosomal dominant (AD) genetic disorder only requires a single variant in order to cause disease. This means that an affected person has one working copy of the gene and one altered copy. When that person has children, there is a 50% chance of passing on the altered copy of the gene, and the child inheriting the genetic condition.

Autosomal Recessive

A genetic disorder that shows autosomal recessive (AR) inheritance requires both copies of a gene to be altered to cause the condition. An individual who has one working copy and one altered copy of a gene linked to an AR disorder is said to be a 'carrier' of that condition. In most circumstances, being a carrier for an AR condition does not cause any health concerns for that individual. Indeed, it is believed that we are all carriers for multiple rare, recessive disorders.

If two people who are both carriers for the same AR disorder have a baby, they have a 25% chance of a healthy child, 50% chance of a (usually healthy) carrier and 25% chance of an affected child. The chance of both partners being a carrier for the same disorder is generally low; however, this chance is increased if the couple is consanguineous (i.e. genetically related to each other). It is sometimes possible to offer carrier testing for diseases known to be common in a given population, e.g. cystic fibrosis carrier testing in Northern European White Caucasian populations.

X-Linked (Dominant and Recessive)

An X-linked condition is one in which the associated gene is located on the X chromosome. Females have two copies of the X chromosome, whereas males have one X and one Y chromosome.

Some X-linked disorders show X-linked recessive inheritance, meaning that females can be carriers and males are usually affected. This is because males with a variant associated with an X-linked recessive condition do not have a second copy of that gene to compensate and, therefore, tend to develop the disease. In some X-linked recessive conditions, carrier females can be at risk of developing features, but usually more mildly than affected males.

Table 7.3 Summary table of characteristic findings according to inheritance pattern

	Autosomal dominant	Autosomal recessive	X-linked dominant	X-linked recessive	Mitochondrial
Affected individuals	Equal number of males and females affected	Equal number of males and females affected	Usually females (often lethal in utero in males)	Usually males (can sometimes have mildly affected females)	Equal number of males and females affected
Multiple generations affected	Likely	Usually not	Possible on the maternal lineage	Likely, the condition may appear to 'skip' a generation with an unaffected carrier female	Likely on the maternal lineage
Mother to child transmission	50% chance, sons and daughters equally likely to be affected	Usually none	Affected females have: • 25% chance of an affected daughter • 25% chance of an affected son (usually lethal) • 25% chance of a healthy son • 25% chance of a healthy daughter	Carrier females have: • 25% chance of an affected son • 25% chance of a carrier daughter • 25% chance of a healthy son • 25% chance of a healthy (non-carrier) daughter	All offspring of a woman with a mitochondrial variant will be at risk of developing the condition
Father to child transmission	50% chance, sons and daughters equally likely to be affected	Usually none	Usually not relevant as males do not survive to reproduce	Affected males will have: 50% chance of a carrier daughter and 50% chance of a healthy son (i.e. all daughters will be carriers and no sons will be affected)	Affected males will not pass the variant on

Other X-linked conditions are described as X-linked dominant. This usually means that females are affected. Males are sometimes severely affected, but often X-linked dominant conditions are lethal in utero to males, i.e. affected boys do not survive pregnancy.

Mitochondrial

The mitochondria are small organelles that essentially produce energy for the cell. Whilst most DNA is held within the nucleus (nuclear DNA), the mitochondria contain a small amount of their own DNA (mitochondrial DNA).

Determining the genetic basis of mitochondrial disease can be complex, as there are both nuclear-encoded and mitochondrial-encoded genes that govern the function of the mitochondria. For nuclear-encoded genes, the usual mode of inheritance (usually AR) will apply. For mitochondrial variants, these can usually only be passed through the maternal lineage, i.e. women can pass on mitochondrial variants to their offspring (male or female), whereas men do not. This is because ova contain mitochondria but sperm cells generally do not.

Each cell contains multiple copies of the mitochondrial DNA. If a variant is present in all copies, this is termed homoplasmy. If a

variant is present in only some of the copies, then this is described as heteroplasmy. The level of heteroplasmy can vary between different tissues and organs, even within the same individual.

Broadly speaking, a woman with a mitochondrial variant is assumed to pass on the variant to all of her children. However, the severity of the disease can be hugely variable, from completely asymptomatic children through to being more severely affected than the mother.

Genetic Diagnoses to Consider

General Approach

In patients who present with features suggestive of a genetic diagnosis, try to gather as much relevant information as possible. Ask about systemic features that may help to formulate a differential diagnosis. Do not forget to enquire about the family history—are there relatives with similar clinical features? Is there already a known genetic diagnosis in the family?

If the clinical suspicion for a genetic cause remains high, it may be pertinent to explore the idea of a genetic test. Be aware of local policies and access to genetic testing—it may be possible to request a diagnostic test from your outpatient clinic, or you may be required to refer the patient for a review by the Clinical Genetics team. If requesting a genetic test, make sure you are familiar with the local consent process, the expected timescale and how to interpret the result.

Epistaxis

Many patients with epistaxis will not have an underlying genetic disorder. However, there may be features in the history or examination that may raise the suspicion of an inherited cause.

Hereditary haemorrhagic telangiectasia (HHT) is an autosomal dominant condition that causes epistaxis, characteristic telangiectasia on the lips, fingertips and tongue and visceral arterio-venous malformations (AVMs), typically affecting the lung, brain and liver. HHT affects males and females equally and will often be seen in multiple generations of the same family. Correctly diagnosing HHT is important, as patients are at increased risk of stroke, cerebral abscess and maternal death in pregnancy if they have undiagnosed and untreated pulmonary AVMs. There are at least three genes (*ACVRL1*, *ENG* and *SMAD4*) that are associated with HHT.

The Curaçao criteria in Table 7.4 can be used to assess the likelihood of a clinical diagnosis of HHT. A comprehensive set of consensus guidelines for the management of patients with HHT has been published [2].

Bleeding disorders, such as haemophilia, von Willebrand disease and other coagulation factor deficiencies, should also be considered in patients with severe epistaxis. These patients may report spontaneous bleeding from the gums or excessive bleeding after minor injuries and will not have the characteristic telangiectasia seen in HHT. Haemophilia A and B are both X-linked recessive disorders; therefore, males are more likely to be severely affected than females. Patients with a suspected bleeding or clotting disorder should be referred to a haematologist for further assessment.

Anosmia

The genetic basis of anosmia is poorly understood. There are some known syndromic associations, including Kallmann syndrome and

Table 7.4 Diagnostic Curaçao criteria for HHT (adapted from Shovlin et al. [3]). A score of 3 or more confers a definite clinical diagnosis of HHT, a score of 2 indicates a possible diagnosis of HHT and a score of less than 2 means that the diagnosis of HHT is unlikely

One point is awarded for each criterion, with a maximum score of 4
Severe, recurrent epistaxis
Characteristic mucocutaneous telangiectasia
Visceral arterio-venous malformations (AVMs)
Family history in a first-degree relative (parent, sibling or child)

congenital insensitivity to pain, as described below. However, there have been very few breakthroughs in understanding the genetic basis of isolated anosmia, in the absence of a syndromic diagnosis.

Kallmann syndrome is characterised by the presence of hypogonadotropic hypogonadism and anosmia, associated with aplasia (or hypoplasia) of the olfactory bulbs and tracts. It is far more common in males than females, and most patients present sporadically, without a known family history. There are different inheritance patterns linked to Kallmann syndrome, and it can follow autosomal dominant, autosomal recessive or X-linked inheritance.

Congenital insensitivity to pain is a rare phenotype where the molecular basis is not fully understood. However, this condition can be seen in conjunction with anosmia, and variants in the *SCN9A* gene have been implicated in some of these cases [4].

Nasal Polyps and Tumours

In adults, the cause of nasal polyps is not always well-understood. Often, patients may report a family history of nasal polyps, but the exact genetic and environmental factors that influence their development are not clear. Very rarely, nasal polyps may be linked to an underlying polyposis disorder such as Peutz–Jeghers syndrome, a dominant disorder which is usually associated with hamartomatous polyposis in the GI tract.

In children, nasal polyps are far less common, and their presence should raise suspicions of an underlying genetic diagnosis such as cystic fibrosis.

Inverted papilloma is an uncommon, benign tumour that has a propensity for malignant transformation in some patients. It is more common in men, especially around the fifth decade. Inverted papilloma is not known to be associated with a specific underlying genetic disorder. Whilst environmental factors such as exposure to human papillomavirus have been implicated, the aetiology and any genetic predisposition remain poorly understood.

Malignancies of the sino-nasal tract can vary according to their site, stage and histology. A cancer predisposition syndrome should be considered in patients who have a rare tumour type, such as a neuroendocrine tumour or soft tissue sarcoma. It is important to ask about other cancers, both in the patient and within the family. Features suggestive of an underlying cancer predisposition syndrome are summarised in Table 7.5.

If an inherited cancer predisposition syndrome is suspected, referral to a Clinical Geneticist for further assessment is warranted.

Recurrent Infections

There are many different causes for recurrent sino-nasal and sino-pulmonary infections. From a genetic perspective, it is important to elicit whether there are features of a syndromic disorder or any evidence of an underlying immunodeficiency.

Cystic Fibrosis

Cystic fibrosis (CF) is one of the most common genetic disorders among Northern European populations. It is an autosomal recessive condition with an estimated carrier frequency of approximately 1 in 25. CF can sometimes be detected antenatally due to the presence of bright, echogenic bowel, or it may be diagnosed in the newborn period with meconium ileus. However, some children with CF present later with failure to thrive, recurrent sinusitis, nasal polyps, diabetes and gastrointestinal symptoms. CF is an important differential to consider in a child with nasal polyps and sinusitis, and if the diagnosis is confirmed, genetic counselling should be offered to the family regarding options for future pregnancies.

Table 7.5 Features suggestive of an underlying inherited cancer predisposition syndrome

Multiple primary cancers in one individual
Cancers diagnosed at a younger age than expected
A family where multiple individuals have been diagnosed with the same (or related) cancers
A family where the same (or related) cancers affect more than one generation

Primary Ciliary Dyskinesia

Another genetic disorder that can result in recurrent sino-nasal infections is primary ciliary dyskinesia (PCD). PCD is a ciliopathy, resulting from dysfunction of motile cilia. Clinical features suggestive of PCD include situs inversus, respiratory distress, recurrent infections, hearing loss and infertility. The understanding of the genetic basis of PCD is rapidly advancing, and more than 40 genes have been described to date.

Immunodeficiency

Individuals with an underlying primary immunodeficiency are more likely to develop recurrent, severe and atypical infections. Many of the primary immunodeficiency disorders have a genetic basis, and genetic testing is available for many of these conditions. Primary immunodeficiency should be considered in patients who present with a history of more generalised recurrent infections, particularly in the context of a child who has feeding difficulties and/or failure to thrive.

Structural Anomalies of the Nose

There are many different structural anomalies that can affect the nose, including bifid nasal tip, flat nasal bridge, bulbous or beaked nose or hypoplastic alae nasi. An excellent summary is available in the Oxford Desk Reference for Clinical Genetics and Genomics [5].

Whilst some of these may be non-specific and not of clinical significance, there may be times where the nasal structure can indicate an underlying syndromic diagnosis. The majority of individuals with a syndromic diagnosis will exhibit other clinical features, for example, facial dysmorphism, intellectual disability, other congenital anomalies, cleft lip and/or palate or craniosynostosis.

Choanal atresia can also be associated with a range of underlying syndromic diagnoses. One of the more common syndromic causes of choanal atresia is CHARGE syndrome, which encompasses coloboma, heart defects, atresia choanae, retardation of growth and/or development, genital anomalies and ear anomalies or deafness. CHARGE syndrome is an autosomal dominant disorder associated with variants in the *CHD7* gene.

Any patient in whom there is a high clinical suspicion of an underlying syndromic diagnosis should be referred to a Clinical Geneticist for further evaluation.

Genetics of Common Diseases

Common diseases, such as asthma, diabetes or hypertension, are generally not caused by a single change in a specific gene. Instead, these diseases tend to be multifactorial, with some environmental influences and some genetic contribution.

There are many single-nucleotide polymorphisms (variations in the genetic code that are not directly disease-causing) that contribute a small genetic susceptibility to particular common diseases. Having certain polymorphisms, or combinations of polymorphisms, will increase the patient's susceptibility to developing a disease, but on their own, they are not sufficient to cause disease. Large-scale studies, known as genome-wide association studies (GWAS), can identify polymorphisms to help further our understanding of the genetic influences on a given condition.

Genetic polymorphisms have been studied in the context of disorders affecting the nose and sinus, particularly in chronic rhinosinusitis (CRS) with or without nasal polyposis [6]. Genetic variation has been detected in a number of different genes in patients with CRS, including the *CFTR* gene (more commonly associated with autosomal recessive cystic fibrosis).

Whilst the study of genetic susceptibility can be helpful in a research setting to investigate the underlying genetic contribution to common diseases, the clinical utility of looking for these polymorphisms is currently very limited. The presence or absence of polymorphisms is not routinely used to aid diagnosis or change clinical management. In most healthcare settings, testing for polymorphisms would only be considered within a research study, and not on a clinical basis. Furthermore, the analysis of common polymorphisms currently falls outside the remit of most Clinical Genetics services.

Key Learning Points

- Systemic genetic disorders may present with pathology of the nose or sinus. Remember to enquire about other relevant systemic features, and family history, if there is a suspicion of an underlying genetic diagnosis.
- Genetic testing is evolving. Be aware of local policy regarding which genetic tests you can request and how and when to refer to local Clinical Genetics services.
- Genetic changes are referred to as variants, and not every variant is causative of disease. The results from genetic testing can be complex or uncertain—ask for help from the reporting laboratory or your local Clinical Genetics service if needed.

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8 The Current Concepts of Biofilms and Superantigens

Sarah Vreugde and Peter-John Wormald

Bacterial Biofilms: Definition

A bacterial biofilm is defined as a community of bacterial cells encompassed by a self-produced matrix consisting of **Extracellular Polymeric Substances (EPS)**. A fully developed biofilm has a three-dimensional (3D) structure, containing both live and dead bacterial cells, an EPS matrix, and interstitial water channels or pores that can facilitate the exchange of solutes from the surrounding environment [1]. The EPS matrix contains viscoelastic biopolymers, mainly polysaccharides, proteins, glycoproteins, and extracellular DNA and, depending on the microenvironment, can contain host-derived inflammatory proteins. The biopolymers and bacterial molecules facilitate strong irreversible attachment of biofilms to inert or mucosal surfaces [2].

Biofilms: The Preferred Microbial Lifestyle

Biofilms are the preferred mode of growth and are regarded as a survival strategy for virtually all microorganisms, including various bacterial and fungal human pathogens [3]. Microorganisms within biofilms benefit from a number of advantages over their planktonic counterparts. The EPS matrix provides for a nutritionally rich ecological niche as it can capture and concentrate environmental nutrients such as carbon, nitrogen, and phosphate [4]. At the same time, the EPS matrix provides for a robust shelter that allows the bacterial cells to evade multiple clearance mechanisms produced by the host and synthetic sources. These include, for example, antimicrobial and anti-fouling agents, shear stress, and host phagocytic elimination. The EPS matrix furthermore facilitates communication between cells by *quorum sensing* signalling, a cell density-dependent communication system that regulates cooperative behaviours. Biofilms also support processes of adaptation to the environment and are considered hot spots for **Horizontal Gene Transfer (HGT)** [5]. Both HGT and quorum sensing signalling are important in the bacterial adaptation and thus defence of the bacteria to the presence of antibiotics and enhance the spread of resistance to antibiotics.

S. Vreugde · P.-J. Wormald (✉)
Department of Surgery-Otolaryngology Head and Neck Surgery, Central Adelaide Local Health Network, Woodville South, Australia

The University of Adelaide, Adelaide, Australia
e-mail: pjwormald@professorwormald.com.au

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Bacterial Species Involved in Biofilms

Staphylococcus aureus is one of the bacterial species most frequently associated with biofilm mediated infections. *S. aureus* biofilms can occur on various host tissues such as heart valves (endocarditis), bone tissue (osteomyelitis), mucosal tissue (chronic rhinosinusitis), and open wounds (diabetic ulcers) and they are frequently related to medical devices (catheters, prostheses). However, other species are notorious for causing difficult to treat biofilm infections. These include, for example, *Staphylococcus epidermidis* (orthopaedic implants), *Pseudomonas aeruginosa* (cystic fibrosis lung infections), and enterococci (orthopaedic implants) [3].

The Establishment, Life Cycle, and Structure of Biofilms

Biofilm formation is a multistep process involving a plethora of bacterial molecules. A critical initial step during successful colonization is the attachment of the planktonic bacterial cells to the mucosal or implant surface. This initial step can be further divided into two distinct phases: primary, reversible adhesion (abiotic surfaces) and secondary, irreversible adhesion (abiotic and living tissue). The primary adhesion is mediated by nonspecific interactions, whereas secondary irreversible adhesion is accomplished through specific molecular docking mechanisms [6].

This irreversible adhesion critically depends on stable pathogen binding to host-derived **extracellular matrix (ECM) components** such as collagen, fibronectin (Fn), fibrinogen, vitronectin, and thrombospondin. Some of these ECM components cover inserted devices in vast amounts almost immediately after being introduced into the human body [7]. Bacterial cell surface proteins specifically binding serum and ECM components are called **Microbial Surface Components Recognizing Adhesive Matrix Molecules [MSCRAMM]** [8] and are of critical importance for the initiation of surface colonization. Well over 100 bacterial MSCRAMM with Fn-binding activity have been identified so far [9], indicative of the importance of adherence activity for establishing and maintaining the bacterial biofilm lifestyle. Adhesins are multifunctional proteins however and do not just mediate adhesion to ECM proteins: some MSCRAMMs can modulate the host immune response or can mediate bacterial internalization into host cells [10].

During this early stage of adhesion, planktonic microorganisms can also stick to each other or to different species of surface-bound organisms, forming aggregates on the substratum. A microcolony is then formed and the bacterial cells start to produce Extracellular Polymeric Substances (EPS) that will eventually form the EPS matrix. Many of these substances have adhesive properties and foster intercellular adhesion and cell aggregation. These include, for example, **Polysaccharide Intercellular Adhesin [PIA]**, Accumulation-associated protein ,**[Aap]** and **extracellular DNA [eDNA]** [11].

The process of biofilm maturation then begins. The bacteria replicate further producing extracellular substances which can interact with organic and inorganic molecules in the immediate environment to create the EPS matrix. The growth potential of the biofilm is grossly dependent on the availability of nutrients in the immediate environment and the efficiency of perfusion of those nutrients to the bacterial cells within the biofilm, and the removal of waste products. Other factors that control biofilm maturation include the pH, oxygen perfusion, and osmolarity [6]. Once a dynamic equilibrium is reached, cells within the biofilm core become dormant or die due to a lack of nutrients, oxygen, decreased pH, and/or an accumulation of toxic metabolic by-products [12, 13]. Once fully matured, biofilms are highly hydrated complex structures with

intricate channel networks flowing through these complex structures providing essential nutrients even in the deepest regions of those biofilms. Their structural and functional communal coordination and properties of coordinated bacterial growth, physiological cooperation, and metabolic efficiency have been proposed to mimic a primitive eukaryotic organ [2]. When the environment ceases to support the bacterial load, this equilibrium is shifted at which planktonic organisms escape the biofilm and colonize other surfaces recommencing the cycle.

The EPS Matrix: Not Just Slime

The EPS matrix (also termed glycocalyx or "slime") accounts for a variable amount (usually between 50 and 90%) of the total organic matter in the biofilm and mediates numerous virulence traits including host colonization, immune evasion, and tolerance to antibiotics [14]. Exoproteome analyses of the *S. aureus* EPS matrix revealed the presence of many proteins involved in pathogenesis, such as toxins (leukocidin, EsaA, and beta-hemolysin) and immunomodulatory proteins (lipoprotein, immunodominant antigen B, immunodominant antigen A, protein A, IgG-binding protein, secretory antigen precursor SsaA, and SceD), enzymes involved in cell wall peptidoglycan synthesis (autolysin and *N*-acetylmuramoyl-l-alanine amidase) and DNA metabolism and stress proteins (foldase protein, DNA binding protein II, nuclease, and superoxide dismutase) [15]. The biofilm matrix also contains a large number of proteins/enzymes involved in carbohydrate metabolism and synthesis, and bacterial exopolysaccharides are the main component of the biofilm glycocalyx [15]. The EPS matrix composition is furthermore influenced by the microenvironment creating a scavenging system for trapping and concentrating molecules including essential minerals and nutrients from the surrounding environment. In the case of infection, this also includes host-derived inflammatory response proteins or matrix proteins such as complement, fibrinogen, fibronectin, and glycosaminoglycans.

Spatial Patterns of Protein and DNA Synthesis in Biofilms

The spatial patterns of protein and DNA synthesis are highly stratified in biofilms. The EPS matrix sustains gradients in oxygen and nutrients creating differential environmental conditions throughout the biofilm potentiating heterogeneous gene expression and the development of distinct bacterial subpopulations [16]. It has been shown that in in vitro colony biofilms, oxygen penetrated only approximately 50 μm into 48 hr. biofilms formed by either *S. epidermidis* or *S. aureus* leaving the lower two-thirds of these biofilms anoxic [12]. This is similar for various bacteria including *P. aeruginosa* strains [13]. Most of the bacteria in those anoxic regions (around 70%) were metabolically inactive ("dormant") but still viable as only 10% of the cells within the biofilm were dead. Staphylococci located deep within the biofilm at the membrane interface from where nutrients originated showed evidence of fermentative growth. In contrast, the zone and dimension of protein synthesis in *P. aeruginosa* biofilms were located exclusively at the biofilm-oxygen source interface corresponding to the dimension of the oxic zone [12, 13]. Regions of anabolic activity (protein and DNA synthesis) are therefore only localized at the interface between the biofilm and oxygen and/or nutrient source leaving the inner part of the biofilm metabolically inactive but viable. These regions of anabolic activity are a few tens of micrometres in dimension but can expand upon addition of glucose or pure oxygen to the biofilm expanding the metabolically active zone into regions that were previously inactive.

Microbial biofilms therefore contain cells in at least four distinct growth states: growing aerobically, growing fermentatively, dead, and dormant (persisters) [17] (Fig. 8.1).

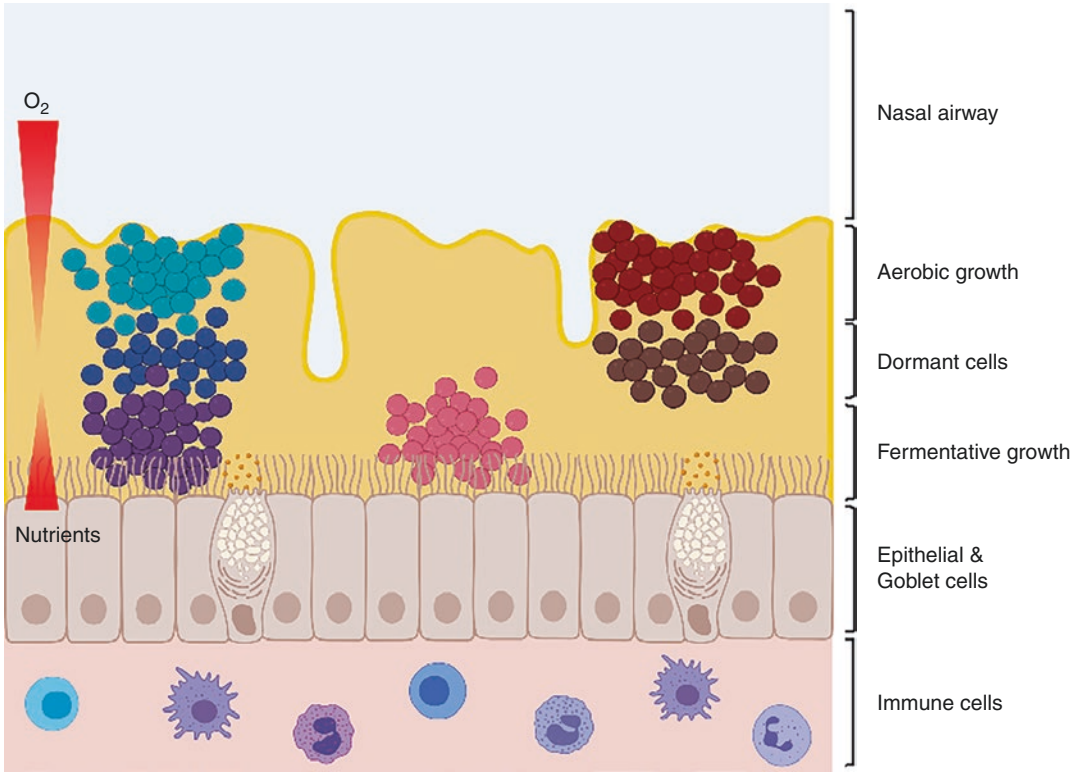

Fig. 8.1 Illustration of a polymicrobial biofilm attached to nose and sinus epithelium. The various species within a polymicrobial biofilm form clusters of bacterial cells. Their metabolic activity depends on their position within the biofilm and their oxygen requirements. Oxygen penetrates only approximately 50 μm [12]. Aerobic bacteria show active metabolism in the superficial biofilm layers whilst anaerobic bacteria or facultatively anaerobic bacteria are able to grow in the absence of molecular oxygen by fermentation and are thought to be preferentially located deep within the biofilm. Bacteria located in the biofilm centre are metabolically inactive (dormant) or dead

Biofilms Show Chemical and Physiological Heterogeneity

It has been shown that bacterial cells within biofilms are not distributed uniformly but rather that they grow in clusters (Fig. 8.1). Active metabolism of the cells within those clusters results in the accumulation of acidic metabolites or waste products creating a localized acidic microenvironment, which is unaffected by the external pH [16]. This results in discrete pockets of low pH in both the axial and lateral direction within the biofilm corresponding to sites of active metabolism ongoing in bacterial cell clusters. These acidic by-products may become trapped within the confines of the EPS matrix and are thought to be transferred through the matrix accumulating and presumably excreted via the pores existing in mature biofilms [16]. It has been shown that multi-species biofilms comprising bacteria with different metabolisms (e.g. aerobic, fermentative, and anaerobic) will produce more acidic by-products under oxygen-limiting conditions found in the deepest regions of the biofilm than single-species biofilms consisting of obligate aerobic bacteria [18]. It is also known that for some species (e.g. *Pseudomonas*), the bacterial cells are preferentially located deep within those biofilms whilst others are located more towards the biofilm surface [19].

Role of Bacterial Biofilms in the Pathophysiology of Chronic Rhinosinusitis

The presence of mucosal biofilms in the context of chronic rhinosinusitis was first reported in 2005 [20]. Biofilms, particularly those comprising the pathogens *S. aureus* and *P. aeruginosa,* have since been associated with unfavourable prognosis and disease recalcitrance in CRS [21–25]. Paradoxically, *S. aureus* biofilms are also found in healthy sinuses, so the exact role of biofilms and in particular *S. aureus* biofilms in the pathophysiology of CRS is not clear and highly debated [26–28]. Similarly, in the gut, studies have shown evidence of mucosal biofilms attached to the intestinal mucosa or growing in the mucus layer in both healthy and diseased individuals [29]. Because they are located in close proximity to host cells, mucosal bacteria are thought to play a particularly important role in mucosal health, promoting balanced immune responses. In the context of chronic colonic mucosal inflammation (e.g. Inflammatory Bowel Disease-IBD), it has been shown that a dysbiosis exists in the microbial community structure, and that there is a reduction in putatively protective mucosal organisms such as bifidobacteria [30]. Similarly, in a recent multicentre study investigating the sinonasal microbiome in health and disease, using 16S rRNA gene sequencing of 410 individuals, dysbiosis with a significant depletion of *Corynebacterium* (40.29% vs 50.43%; $p = 0.02$), and overrepresentation of *Streptococcus* (7.21% vs 2.73%; $p = 0.032$) was identified in CRSwNP patients [31]. Whilst the composition of the sinus bacterial microbiota is directly related with host immune response features, the inflammatory phenotypes or endotypes and microbiome or microbial biofilm compositions vary considerably across individuals with CRS [32]. Therefore, the exact role of biofilms and dysbiosis in eliciting or maintaining persistent mucosal inflammation in the context of CRS is not known. Given the prominent role of biofilms in eliciting and maintaining chronic infections in various niches, further research into the role of biofilms and dysbiosis into CRS disease recalcitrance is urgently needed.

Differences Between Planktonic Cells and Biofilms

Bacteria living in a biofilm exhibit an altered phenotype with regard to growth and express a different set of genes than their planktonic counterparts. This results in an enrichment in biofilms of many proteins involved in the inflammatory process including immunomodulatory proteins and a large number of proteins involved in cell envelope synthesis and function and carbohydrate metabolism [15, 33]. In addition, various metabolic processes such as those involved in pyruvate fermentation, urease activity, and response to oxidative stress are upregulated in a biofilm relative to planktonic cells [34, 35]. Interestingly, differences in gene expression by biofilms and corresponding planktonic cells are reflected in differences in immune activation with *S. aureus* biofilms inducing a distinct inflammatory response compared to their planktonic counterparts [36]. Biofilm secreted proteins (and not planktonic secreted proteins) have also been reported to induce apoptosis of epithelial cells [36, 37]. Recent research has shown differences between planktonic and biofilm secreted proteins in their effect on mucosal barrier structure and function. Using air-liquid interface cultures of primary human nasal epithelial cells, it was shown that biofilm exoproteins from 39 *S. aureus* clinical isolates induced a significant dose- and time-dependent reduction of transepithelial electrical resistance, increased cell toxicity, and increased permeability compared with equal concentrations of exoproteins from corresponding planktonic cultures [38]. Previous research has also demonstrated an association between mucosal biofilms and ciliary denudation and epithelial damage in the context of CRS [39]. Together, these studies support the notion that *S. aureus* biofilms produce factors that might induce higher

levels of toxicity compared to planktonic cells. This may differentially activate immune responses potentially contributing to their survival, persistence, and growth and reflect their capacity to adapt to their environment and establish a chronic infection.

Bacterial Biofilms as Immune Evasion Strategy

In addition to the EPS matrix forming an effective diffusion barrier protecting the encapsulated bacteria against immune defence molecules, bacterial cells growing in biofilms are known to produce various immunomodulatory proteins and polysaccharides to resist attack by the innate immune system. These molecules include, e.g. the biofilm exopolysaccharide Polysaccharide Intercellular Adhesion (PIA), as well as the Accumulation-associated protein (Aap), the Extracellular matrix binding protein (Embp), and the Phenol-Soluble Modulins (PSMs) that have been shown to modulate immune effector cell-mediated killing of *S. epidermidis* [40]. The enrichment of specific antigenic proteins within the biofilm matrix can also protect the bacterial cells within the biofilm from antibody-mediated phagocytic killing. Namely, whereas the biofilm EPS matrix of *S. epidermidis* biofilms did not pose an overall diffusion barrier to antibodies, it could protect bacteria from antibody-mediated phagocytosis in the presence of an antibody opsonically active against planktonic cells. It is thought that this is due to the large amount of antigen present within the matrix, preventing a close approximation of antibody and bacterial cells, thereby limiting opsonophagocytosis [41].

Bacterial Biofilms Show Reduced Susceptibility to Antibiotics

Bacterial biofilms have mastered coordinated defence mechanisms that render them over 1000-fold more tolerant to antimicrobial therapy than their planktonic forms [42]. Whilst the EPS matrix can reduce antibiotic penetration, low metabolic activity of the bacterial cells in relation to low oxygen pressure and/or limited access to nutrients in the interior of the biofilm is one of the leading hypotheses to explain the reduced susceptibility of biofilms to antibiotics and other antimicrobial challenges [43, 44]. These slow-growing, "dormant" bacterial cells, present within the core of bacterial biofilms are also named persisters and show downregulated biosynthetic pathways and overexpression of Toxin/Antitoxin (TA) modules that inhibit essential functions such as translation [17]. The ability of a biofilm to limit the access of the immune system molecules and cells coupled with the ability of persisters to resist an antibiotic attack is thought to account for the recalcitrance of biofilm mediated infections in vivo [17]. Indeed, once antibiotic regimens are halted and growth conditions improve, these persister cells are able to spontaneously shift out of their dormant state and produce a relapsing course of disease [17, 45].

Superantigens

Superantigens are a family of nonglycosylated low-molecular weight exoproteins secreted by all human pathogenic *S. aureus* and group A streptococci. The *S. aureus* superantigens include Toxic Shock Syndrome Toxin 1 (TSST-1), the Staphylococcal Enterotoxins (SEs), and the SE-like superantigens (or SSLs) [46]. Superantigens target the adaptive immune system whilst the related superantigen-like proteins (SSLs) target the innate immune system. Superantigens are a class of antigens that bind directly to both MHC-II and TCR molecules activating as much as 20% of the T cell population. This is in contrast to "normal" antigens that are taken up and processed by MHC-II antigen-presenting cells; antigen-carrying MHC-II complex is then recognized by receptors on circulating T cells resulting in activation of only about 0.001–0.01% of all T cells [47]. By directly and non-specifically linking the TCR and MHC-II, superantigens put these complexes in close contact with each other for much longer than normal, resulting in excessive polyclonal activation of the

immune system. Superantigen induced T cell activation results in the release of a variety of pro-inflammatory cytokines including interleukin (IL)-1, IL-2, IL-6, tumour necrosis factor (TNF)-α, interferon (IFN)-γ, and chemokines C-C motif chemokine ligand (CCL)2 and CCL3 from a combination of T cells, Antigen-Presenting Cells (APCs), and cells that are subsequently stimulated such as epithelial cells [48]. Despite this apparent non-targeted massive immune activation, *S. aureus* superantigen driven inflammation can subvert both activation and recruitment of important effector cells such as phagocytes promoting *S. aureus* survival and can drive a suppressor or regulatory phenotype in both human $CD4^+$ and $CD8^+$ T cells. It is thought that staphylococcal superantigen activity may be more 'targeted', and that by driving specific T cell activation pathways, these toxins can skew adaptive immune responses of the host away from a protective response against *S. aureus* to the benefit of its own survival [48].

In contrast to superantigens, SSLs do not bind MHC-II or TCR but target molecules of the innate immune system and limit the access of antibodies to their target or reduce adherence and function of neutrophils [47]. Superantigens and SSLs are mainly located on mobile genetic elements and there is strain dependent variation in the number of superantigens carried by those pathogens.

The Role of Superantigens in the Etiopathogenesis of CRS

A role for superantigens in the etiopathogenesis of CRS has first been proposed by Schubert in 2001 [49] and by Bachert et al in 2002 [50]. This hypothesis was then supported by evidence indicating a systemic IgE response to *S. aureus* superantigens in CRS patients [51, 52]. Superantigens were subsequently also identified within CRS patient tissue, mainly in CRSwNP patients [53]. CRSwNP patients demonstrating IgE to superantigens had significantly higher concentrations of IgG and IgE and also showed a significantly higher fraction of IgG4 ($P = 0.003$) than those without specific IgE production [54]. From those and other studies, the net effect of superantigens in CRSwNPs appears to be the Th2 skewing of immune responses with regulatory T cell reduction, and an influx of eosinophils often in association with asthma [55–57]. A recent study furthermore extends the potential role of *S. aureus* superantigen-dependent T cell expansion and Th2 polarization to non-asthmatic CRS patients, in association with the Lund-Mackay Computed Tomography score, indicating a relation to disease extent [58]. A microbial genome-wide association study (mGWAS) of 58 *S. aureus* clinical isolates from CRS patients identified 14 of the known superantigen genes across all isolates and only three superantigen genes were identified in >50% of the isolates (SEG, SEM, SEO). Assessment of the pan-genome content for correlation with disease presentation showed no relation with any of the superantigens. Only two SSL genes, superantigen-like protein 5 (higher prevalence in the CRSsNP cohort) and superantigen-like protein 14 (more prevalent in CRSwNP) were significantly associated with CRS disease phenotype [59]. Therefore, whilst research findings support a role for superantigens in driving or maintaining eosinophilic inflammation in CRS patients, their exact role and the role of SSL genes and gene products in CRS pathophysiology remain to be investigated.

Key Learning Points

- Biofilms are the preferred mode of growth for virtually all microorganisms, including various bacterial and fungal human pathogens.
- Biofilms show high levels of structural organization and support functional coordination between the various strains and species present within those biofilms.
- The biofilm matrix limits the penetration of oxygen and nutrients resulting in a stratification of bacterial cells according to their oxygen and nutrient requirements with active metabolism occurring only in the external layers of the biofilm.
- The biofilm core contains slow-growing "dormant" bacterial cells, that are thought to significantly contribute to the recalcitrant nature

of biofilm mediated infections and their relapsing course of infectious exacerbations.

- Biofilms, particularly those comprising the pathogens *S. aureus* and *P. aeruginosa,* have been associated with disease recalcitrance in CRS. Paradoxically, *S. aureus* biofilms are also found in healthy sinuses, so the exact role of biofilms and in particular *S. aureus* biofilms in the pathophysiology of CRS is not clear.

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9 Bacteria, Viruses and Fungi in Healthy and Diseased Paranasal Sinuses

Tary Yin and Raymond Kim

Introduction

Technological advancements in the field of microbiology have led to significant progress in our understanding of the role of bacteria, viruses and fungi in healthy and diseased paranasal sinuses. It is now known that the sinonasal tract is not sterile and that the microbes colonising the mucosa are not necessarily pathological. The sinonasal microbiota, which consists of the entire collection of microbes, including bacteria, viruses, fungi and archaea, existing within the sinuses has multiple functions, including maintaining mucosal health and effective local immune responses.

This chapter will cover: (1) the role of microbes in health and various sinonasal conditions and the relationship between the microbiota and antimicrobial treatments; (2) the various laboratory techniques utilised to investigate microbes (including culture, fluorescence in situ hybridisation and sequencing approaches); (3) current limitations and areas of controversy in the literature, particularly with regard to culture and sequencing studies of the sinonasal microbiota.

Bacteria, Viruses and Fungi in Healthy Paranasal Sinuses

Microbes begin to colonise the sinonasal mucosa from birth. The diversity of the bacterial community increases during the first 3 years of life and in adulthood becomes individualised and relatively stable over time [1]. Culture techniques have most frequently detected members from the genus *Staphylococcus*, *Corynebacterium* species and *Propionibacterium acnes* [2–4]. Sequencing approaches have similarly seen a high prevalence of *Staphylococcus* sp., *Corynebacterium* sp. and *Propionibacterium* sp. [5, 6]. These findings are summarised in Table 9.1.

The nasal metagenome (the collective genomic representation of the many organisms existing in a community) suggests that there is a set of core functional genes present in all individuals that code metabolic processes, transport systems and biosynthesis [6]. The stability of the bacterial community is achieved by key central bacteria, such as *Propionibacterium* sp., that connect many parts of this network [7]. Both culture and sequencing methods report low abundances of members from the genera (*Fusobacteria*, *Bacteroidetes*), potential pathogens (*Streptococcus pneumoniae*, *Neisseria meningitidis*, *Haemophilus influenzae*, *Moraxella catarrhalis*) and anaerobes [6–8].

T. Yin · R. Kim (✉)
Department of Surgery, University of Auckland, Auckland, New Zealand
e-mail: raymond.kim@auckland.ac.nz

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Fungi are ubiquitous in our environment and fungal communities have also been detected in healthy sinonasal samples, dominated by the genus *Malassezia*, suggesting that they have a commensal role in the sinus microbiome [9, 10]. Furthermore, a variety of viruses and archaea (prokaryote organisms that are obligate anaerobes) have been found in healthy sinonasal samples without causing disease. The roles of these less-common microbes in the healthy microbiome are yet to be determined [11, 12].

Staphylococcus aureus, a bacteria that can cause a wide variety of illnesses, is persistently carried by 20% of the population and transiently carried by 60% [13]. While persistent *S. aureus* carriage in the anterior nares is a risk factor for infection, the mechanism of the transition from a commensal to a pathogenic bacteria is unknown. One hypothesis suggests that when the mucosal barrier is breached by a pathogen, a self-limited host immune response is generated. The mucosa interacts with the host immune system to act as a barrier against pathogens. Type 1 immune responses target viruses, type 2 immune responses target parasites and type 3 immune responses target extracellular bacteria and fungi. These responses result in the elimination of the pathogen and encourage restoration of the mucosal barrier.

Bacteria, Viruses and Fungi in Diseased Paranasal Sinuses

Culture and sequencing studies investigating the various phenotypes of sinusitis have shown that there are several potential pathogenic mechanisms that can be implicated in each of these groups. The most prevalent microbes detected from these studies are summarised in Table 9.1. The role of these microbes and the relationship between sinusitis and antimicrobial treatments will be discussed in this section.

Acute Rhinosinusitis

Acute rhinosinusitis (ARS) is a condition characterised by the sudden onset of sinonasal symptoms for less than 12 weeks. It can be subclassed into viral ARS, bacterial ARS and recurrent acute rhinosinusitis (RARS).

Table 9.1 The most prevalent bacteria, viruses and fungi detected using culture and sequencing approaches

	Culture	Sequencing
Health	Genus: *Staphylococcus*, *Corynebacterium* Species: *P. acnes*, *Staph. aureus* [2–4]	Genus: *Staphylococcus*, *Corynebacterium*, *Propionibacterium*, *Malassezia* [5, 6]
Acute rhinosinusitis	Genus: *Pneumococcus* Species: *S. pneumoniae*, *H. influenza*, *M. catarrhalis* [14, 15]	Species: *Rhinovirus*
Chronic rhinosinusitis	Genus: *Corynebacterium*, *Streptococcus*, *Prevotella*, *Porphyromonas*, *Peptostreptococcus*, *Fusobacterium*, *Candida*, *Aspergillus*, *Penicillium*, *Cladosporium* Species: *Staph. aureus*, *Staph. epidermidis*, *Propionibacterium acnes*, *Pseudomonas aeruginosa*, *S. pneumoniae*, *Haemophilus influenza* [16]	Genus: *Staphylococcus*, *Streptococcus*, *Corynebacterium*, *Pseudomonas*, *Haemophilus*, *Achromobacter*, *Candida*, *Aspergillus*, *Penicillium*, *Malassezia* Subfamily: *Orthocoronavirinae (Coronavirus)* Species: *Pseudomonas aeruginosa*, *Haem. influenzae*, *Staph. aureus*, *Corynebacterium neoformans*, *Rhinovirus* [7, 17–19]
Odontogenic sinusitis	Genus: *Streptococcus*, *Staphylococcus*, *Prevotella* Species: *H. influenzae* [20]	
Fungal rhinosinusitis		Genus: *Aspergillus*, *Mucor*, *Rhizomucor* [21]
Cystic fibrosis	Genus: *Pseudomonas*, *Burkholderia* Species: *Pseud. aeruginosa*, *Staph. aureus* [22]	Genus: *Pseudomonas*, *Staphylococcus*, *Streptococcus*, *Burkholderia* [22–24]
Primary ciliary dyskinesia	Species: *H. influenza*, *S. pneumoniae*, *M. catarrhalis*, *P. aeruginosa* [25]	

Viral ARS: The symptoms of ARS last fewer than 10 days. Studies have shown that viruses damage and enter the nasal epithelium, initiating host inflammatory responses leading to ARS [11]. One hypothesis is that this process may occur by the degradation of the epithelial barrier by reactive oxygen species stimulated during viral replication. Rhinoviruses are the predominant virus implicated in ARS. There is no beneficial evidence for the prescribing of antibiotics in ARS.

Acute Bacterial Rhinosinusitis (ABRS): It is defined as ARS that does not improve within 10 days of onset or ARS that worsens within 10 days after an initial improvement. Viral upper respiratory tract infection with subsequent bacterial superinfection has been suggested as a contributing factor in a proportion of these cases. Viral-induced mucosal injury may lead to translocation and overgrowth of pathogenic bacteria [26]. Commonly cultured pathogens from the sinuses of patients with bacterial ARS include *Streptococcus pneumoniae*, *Haemophilus influenzae* and *Moraxella catarrhalis* [14]. Penicillin-resistant *pneumococcus*, ampicillin-resistant *H. influenzae* and *M. catarrhalis* occur to a lesser extent, but are also commonly cultured [15]. In uncomplicated cases, the benefits of antibiotics are uncertain and these should only be considered if symptoms fail to resolve or worsen after a period of watchful waiting. Antibiotics can cause significant adverse effects that include gastrointestinal complaints, growing bacterial resistance and anaphylaxis. Accordingly, careful patient selection is needed.

Recurrent Acute Rhinosinusitis (RARS): This condition is characterised by four or more episodes of ARS per year with symptom-free intervals. Pathogens cultured from nasal swabs are similar to those seen for ABRS (*Streptococcus pneumoniae*, *Haemophilus influenzae* and *Moraxella catarrhalis*). However, these bacteria may have a higher degree of antimicrobial resistance [14, 27]. Patients with immunodeficiency have a predisposition to developing RARS. Given the absence of studies specifically investigating antibiotic use in RARS, the criteria for antibiotic use in ARS may be adopted for this diagnosis [28].

Chronic Rhinosinusitis

Chronic rhinosinusitis (CRS) is a complex condition in which several phenotypes and endotypes have been described. However, the role of microbes in most cases of CRS remains unclear. Defining the role of bacteria, viruses and fungi in CRS, as well as the implications for appropriate antimicrobial treatment, requires careful consideration.

Bacteria that are frequently cultured from nasal swabs of patients with CRS include *Staphylococcus aureus*, *Corynebacterium* species, *Streptococcus* species, *Staphylococcus epidermidis* and *Propionibacterium acnes* [16]. It has been found that patients with more severe CRS disease, based on imaging, are more likely to culture pathogenic bacteria [29]. Sequencing studies also suggest that CRS patients have an altered microbiome with more pathogenic microbes [12, 19]. In CRS, these dysbiotic microbial communities possibly interact with a compromised mucosal barrier and host immune responses. If the damage to the mucosal barrier caused by pathogens fails to resolve, this can lead to chronic inflammation of the mucosa and tissue remodelling. The following section will discuss these potential disease mechanisms in more detail.

Single Pathogen Hypotheses

Specific pathogens, such as *Staphylococcus aureus*, *Streptococcus pneumoniae* and *Pseudomonas aeruginosa*, are frequently cultured from the middle meatus of patients with CRS. These pathogens, in particular *Staphylococcus aureus* and its superantigens, have been proposed as potential key aetiologic agents in CRS. Staphylococcal enterotoxins are superantigens that stimulate a polyclonal activation of T cells resulting in an increased cytokine release. These enterotoxins likely act as a disease modifier by amplifying the inflammatory response in CRS; their presence has been associated both with asthma and recalcitrance after surgery [30, 31].

Studies have demonstrated an increased detection rate of serum-specific IgE to *S. aureus* enterotoxin in CRS with nasal polyps (CRSwNP),

but there are limited data to support the role of superantigens in CRS without nasal polyps (CRSsNP). In CRSwNP, specific IgE to *S. aureus* has been associated with eosinophilic and type 2 inflammation [31, 32].

Staphylococcus aureus has also been detected within the epithelium and the interstitium in sinus mucosa, and these intraepithelial and interstitial bacteria may possibly act as a reservoir of pathogenic microbes in CRS [33, 34].

More recently, instead of a single pathogen dominating all CRS microbial communities, CRS patients have been found to cluster into sub-groups, with each sub-group dominated by either *Staphylococcaceae*, *Streptococcaceae*, *Pseudomonadaceae*, or *Corynebacteriaceae*. This variation of microbial community composition may contribute to CRS disease heterogeneity [17].

Biofilms

A biofilm is a community of bacteria or fungi surrounded by an extracellular matrix that provides increased protection to the resident microbes in several ways. They are formed by planktonic bacteria that communicate their density status to other bacteria via quorum sensing molecules. Once the microbes are present in an appropriate concentration, these molecules encourage them to begin forming a biofilm [35]. There is a high prevalence of *Staphylococcus aureus* and *Pseudomonas aeruginosa* biofilms in CRS, and it has been hypothesised that these contribute to CRS pathogenesis [36]. However, biofilms can also be found in control patients without CRS, although usually in much less dense formations [37, 38].

Biofilms may cause recurrent infections by the release of pathogenic microbes that stimulate a host immune response and also by the release of superantigens by *Staphylococcus aureus* biofilms [39]. The biofilm provides its residents with effective protection against host immune responses by phagocytosis and complement binding. Microbes within biofilms also undergo phenotypic changes to require less oxygen and nutrients. This slows down cell growth, which contributes to the likelihood of antibiotic resistance because almost all antimicrobials are more effective at killing rapidly dividing cells [40]. Sinonasal biofilms have been associated with recalcitrant CRS, an increased need for surgical intervention and worse outcomes after functional endoscopic sinus surgery (FESS) [41, 42]. As conventional culture techniques enrich the fastest-growing microorganisms, accurate identification of biofilm-forming pathogens requires sensitive histopathological methods such as fluorescent in situ hybridisation. Biofilms are typically resistant to standard antibiotics but potential biofilm-specific systemic and topical therapies are under investigation.

Microbial Dysbiosis

Studies utilising sophisticated gene-targeted and meta-omic sequencing approaches have suggested that CRS is caused by disturbances in the overall bacterial community composition and function rather than by a consistent single causative pathogen. These dysbiotic imbalanced microbial communities, otherwise known as microbial dysbiosis, interfere with the colonisation of healthy microbes and contribute to provoking host immune responses [7, 17, 24] (Fig. 9.1).

The CRS microbiome is both less diverse and stable than that seen in healthy controls, and it also has a higher total bacterial load [43–45]. CRS patients tend to have an increased relative abundance of opportunistic pathogens (such as members from the genera *Corynebacterium*, *Streptococcus* and *Staphylococcus*) and anaerobes [7, 18], which may contribute to recalcitrant CRS. Specific pathogens involved in dysbiosis may include *P. aeruginosa*, *H. influenzae* and *S. aureus* [18, 19]. Furthermore, the CRS microbiome tends to have fewer commensal bacteria, such as *Actinobacteria* sp., *Propionibacteria* sp., *Corynebacterium* sp. and *Acinetobacter johnsonii*. Key commensal bacteria may have a role in suppressing pathogenic species and therefore the loss of these communities could potentially result in pathogen outgrowth [46].

CRS patients with asthma are more likely to exhibit dysbiosis. Smoking, purulent secretions and aspirin sensitivity have also been associated

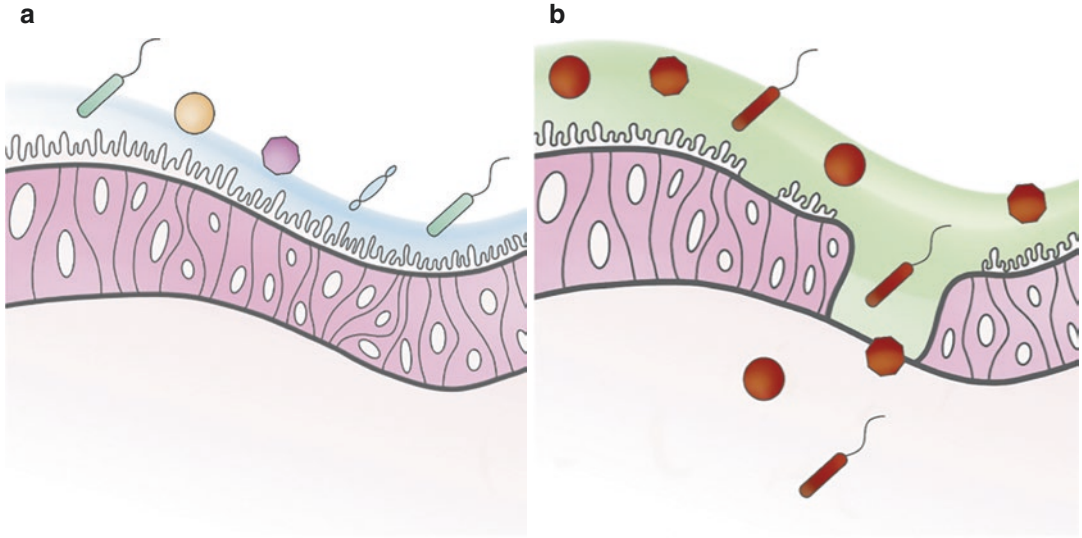

Fig. 9.1 The microbial dysbiosis theory in chronic rhinosinusitis. (**a**) Healthy mucosa with an intact mucosal barrier. The microbiota is diverse with a network of key commensal microbes. (**b**) Diseased mucosa with epithelial damage and increased mucus. The microbiota is less diverse, with an increased proportion of pathogenic microbes and loss of commensal microbes

with shifts in the sinonasal microbiome [24, 47]. Antibiotics may disrupt the commensal microbiome by decreasing bacterial diversity and increasing the relative abundance of antibiotic-resistant microbes, leading to ongoing disease [24, 48]. Furthermore, FESS has been shown to result in changes to the bacterial community composition in the sinuses, with an increased relative abundance of *Staphylococcal* species [49, 50].

Overall, the evidence is varied, and investigations into the causal relationships between microbial dysbiosis and host immunity in CRS patients are ongoing. Novel research topics in this area include:

- the identification of CRS subtypes based on their bacterial community composition profiles,
- co-culture studies that show how microbial community composition can influence the co-occurrence of certain bacteria through niche-specific competition, and
- the role of the interactions between microbe co-occurrence patterns and an altered immune response in CRS [17, 47].

Fungi

Fungal spores are ubiquitous in our environment and can be detected in both CRS and healthy sinuses. One recent study has demonstrated fungi in the maxillary sinus of over 80% of CRSwNP patients, compared with only 20% of controls [51]. Therefore, some researchers have suggested that fungi have a possible role in CRS [51–53]. Fungi have been reported to stimulate a type 2 immune response, although studies demonstrating a direct link between fungi and CRS are lacking [51–53].

The most frequently identified fungi from the sinuses of CRS and control subjects using polymerase chain reaction (PCR) and culture include members from the genera *Aspergillus*, *Cladosporium* and *Candida* [54, 55]. Only a handful of studies have performed amplicon sequencing to investigate the community composition of fungi in the sinuses. The most prevalent fungi identified include *Cryptococcus neoformans*, *Aspergillus* species and *Malassezia* species; however, results are inconsistent between studies [56, 57].

Viruses

The pathogenic role of viruses in CRS is unknown. Studies suggest higher rates of viruses in the sinuses of CRS patients compared with controls and peak viral isolation occurs in winter and spring [11, 58, 59]. Rhinovirus and coronavirus species are the most frequently isolated in CRS, although respiratory syncytial viruses, bocavirus, adenoviruses, human metapneumovirus and influenza viruses have also been detected in sinusitis [58, 59]. In vitro studies investigating CRS-derived nasal epithelial cells suggest that rhinoviruses decrease host immune responses [60, 61]. However, whether viral infections play an aetiological role in CRS or only lead to acute exacerbations of CRS (AECRS) is yet to be established. The literature has so far been inconsistent, which may be explained by seasonal fluctuations of respiratory viruses and differences in study sample collection and laboratory measures.

Acute Exacerbation of Chronic Rhinosinusitis (AECRS)

Bacterial infections probably contribute to AECRS, although there is little good evidence to support this. It has been hypothesised that impaired mucociliary clearance, evident in a subgroup of patients with chronic inflammatory mucosal changes, leads to prolonged contact with microbes [62]. Cultured organisms in AECRS included *Prevotella* sp., *Porphyromonas* sp., *Peptostreptococcus* sp., *Fusobacterium* sp., *S. pneumoniae* and *H. influenzae* [63]. Microbial dysbiosis may also elicit a host inflammatory response, and there is evidence that rhinovirus infections can drive eosinophilic inflammation. Short courses of antibiotics are often prescribed for AECRS. However, the evidence supporting the efficacy of these courses is not strong.

Odontogenic Sinusitis

Odontogenic sinusitis has been associated with the overgrowth of oral microbes into the sinuses, which tend to be more anaerobic than typical sinonasal pathogens. Common bacteria include *H. influenzae* and members of the genera *Streptococcus*, *Staphylococcus* and *Prevotella* [20].

Fungal Rhinosinusitis

Fungal spores are ubiquitous and are being inhaled into the nasal cavity continuously. While the species vary according to the locality, most fungal sinusitis cases are caused by dematiaceous fungi or *Aspergillus* spp. Manifestations of fungal sinusitis include fungal ball, invasive fungal rhinosinusitis and allergic fungal rhinosinusitis. *Aspergillus* and *Zygomycetes* (*Mucor*, *Rhizomucor*) are the genera of fungi most commonly associated with tissue invasion in invasive fungal rhinosinusitis [21]. First-line antifungal treatments for acute invasive fungal rhinosinusitis include systemic azoles (voriconazole and isavuconazole) for *Aspergillus* and amphotericin for *Zygomycetes* [64].

Cystic Fibrosis

Cystic fibrosis leads to highly viscous secretions and impaired mucociliary clearance, resulting in both sinus and lung infections. Bacteria cultured from these sites (such as genera *Pseudomonas* and *Burkholderia*) have a high degree of concordance, suggesting that the sinuses may act as a reservoir for bacterial transmission to the lower respiratory tract. CRS patients with cystic fibrosis have a higher bacterial load and are almost completely dominated by one bacterial species [23, 24]. This may well reflect the high number of powerful, broad-spectrum antibiotics administered to these patients.

Primary Ciliary Dyskinesia

Patients with primary cilia dyskinesia have a predisposition to bacterial infections, including *H. influenza*, *S. pneumoniae*, *M. catarrhalis* and *P. aeruginosa*. Influenza, pneumococcal and RSV vaccines, as well as standard vaccinations and prompt antibiotic therapy for respiratory tract infections, have been recommended [25]. Antibiotic therapy, sinus rinses and surgery may decrease pathogenic sinus bacteria, improve symptoms, reduce lung infections and improve quality of life [25, 65].

Technology

Culture

Culture methods have been used for more than a century to detect pathogenic and commensal microbes. This technique requires specific growth media and conditions depending on the microbe targeted [2] (Fig. 9.2). It remains the most common method for detecting specific pathogens, for example, *P. aeruginosa* in cystic fibrosis [66]. However, only a limited variety of microbes will grow on a specific culture medium. Therefore, culture methods tend to underestimate the diversity of the sinonasal microbial community. Culture studies in both healthy controls and patients with CRS detect approximately 3–9 microbes per subject [2]. One significant advantage of culture techniques is that they enable fast and accurate in vitro determination of antibiotic sensitivity of the isolated pathogen. Furthermore, culture remains the primary method for detecting pathogenic bacteria in clinical settings and much of our understanding of the microbiology of CRS is based on these techniques.

The following sections will discuss modern culture-independent, or molecular, approaches. These methods do not require the in vitro growth of microbes but rather detect the genes of the microbes present. These techniques have revealed the complexity of the sinonasal microbial community.

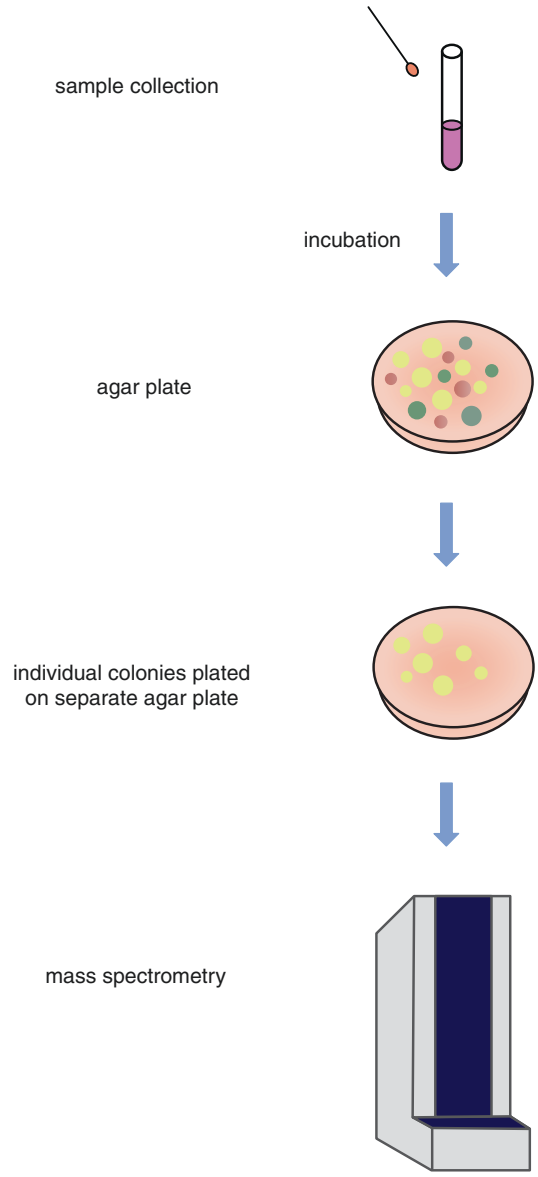

Fig. 9.2 Culture. Collected samples are placed onto agar plates, which are then incubated to promote microbial growth. Individual colonies that are morphologically or phenotypically different are plated again on separate agar plates. These microbes are then identified through MALDI-TOF (matrix-assisted laser desorption/ionisation-time of flight) mass spectrometry. Sanger sequencing can also be used to identify these individual colonies

Immunohistochemistry

Immunohistochemistry can be used to localise species-specific microbial molecules with labelled antibodies on tissue sections, which can then be visualised using microscopy. Multiple antigen–antibody labels can be used in a sample giving spatial and structural information. For example, bacteria can be seen on the surface of the epithelium (planktonic), within the epithelium (intraepithelial) or deep to the epithelium (intramucosal) (Figs. 9.3 and 9.4).

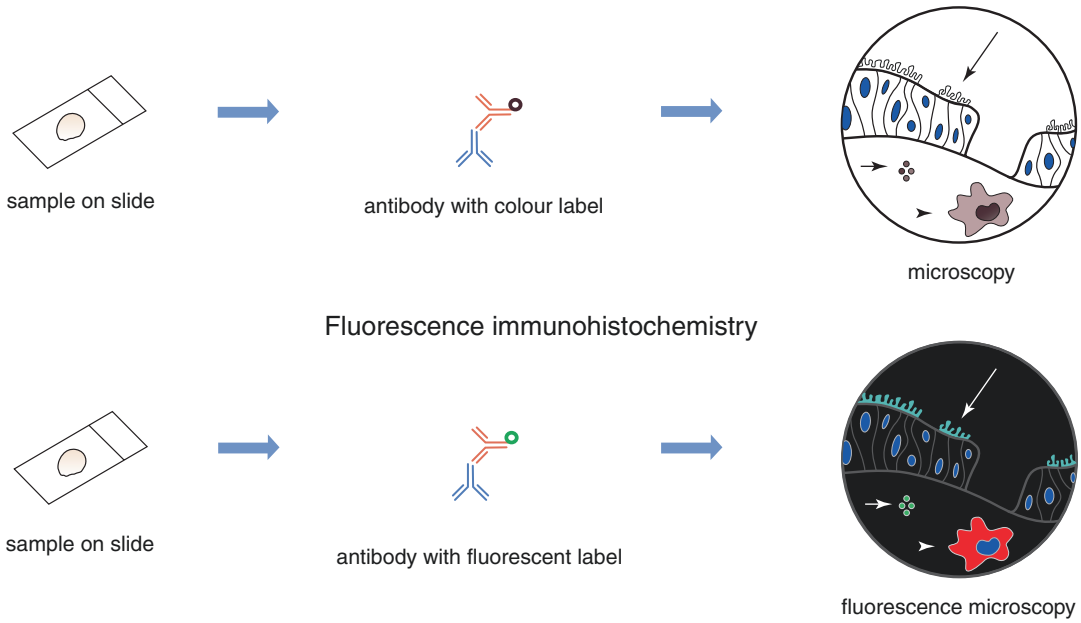

Fig. 9.3 Immunohistochemistry. Tissue sections on a slide are labelled with antibodies attached to a colour or fluorescent label. These are then visualised using microscopy. Multiple structures can be targeted, allowing the simultaneous labelling of microbes (short arrow), immune cells (arrowhead) and anatomical features such as cilia (long arrow)

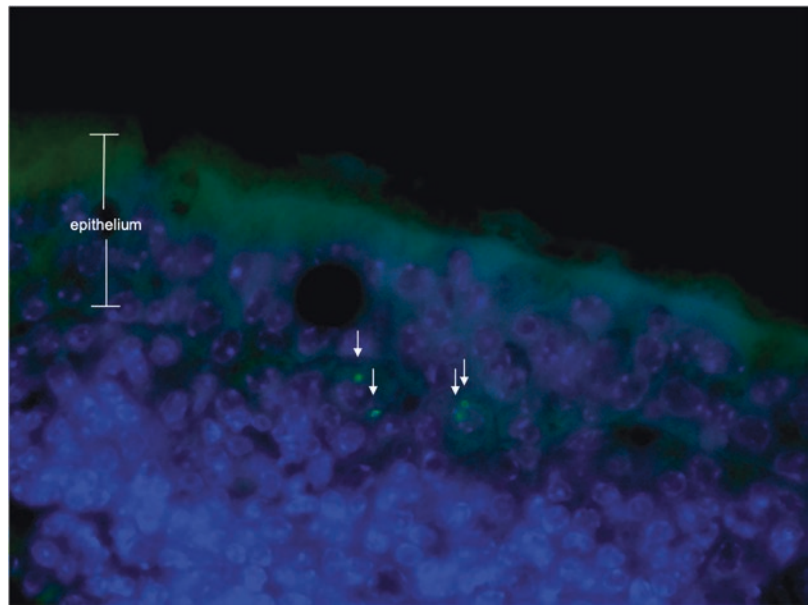

Fig. 9.4 Mouse sinus mucosa fluorescence immunohistochemistry demonstrating *S. aureus* antibody (arrows) and DAPI (4,6-diamidino-2-phenylindole) nucleic acid stain. Magnification: ×100. Unpublished image

Fluorescence In Situ Hybridisation

Fluorescence in situ hybridisation (FISH) utilises targeted probes attached to fluorescent dye molecules to identify individual microbial cells (Fig. 9.5). Classically, FISH utilised ribosomal RNA probes but modern techniques have targeted messenger RNA, plasmids and single-copy

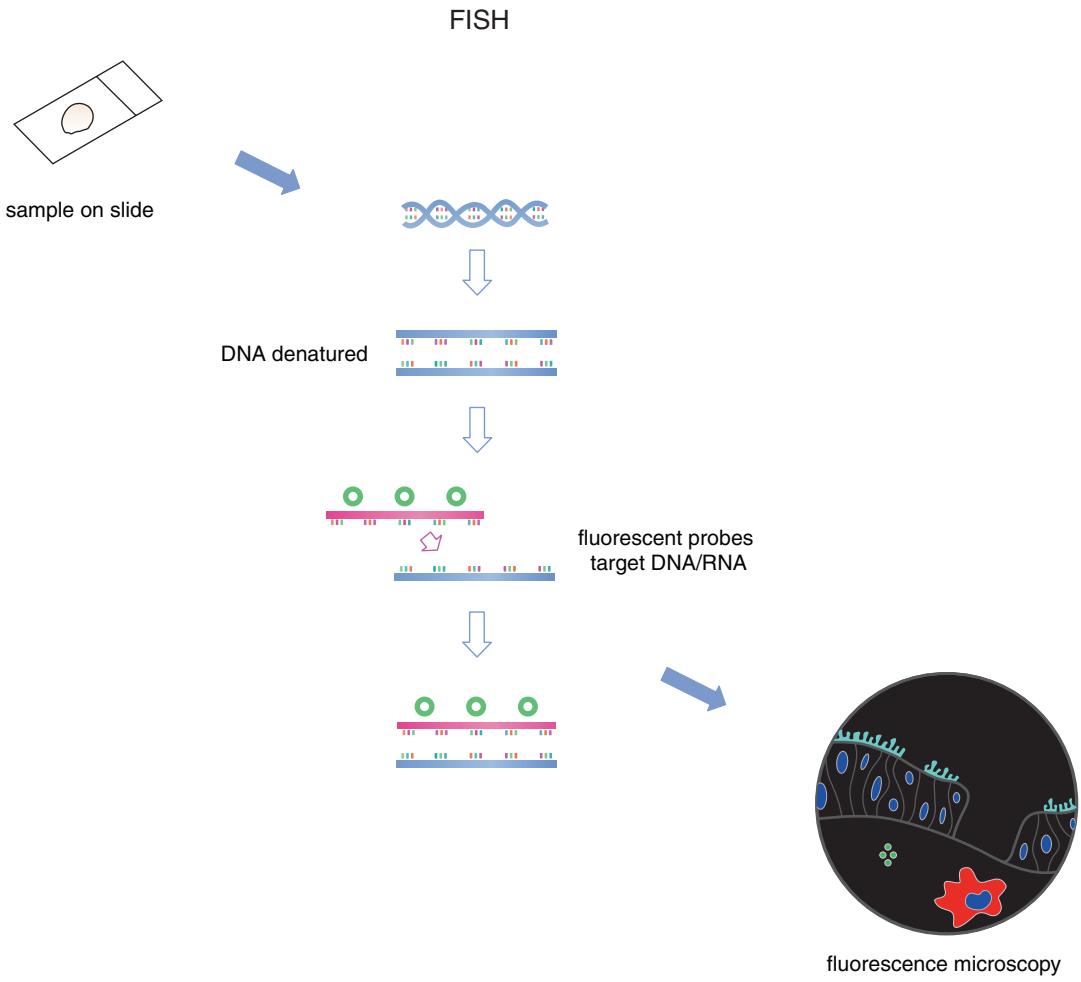

Fig. 9.5 Fluorescence in situ hybridisation. DNA within cells on the slide are denatured. Labelled probe (circles) hybridises to targeted DNA/RNA regions on the sample. These fluorescent probes are then visualised using fluorescence microscopy

genes. FISH probes can target all species (e.g. eubacterial, eufungal) or specific species. FISH allows the localisation and enumeration of these targets via either fluorescence microscopy or flow cytometry.

Amplicon Sequencing

Sequencing approaches amplify genes from the extracted genomic DNA of samples (swabs, tissue, mucus) using PCR. The amplified products are purified and then sequenced. The raw sequence reads are matched against known sequences in databases to provide a microbial profile for the sample (Fig. 9.6). This method allows the identification of potentially all of the microbes present within a sample. Gene-targeted sequencing looks at specific microbial gene sequences. The bacterial 16S rRNA gene, which is present in all bacteria, is the most common target used in sinonasal studies and can detect an average of 30 bacterial taxa (a taxonomic group of any rank, such as species, genus or phylum) per subject [7]. Fungi have also been investigated using a number of genes targets (18S rRNA and internal transcribed spacer regions), which similarly can encompass all fungal species. Unlike

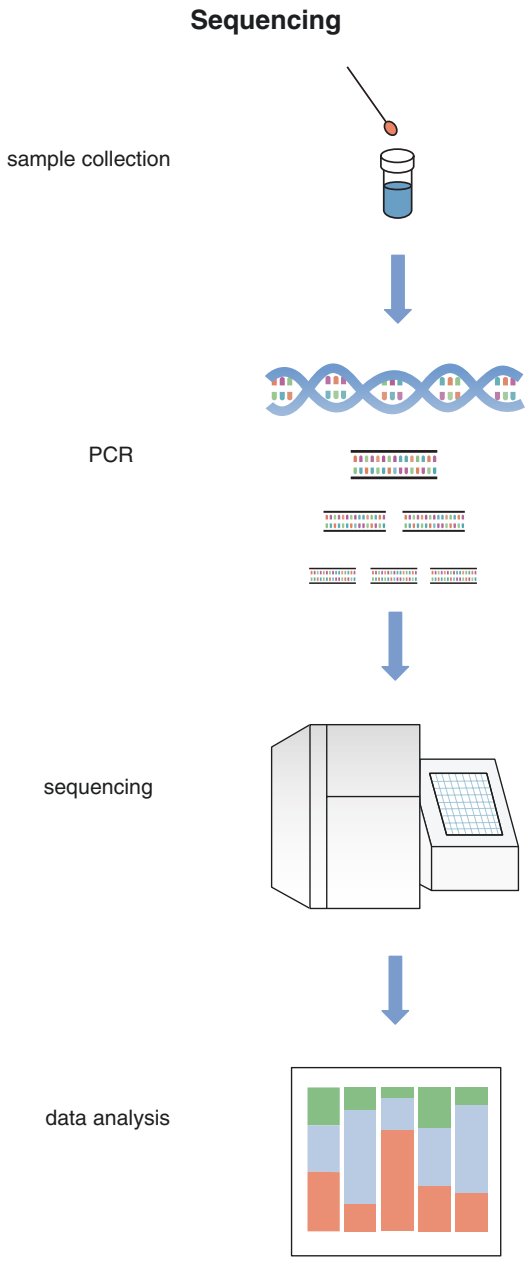

Fig. 9.6 Gene-targeted sequencing. Collected samples undergo PCR amplification. Amplicon sequencing determines the order of nucleotides in DNA. These sequences are then matched to a database to identify the microbes. Data analysis can include taxa plots, which allow comparisons of the microbiota between samples (each column represents a sample and each colour represents a microbial species)

bacteria and fungi, viruses do not have a universal gene target and so different targets are required to detect specific viruses. Consequently, novel viruses or viruses not included in a designed panel of targets cannot be detected. The presence of viruses in the sinonasal tract is therefore likely to be underreported. A weakness of the bacterial 16S rRNA gene-targeted approach is a limited resolution (the ability to resolve strains within a species), although this will improve with technological advances in this field [67].

In contrast to gene-targeted approaches for species identification, meta-omics can detect the total genetic composition or function from the organisms within a sample (whole genome sequencing). It can focus on DNA (metagenomics), RNA (metatranscriptomics) and proteins involved in cellular functions (metaproteomics). These techniques are able to simultaneously provide information on microbial community composition and function. Metagenomic approaches also allow the simultaneous detection of a wide variety of viruses.

Longitudinal gene-targeted and meta-omic studies that collect samples over multiple time points have enabled investigation into how the sinonasal microbiome changes over time. These studies have shown that the microbiota is reasonably stable over time in healthy controls and that this stability is achieved by certain commensal bacteria [7]. Contrastingly, in microbial dysbiosis, there is temporal volatility in microbial composition. This instability is also significantly affected by variables such as asthma, smoking, antibiotics and surgery [24, 49, 50]. However, these methods are resource-intensive, expensive and not easily standardised across studies. For these reasons, their clinical applications are limited. Nevertheless, as this technology improves, it will enable the sinonasal metagenome to be investigated with increasing accuracy and efficiency.

Summary of Areas of Controversy or Uncertainty

Bacteria, viruses and fungi colonise the sinonasal mucosa and have various roles and functions in healthy and disease states. With the development of sequencing technologies for investigating the microbiota, we now understand that culture tech-

niques vastly underestimate the diversity of these complex microbial communities. However, sequencing methods also have their limitations. Current evidence in the literature can often be inconsistent due to non-standardised methods and small sample sizes, reflecting the resource-intensive nature of these modern laboratory approaches.

It has been suggested that a core part of the healthy sinonasal microbiome codes metabolic processes, transport systems and biosynthesis. Furthermore, the stability of these communities is thought to be achieved by key central bacteria that connect many parts of the network [6]. Studies utilising sequencing approaches have also hypothesised that CRS is caused by microbial dysbiosis rather than a consistent single causative pathogen. These theories are not necessarily mutually exclusive. Instead, microbial dysbiosis arguably better reflects the evidence that disruption and instability of the microbiota as a whole occur in CRS. Even when single pathogens or biofilms are implicated in a patient's disease pathogenesis, these likely reflect microbial community composition shifts, with a decrease in key healthy microbes. Novel research in this field has focused on identifying CRS subtypes based on their microbiota, co-culture studies that demonstrate niche-specific competition between certain bacteria and the interactions between microbes and immune dysfunction in CRS [17, 47, 68, 69]. However, further longitudinal studies that assess the long-term stability of the microbiota rather than a single time point are required.

Key Learning Points

- The healthy sinonasal mucosa is colonised by bacteria, viruses and fungi from birth.
- The sinonasal microbiota has been investigated using traditional culture and modern sequencing approaches.
- Sequencing approaches have led to novel hypotheses on the role of the microbiota in health and various diseases.
- The current understanding of the role of pathogenic microbes in CRS is incomplete and limited by the resource-intensive nature of these methods and data from cross-sectional studies.

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Sleep Disorders and the Nose: What Is the Evidence Base?

10

Thomas Verse and Stefan Müller

Summary

This chapter considers the evidence base between the nasal airway and sleep. This important relationship will be considered for both obstructive sleep apnoea and simple snoring.

The pathophysiology is explained and will cover the various theories of airway dynamics and airway collapse during sleep. This includes a short resumé of nitric oxide and its physiological effects.

The evidence base for effects of medication and alar splints is presented. The effect of nasal surgery on obstructive sleep apnoea in the application of positive airway pressure and simple snoring is then considered.

Introduction

Neither airway obstruction nor the generation of snoring sounds occur in the nose. Nevertheless, the topic '*Nose*' always features prominently on the agenda of conferences about sleep medicine. Even the often-cited Hippocrates (460–370 BC) described a causal connection between nasal polyps and non-restorative sleep. As early as 1581, Levinus Lemnious first mentioned non-restorative sleep caused by oral breathing in supine position [1]. The first modern scientific reports date back to the end of the nineteenth century. In 1898, Wells [2] reported an improvement of vigilance in eight out of ten patients following nasal septoplasty.

Both, during the awake state and during sleep, nasal breathing is the natural physiological route for breathing [3, 4]. Under normal circumstances, less than 10% of humans breathe through their mouth. The nose is our major portal for inspired air, and nasal pathology is responsible for causing significant disturbance of inspirational air flow [5, 6]. With this in mind, many people and physicians likewise assume that nasal pathology also plays a significant role in the pathophysiology of sleep-related breathing disorders (SDB).

In addition, many patients suffering from acute or chronic impairment of nasal breathing report a subjective deterioration of their individual sleep quality with consecutive daytime symptoms such as fatigue, sleepiness and lack of concentration. This in turn leads to many rhinologists having to face expectations from their patients that improvement of nasal obstruction not only solves their daytime nasal symptoms but also reduces the severity of SDB and the effects on their daily routines.

This chapter focusses on the relationship between nasal obstruction and sleep quality, as well as on the relationship between nasal obstruction and severity of SDB.

T. Verse (✉) · S. Müller
Department for Otorhinolaryngology, Head and Neck Surgery, Asklepios Klinikum Harburg, Asklepios Campus Hamburg, Semmelweis University Budapest, Hamburg, Germany
e-mail: t.verse@asklepios.com

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Pathophysiology

Nasal Breathing During the Awake State

In the awake state, about 50–60% of the resistance of the complete upper airway is allotted to the nose [7]. This means the largest component of the entire upper airway resistance is located in the nose. As stated above, the nose can be regarded as the physiological breathing path. In healthy, awake and upright sitting subjects, as much as 92% of the entire airway resistance was found in the nose and only 8% in the oral section of the upper airway [8].

The body position has a considerable influence on nasal resistance. Nasal resistance (Rn) increases if the body position changes from sitting to supine. A shift as little as 10° leads to a significant alteration of Rn. These changes were even more clearly seen in patients with allergic or acute rhinitis as compared to a control group [9].

Nasal Breathing During Sleep

In comparison to being awake, nasal resistance (Rn) does not change if the subject falls asleep [10], but the entire upper airway resistance increases distinctively. This implies an increased airway resistance within the pharyngeal sections of the upper airway. In fact, during sleep, the largest contributor to total upper airway resistance is located in the pharynx. In other words, the most significant change of the entire upper airway resistance, whilst falling asleep, occurs in the pharynx and not the nose.

How Can Nasal Obstruction Promote Upper Airway Collapse?

This important question has several hypotheses and is still open to debate. Currently, there are four possible theories.

Starling Resistor

An increase in nasal resistance (Rn) increases the total resistance of the upper airway (R_{UA}). However, during sleep, Rn only represents a small component of $R_{UA.}$ This infers that changes in Rn result in relatively slight changes in $R_{UA.}$

In contrast to the nose, the pharynx lacks bony or cartilaginous structures to resist the negative pressure of inspiration. Hence, we can assume that the pharynx reacts like a Starling resistor. A higher preload, in terms of an increased Rn, should create a greater negative pressure that induces collapse during inspiration, causing obstruction in the weakest segment of the chain, namely the pharynx.

Investigations with unilateral nasal dressings were able to provoke some obstructive apnoeas in non-OSA patients, but the effects were not enough to induce clinically significant obstructive sleep apnoea [11–13].

The effects of temporary nasal obstruction were investigated in subjects with seasonal allergic rhinitis as a more natural, physiological model. Polysomnographic data showed significantly more obstructive breathing events during the allergic season as compared to the period outside of the allergic season [14]. However, whilst the effect was statistically significant, the change in absolute values was not strong enough to induce clinically significant OSA (apnoea index: 0.7/h versus 1.7/h).

In conclusion, if we consider the background of reported published data, we can assume that partial nasal obstruction may worsen pre-existing OSA or annoying snoring. However, based on current evidence, partial nasal obstruction is most unlikely to represent a major factor in the pathogenesis of OSA.

Increase in Oral Breathing

When the nose is completely blocked there is an automatic switch to oral breathing. It has been demonstrated that, in healthy subjects, the critical collapse pressure (Pcrit) during sleep is significantly reduced by blocking both nares with a dressing [15]. A decreased Pcrit in turn increases the likeliness of airway obstruction. In other words, increased oral breathing destabilizes the upper airway.

A similar study showed the upper airway resistance to increase significantly for oral compared with nasal breathing [16]. Two out of ten

healthy subjects developed clinically significant OSA whilst their noses were completely occluded, but the other eight subjects showed little or no change in their polysomnographic data [17]. The evidence suggests that the change from nasal to oral breathing results in clinically notable consequences a subgroup of patients (20% in the before mentioned study), whilst the majority of patients do not show any significant clinical effects. It may be surmised that this particular subgroup already had pre-existing subclinical SDB, even with an open nasal airway.

Loss of Nasal Reflexes

Trigeminally mediated nasal reflexes are crucial to maintaining nasal patency. Several studies show that the application of local anaesthesia to the nasal mucosa induces a combination of central and obstructive apnoeas [18, 19]. White et al. described transient, severe OSA after local anaesthesia in the nose in three out of ten healthy subjects, whilst seven patients did not show any change in their sleep parameters. When the local anaesthetic was replaced by a placebo, none of the subjects developed transient OSA.

In addition to this, there seems to be a subgroup of patients in whom nasal reflexes play an important role in maintaining airway patency.

Nitric Oxide (Nitrogen Monoxide: NO)

Nitric oxide (NO) is produced in a significant quantity within the nose and the paranasal sinuses. Nitric oxide reaches the lower parts of the airway with the nasal inspirational airflow [20]. NO is a bronchial dilator, thereby increasing oxygen saturation of arterial blood [21].

In addition to enhancing oxygenation, NO has several other significant effects that include maintaining muscle tone, the neuromuscular control of the pharynx, the respiratory drive and the regulation of sleep.

To our knowledge, a thorough, comprehensive analysis of the role of NO in the pathogenesis of sleep-disordered breathing does not exist.

In summary: Nasal obstruction seems to be associated with snoring and apnoeas. However, a direct correlation between nasal obstruction and the severity of SDB has not been demonstrated [22]. Currently, this implies that the nose adds very little to the severity of obstructive sleep apnoea (OSA).

Clinical Results

The following data is based on two meta-analyses (published in German and English), which form the basis of the German S2E guideline '*ENT-specific therapy of obstructive sleep apnea in adults*' [23] and the German S3 Guideline '*The diagnosis and treatment of snoring in adults*' [24]. These guidelines only include studies investigating nasal interventional treatments, and excludes interventions that do not include the nose. Whilst the chapter does not include all of the references within the guidelines, the list includes more recent, additional references.

Effects of Conservative Treatment

Medication

In a recent meta-analysis, that included 58 RCTs, medication had no significant effect on the severity of OSA in adults [25]. Altogether, a respectable 44 drugs and drug-combinations were investigated. The medications could be classified into seven pathomechanism groups, but none of these focused on nasal obstruction.

The above-mentioned German guidelines include two case–control series with only 22 patients. These two series focused on the effect of nasal decongestion (with xylometazoline) on sleep in patients with OSA. Neither study show any effect on the severity of sleep apnoea, but one report described a subjective improvement in sleep quality.

Anti-allergic Treatments

Topical nasal corticosteroids improve both subjective and objective quality of sleep in adults with allergic rhinitis. The degree of improvement significantly correlates with the width of the nasal airway. Two randomized controlled trials (RCTs) demonstrated a statistically significant reduction of the apnoea–hypopnea index (AHI) after treatment topical steroids for several weeks but use of a placebo showed no effect. However,

the effect was limited to a decrease of 10–20% of the pre-treatment baseline AHI.

In a recent Cochrane review of children with OSA [26], five RCTs were identified (three using topical steroids and two based on Montelukast). All studies could show the superiority of verum versus placebo with regard to objective polysomnographic parameters including AHI, oxygen desaturation index (ODI), respiratory arousal index and nadir oxygen saturation. Again, whilst these effects are highly significant, in most cases they are not sufficient to achieve cure of the underlying OSA. Another meta-analysis [27], including five RCTs (Montelukast with or without additional topical steroids), describes the same effects in a total of 166 children.

It is therefore clear from the present data that anti-allergic treatments can decrease the severity of OSA. However, one question that is left unanswered in our knowledge is the duration of these effects once the anti-allergic treatment is stopped.

Nasal Dilators

These can be divided into external (plasters) and internal nasal dilators (Fig. 10.1). The question as to whether nasal dilators affect the severity of OSA has been considered by probing two meta-analyses. The German guideline [23] included data of 194 patients (11 studies) under this category. The more recent meta- analysis [28] included 147 patients (9 studies). Both meta-analyses were unable to demonstrate any significant effects of nasal dilators on OSA severity.

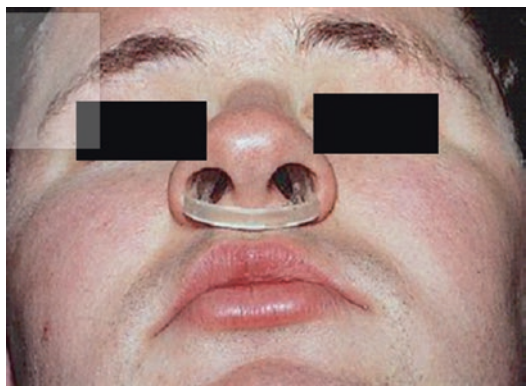

Fig. 10.1 Internal nasal dilator

However, two individual studies within the considered papers provided additional information on subjective outcome: both studies demonstrated significant benefit from the nasal dilation in reducing daytime sleepiness, although the objective AHI remained unchanged.

The effect of nasal dilators on simple snoring has also been considered. Several clinical trials reported nasal dilators having a positive effect on simple snoring [24]. The German guideline recommend a trial with a nasal dilator for the treatment of simple snoring. Trial data has shown that a positive effect from using nasal dilators during sleep can predict the likely effect from nasal surgery. In our unit, we use nasal dilators in this manner in our daily practice, with relatively good results.

Results of Surgical Intervention

Nasal Surgery for OSA

The meta-analysis conducted for the German guideline identified 28 studies, including 717 patients, having isolated nasal surgery for the treatment of OSA. All studies provided pre- and post-operative polysomnographic data. A further four articles on this topic have since been identified [29–32]. With the exception of five studies, 27 papers were case series with a low grade of evidence (Table 10.1 summarizes the data). On collating the data, the average AHI was reduced from 30.5 to 27.9 breathing events per hour of sleep. Only 7 out of 32 studies described a statistically significant decrease of the AHI. These findings are consistent with data that shows that additional nasal surgery does not improve the success rates of multi-level surgery concepts for treating OSA [33]. It is therefore clearly apparent that it is not possible to successfully treat OSA in the vast majority of patients by only performing nasal surgery. Further reviews come to the same conclusion [6, 34, 35].

In contrast, focusing on subjective outcome parameters for nasal surgery, it has a huge impact on the patient's well-being. Altogether, data from 16 studies (446 patients) concerning daytime sleepiness, as assessed by the Epworth Sleepiness

Table 10.1 Effect of isolated nasal surgery on severity of obstructive sleep apnea

Author	*N*	Follow-up	AHI pre	AHI post	*P* value	ESS pre	ESS post	*P* value	EBM
Rubin AH et al. (1983)	9	1–6	37.8	26.7	<0.05	No data	No data		4
Dayal VS and Phillipson EA (1985)	6	4–44	46.8	28.2	n.s.	No data	No data		4
Caldarelli DD et al. (1985)	23	No data	44.2	41.5	n.s.	No data	No data		4
Aubert-Tulkens G et al. (1989)	2	2–3	47.5	48.5	-	No data	No data		4
Sériès F et al. (1992)	20	2–3	39.8	36.8	n.s.	No data	No data		4
Sériès F et al. (1993)	14	2–3	17.8	16	n.s.	No data	No data		4
Utley DS et al. (1997)	4	No data	11.9	27	-	7.8	6.8	n.s.	4
Verse T et al. (1998)	2	3–4	14	57.7	-	6	12	n.s.	4
Friedman M et al. (2000)	22	>1.5	31.6	39.5	n.s.	No data	No data		4
Kalam I. (2002)	21	No data	14	11	<0.05	No data	No data		4
Verse T et al. (2002)	26	3–50	31.6	28.9	n.s.	11.9	7.7	<0.001	4
Kim ST et al. (2004)	21	1	39	29	<0.0001	No data	No data		4
Balcerzak J et al. (2004)	22	2	48.1	48.8	n.s.	No data	No data		4
Nakata S et al. (2005)	12	No data	55.9	47.8	n.s.	11.7	3.3	<0.045	4
Virkkula P et al. (2006)	40	2–6	13.6	14.9	n.s.	No data	No data		4
Koutsourelakis I et al. (2008)	27	3–4	31.5	31.5	n.s.	13.4	11.7	<0.01	2b
Li HY et al. (2008)	51	3	37.4	38.1	n.s.	10.0	8.0	<0.001	4
Nakata S et al. (2008)	49	No data	49.6	42.5	n.s.	10.6	4.5		4
Morinaga M et al. (2009)	35	No data	43.5	38.6	n.s.	No data	No data		4
Tosun F et al. (2009)	27	3	6.7	5.6	n.s.	9.4	4.1	<0.01	4
Li HY et al. (2009)	44	3	36.4	37.5	n.s.	10.6	7.6	<0.05	3b
Bican A et al. (2010)	20	3	43.1	24.6	<0.05	17.1	11.1	<0.01	4
Choi JH et al. (2011)	22	3	28.9	26.1	n.s.	8.8	6.3	<0.001	4
Sufioglu M et al. (2012)	28	3	32.5	32.4	n.s.	9.3	5.9	<0.001	4
Victores AJ and Takashima M (2012)	24	3	23.6	20.4	n.s.	12.3	6.6	<0.05	4
Hu B et al. (2013)	79	6	27.7	26.3	n.s.	No data	No data		3b
Poirier J et al. (2014)	11	6	33.2	29.4	n.s.	No data	No data		4
Yalamanchali S et al. (2014)	56	1.5	33.5	29.4	n.s.	No data	No data		4
Moxness MH et al. (2014)	59	3	18.2	16.6	n.s.	10.7	8.9	<0.001	3b
Park CY et al. (2014)	25	2	23.9	12.2	<0.05	9.7	5.8	<0.05	4
Shuaib SW et al. (2015)	26	4	24.7	16.0	<0.05	11.5	7.5	0.003	4
Xiao Y et al. (2016)	30	3	49.7	43.1	<0.05	No data	No data		3b
Total	**857**	**1–44**	**30.52**	**27.89**		**11.06**	**6.79**		**B**

AHI apnea hypopnea index, *ESS* Epworth Sleepiness scale

Scale (ESS; Table 10.1), shows that the mean ESS values decreased from 11.0 to 7.0. Similar results are shown by a meta-analysis from Li and colleagues [34].

Several other studies demonstrate significant improvements to other parameters and dimensions of quality of life. The Patient Related Outcome Measure (PROMS) tools used include the 'Snore Outcome Survey' [36], the 'SF-36' [37], the NOSE-questionnaire [38], the Pittsburgh Sleep Quality Index [32] amongst various other outcome measure tools.

In summary, isolated nasal surgery rarely completely eliminates OSA, but more recent studies show at least a limited effect on OSA severity. However, nasal surgery has various positive effects on the sleep quality. As patients with OSA often suffer from non-restorative sleep, many patients will benefit from nasal surgery. Our personal belief is that this fact is too often neglected.

Nasal Surgery and PAP

Nasal surgery has been shown to improve or even enable necessary PAP-treatment in patients with various nasal pathologies [39, 40]. Current data shows that the effective level of positive airway pressure can be successfully reduced by about 2 cm H_2O following nasal surgery (Table 10.2). However, the data sets are from non-controlled case series and should therefore be regarded as preliminary. Future scientific results may well change this assessment.

Nasal Surgery and Simple Snoring

The work on the German guideline on snoring in adults [24] identified a number of case–control series, whereby the follow-up period was generally 6 months. A retrospective study compared septoplasty and turbinoplasty with other surgical procedures for simple snoring, and found the former to be effective in significantly improving subjective snoring intensity. Prospective case–control series have also demonstrated the positive effect of septoplasty as the only procedure on subjective, but not objective, snoring intensity.

The results of the above-mentioned studies suggest that a surgical improvement in nasal airflow leads to a subjective reduction in snoring. Not surprisingly, possible side effects and complications of the procedure do not differ from nasal surgery for a primary rhinological indication.

Against the background of data, the German guideline suggests that nasal surgery should be offered to patients with objective nasal pathology combined with a subjective nasal breathing impairment. Due to a lack of evidence, a statement cannot be made on the effectiveness of nasal surgery in snorers with no subjective nasal breathing impairment but objective nasal pathologies. Maybe nasal surgery can help in these cases, too?

Table 10.2 Effect of isolated nasal surgery on effective PAP (positive airway pressure)

Autor	*N*	CPAP pre (cm H_2O)	CPAP post (cm H_2O)	*p*-Wert	EBM
Mayer-Brix J et al. (1989)	3	9.7	6	No data	4
Friedman M et al. (2000)	6	9.3	6.7	<0.05	4
Dorn M et al. (2001)	5	11.8	8.6	<0.05	4
Masdon JL et al. (2004)	35	9.7	8.9	n.s.	4
Nakata S et al. (2005)	5	16.8	12	<0.05	4
Zonato AI et al. (2006)	17	12.4	10.2	<0.001	4
Sofioglu M et al. (2012)	28	11.2	10.4	n.s.	4
Poirier J et al. (2014)	18	11.9	9.2	n.s.	4
Total	**117**	**11.2**	**9.4**		**C**

Conclusion

In the healthy awake subject, the nose contributes up to 60% of the normal airflow and plays a significant role in the total resistance of the upper airway. However, during sleep, the pharyngeal sections of the upper airway become the predominant factor. This is why the nose does not significantly change its resistance during transition from awake to sleep, whilst the resistance of the pharynx considerably increases, thus increasing the overall total airway resistance.

From the evidence base, it is not surprising that the relief of nasal obstruction hardly affects the severity of OSA. Simple snoring, however, does improve to some extent. Patients suffering from allergic or acute rhinitis should benefit from anti-allergic treatment.

In contrast to the relatively discrete objective changes in respiratory parameters, the benefit of nasal surgery regarding the quality of sleep and daytime symptoms, and hence quality of life, is impressive. These subjective improvements apply to patients with sleep disordered breathing disorders as well for sleep-healthy subjects.

In this respect, we should consider including sleep disorders caused by impaired nasal breathing into the international classification of sleep disorders. At present, this clinical scenario is not included nor mentioned.

In conclusion, treatment of nasal obstruction should be considered for patients suffering from subjectively impaired nasal breathing or those with significant daytime fatigue that cannot be successfully treated otherwise.

Working Examples of Clinical Scenarios

Case 1: Presentation and Management

A 54-year-old man with: BMI 32.5 kg m^{-2}; ESS 12; PSQI 6; AHI 28.9; supine: AHI 38.0; non-supine: AHI 20.5.

Significant nasal obstruction due to septal deviation and enlarged conchae.

Tonsillar hypertrophy (Brodsky Grade 3), long uvula, webbing 8 mm (Fig. 10.2).

Small lingual tonsils (Friedman 1). Regular epiglottis (Fig. 10.3).

Non-compliant to PAP treatment.

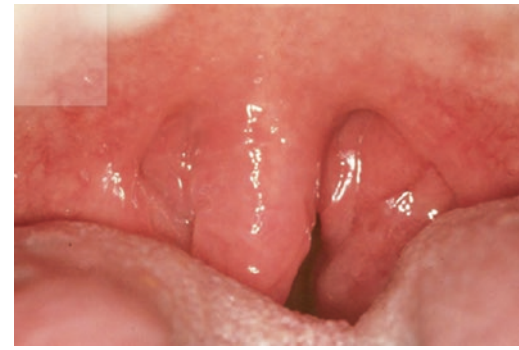

Fig. 10.2 Case 1. Enlarged uvula and tonsillar hypertrophy (Brodsky Grade 3)

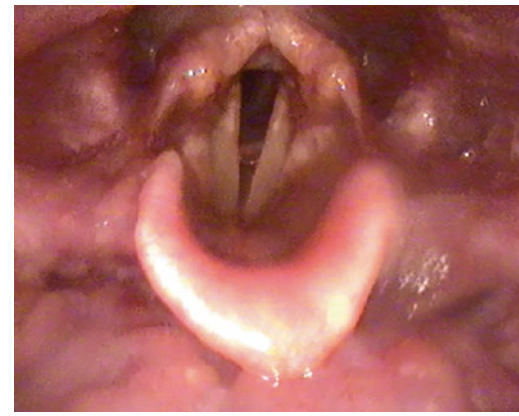

Fig. 10.3 Case 1. Small lingual tonsils (Friedman 1). Regular epiglottis

Factors to consider:

The options

- The nasal obstruction can be resolved by nasal septoplasty and reduction of inferior turbinates.
- The pharyngeal obstruction can be resolved by uvulopalatopharyngoplasty in combination with tonsillectomy. We usually perform radiofrequency treatment of the base of tongue in addition, as this combination does not increase post-operative morbidity and is likely to have an additional positive effect on the clinical outcome of OSA.

The management plans

- We usually avoid performing nasal and pharyngeal surgery at the same time. Combining

both operations would incur much greater post-operative risk and morbidity.
- We would recommend performing the nasal surgery first.
- Following nasal surgery, we offer a new trial with PAP. Effective and successful nasal surgery is likely to improve both the effectiveness and tolerance of PAP.
- Should PAP still be problematic for the patient or something that they would prefer not to use, we would then recommend pharyngeal surgery as described above.
- Nasal surgery can substantially improve sleep quality and daytime symptoms. This may lead to difficulty in convincing some patients that they still have sleep apnoea that requires interventional treatment. We therefore recommend further sleep studies in such patients.

Case 2: Presentation and Management

A 48-year-old woman: BMI 35.5 kg m^{-2}; ESS 7; PSQI 4.

She had severe septal deviation and chronic rhinosinusitis with large nasal polyps.

She was successfully treated with PAP.

Sinonasal surgery was therefore not recommended.

Factors to consider:

- The combination of OSA, general anaesthesia and nasal surgery is associated with increased perioperative risk and is only recommended when necessary.
- Sinonasal surgery in patients with moderate to severe OSA is always preformed as an inpatient.
- The anaesthesiologist should be experienced and informed about the presence of OSA prior to surgery.
- We try to manage these patients without nasal dressings wherever possible.

Post-operative care

- Postoperatively, patients with moderate to severe OSA (AHI >20) are monitored for 4 h in the recovery room. Complications will typically occur within the very first few hours following extubation.
- Patients with complications are monitored overnight in an intermediate care unit.
- Patients are otherwise managed overnight on a regular ward.

Key Learning Points

- Nasal obstruction seems to be associated with snoring and apnoeas.
- Evidence suggests that the nose adds very little to the severity of obstructive sleep apnoea (OSA).
- Medication has no identifiable effect on the severity of sleep apnoea, but subjective improvement in sleep quality may occur.
- Anti-allergic treatments can decrease the severity of OSA.
- Meta-analyses are unable to demonstrate any significant effect from nasal dilators on OSA severity.
- Nasal dilators have a positive effect on simple snoring.
- OSA cannot be successfully treated in the vast majority of patients by only performing nasal surgery.
- Nasal surgery has various positive effects on the sleep quality.
- Nasal surgery has been shown to improve or even enable necessary PAP treatment in patients with various nasal pathologies.
- Septoplasty as the only procedure is effective on subjective, but not objective, snoring intensity.

Conflict of Interest T. Verse and S. Müller do not have any conflicts of interest.

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The Nose and the Effects of SARS-CoV-2 Pandemic

11

Carl Philpott

Introduction

The severe acute respiratory syndrome coronavirus 2 or SARS-CoV-2 (CoV-2) is the coronavirus strain that surfaced in China at the end of 2019, hence the name COVID-19 (Coronavirus Disease 2019). However, it was in 2020 that COVID-19 became a global pandemic and although this was declared by the World Health Organization (WHO) on 12 March 2020, it was not until 1 month later on 17 April that the WHO declared recent loss of smell and/or taste as an official symptom of the infection in addition to the two previously recognised symptoms of cough and fever. In the United States, the Centre for Disease Control and Prevention had already taken this step, yet in the United Kingdom, Public Health England waited until 19 May to make the same declaration.

Why did this declaration matter? Aside from the obvious opportunity to appropriately isolate those infected with COVID-19, it is also raised an awareness that in some cases, loss of smell was in fact the only symptom of the infection and furthermore in some people, virus was being shed from the nose in otherwise asymptomatic individuals.

Olfactory dysfunction has long been recognised as a sequela of viral upper respiratory tract infections including those caused by members of the coronavirus family, but the pattern of rhinological symptoms that include olfactory dysfunction have been observed to differ in COVID-19 compared to previous respiratory virus manifestations.

This chapter will explore the current evidence behind the purported pathophysiological mechanisms that have seen two-thirds of COVID-19 infections involve olfactory dysfunction and left an estimated 8.2 million people globally with persistent olfactory dysfunction (as of 12 April 2021) (Fig. 11.1).

C. Philpott (✉)
The Norfolk Smell & Taste Clinic, Norfolk & Waveney ENT Service, Norwich, UK

Norwich Medical School, University of East Anglia, Norwich, UK
e-mail: C.Philpott@uea.ac.uk

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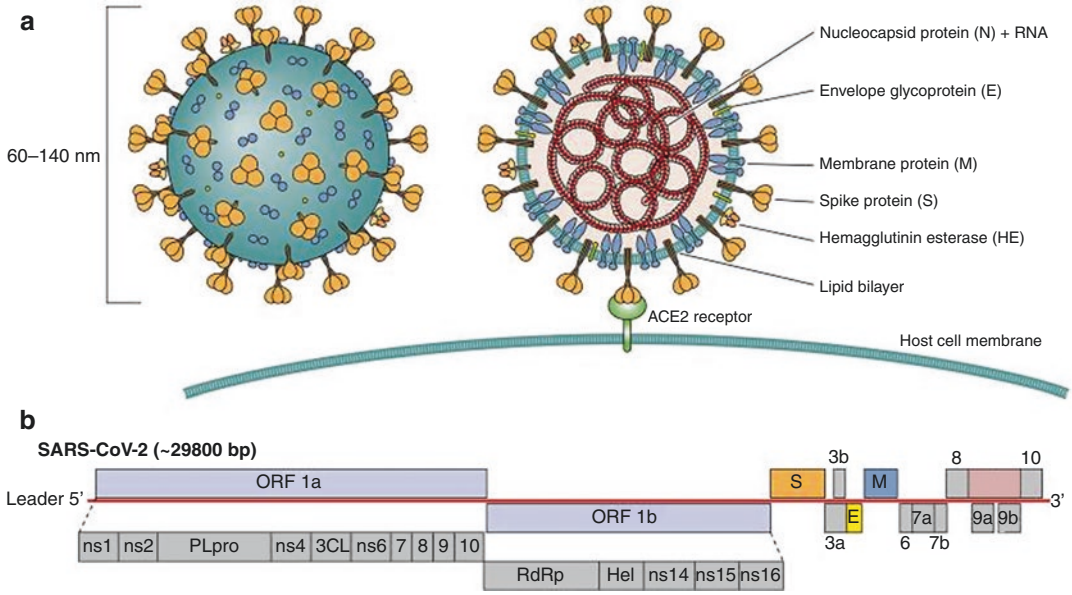

Fig. 11.1 Physical and genome structure of SARS-CoV-2. (**a**) Diagram of the SARS-CoV-2 virion. (**b**) Genome organisation and proteins with known or unknown functions [1]

Evidence from Coronavirus and SARS-CoV-1 (Before the Pandemic)

SARS-CoV-2 is a member of the Coronaviridae family of enveloped, single-stranded, positive-sense RNA viruses and sits within the Betacoronavirus genus along with the original SARS and Middle Eastern Respiratory Syndrome Coronavirus (MERS-CoV) [2]. Typically, these viruses produce upper respiratory tract symptoms much as any other common cold virus would. It is the Spike protein (S glycoprotein) that is present on the viral surface that facilitates entry into respiratory tract cells. The virus infects these cells by changes to its shape configuration as it interacts with the ACE2 protein on the target cell surface; cleavage of the S-protein by the protease TMPRSS2 and possibly other proteases will enable this event to occur. The target cells are principally the goblet and ciliated cells of the nasal cavities and type II pneumocytes in the lower airways.

It was in 2002 that the coronavirus last caused an epidemic when SARS-CoV emerged in southern China. The result was that over 8000 people in 26 countries became infected with an estimated 800 deaths. On this occasion the virus was believed to have originated in bats and transferred to humans via mammals of the Paguma family known as palm civets. The result in humans was a viral pneumonia leading to respiratory distress, but on this occasion, as was the case with the MERS epidemic, olfactory dysfunction was rarely reported, suggesting that both viruses did not elicit the same affinity for the nose as has been seen with SARS-CoV-2 [3].

However, the lack of olfactory dysfunction in SARS-CoV-1 and MERS is not the whole story, as evidence had also emerged of the coronavirus' ability to be neuroinvasive [4], thus suggesting the potential for it to wreak its havoc in a different manner than just local inflammation in the nose.

The Emergence of SARS-CoV-2

As the world watched on, China suffered an outbreak of SARS-CoV-2 as it emerged from the Wuhan province in December of 2019. By March 2020, it had engulfed the globe and had resulted

in a declaration of a pandemic by the World Health Organization. Whilst the early reports of symptoms within the Chinese outbreak showed that smell and taste loss were only present in about 5% of the population, data emerging from Italy and Iran was clearly showing a different picture in the European populations. It was the United States through the Centre for Disease Control (CDC) that first declared anosmia as a diagnostic symptom of the virus, with WHO soon following suit, but in the United Kingdom, it was not until May 2020 that the government formally recognised it. By then many ENT specialists had seen the clear emergence of olfactory dysfunction, namely in the form of sudden onset anosmia. Data quickly accumulated in many countries and in European populations, a prevalence of approximately 60% was emerging [5] and with the formation of the Global Consortium for Chemosensory Research, international data demonstrated that smell loss was occurring early in the pandemic without significant correlation to other rhinological symptoms [6]. In some cases, it became apparent that anosmia was in fact the only symptom in otherwise asymptomatic individuals [7]. Although some reports of localised olfactory cleft oedema emerged, questions were raised as to what the exact mechanism of effect of SARS-CoV-2 was in the nose, especially with the observation that 85–90% of those affected by the sudden onset of anosmia were regaining their sense of smell with 3–4 weeks of onset.

Pathophysiology in SARS-CoV-2

As mentioned above, it is the interaction between the spike (S) protein of SARS-CoV-2 and the angiotensin-converting enzyme 2 (ACE2) protein on target respiratory cells that allow the virus to invade the cell through cleavage of the S protein. The ACE2 protein is commonly expressed in the respiratory tract and predisposes the cells to viral invasion [8]. However, within the olfactory epithelium, it is the sustentacular cells that appear to be most expressive of this protein. So, what does this mean for the mechanism of inflammation? (Fig. 11.2).

Viral Affinity for the Nose

In common with many respiratory virus, SARS-CoV-2 has an affinity for the nose. Studies that have analysed viral load in those with COVID-19 infection have shown evidence of the highest rate of viral replication and shedding occurring in the nasal cavity with a much earlier peak of detectable virus (at 4–10 days after infection) as compared to a peak at 15 days after infection in the lower respiratory tract [10]. This research by Lim et al. also using viral RNA measurements, showed that the time taken for the virus to clear the nose was significantly longer (median 18 days) in symptomatic patients compared to a median of 13 days in asymptomatic patients. This was further enhanced by the number of symptoms—the more symptoms they had the longer the time it took to clear the virus. In sputum samples, viral levels appear to rapidly decrease after the initial peak and Wang et al. showed a significantly higher detection rate of SARS-CoV-2 nuclei acid in nasal swabs compared to oropharyngeal swabs [11], with a longer median duration of detectable viral nucleic acid from nasal swabs (25 versus 20 days).

Within the nasal cavity, the gatekeeper to SARS-CoV-2 entry, the ACE2 receptors are expressed across the mucosa [12] but not uniformly so, with higher expression in the dorsal region and lower in the ventral region as demonstrated by Brann et al. [8]. With over 90% of viral transmission for COVID-19 being due to inhalation of aerosol-generated particles being transmitted via the nasal mucosa (including via the nasolacrimal apparatus), the nose heralds a potent site for viral entry through the ACE2 receptors [13]. So, the nose acts as a potent receptacle and viral generator before it spreads to the lower respiratory tract, and it is therefore not surprising that the olfactory system is highly prone to becoming embroiled in the infective process.

Neuroinvasion

A German post-mortem study has shown some key findings [14]; most subjects were found to

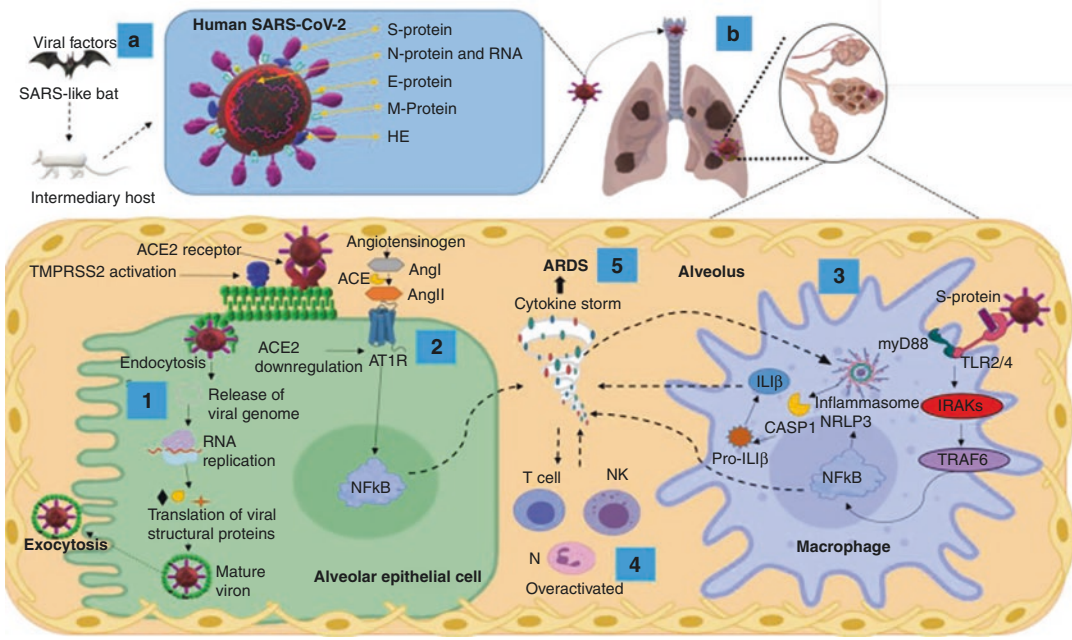

Fig. 11.2 Pathological mechanisms of SARS-CoV-2 in the pulmonary alveolus. (**a**) Mode of transmission and main structural proteins of SARS-CoV-2. (**b**) Mechanisms of SARS-CoV-2 infection and pulmonary inflammatory immune response. *ACE2* Angiotensin-converting enzyme 2, *Ang* Angiotensin, *ARDS* Acute respiratory distress syndrome, *AT1R* Angiotensin II type I receptor, *CASP1* Caspase 1, *E protein* Envelope small membrane protein, *HE* Hemagglutinin esterase, *IL1β* Interleukin 1 beta, *IRAKs* Interleukin-1 receptor-associated kinases, *M protein* Membrane protein, *MyD88* Myeloid differentiation primary response 88, *N protein* Nucleoprotein, *N* Neutrophils, *NF-κB* Nuclear factor Kappa B, *NK* Natural killer cells, *NLRP3* Nucleotide-binding domain-, leucine-rich repeat-containing receptor, pyrin domain-containing 3, *RNA* Ribonucleic acid, *S protein* Spike protein, *TMPRSS2* Transmembrane serine protease 2, *TRAF6* Tumour necrosis factor receptor-associated factor 6 [9]

have widespread astrogliosis in all assessed regions, with an inflammatory response characterised by cytotoxic T lymphocytes being most pronounced in the brainstem, cerebellum and meninges. Most notably, SARS-CoV-2 was detected in half of the brains of the subjects examined including the cranial nerves and brainstem. Furthermore, the presence of SARS-CoV-2 did not correlate with the severity of neuropathological changes. The limitation of this study was the small sample of 43 subjects and the limited clinical data for correlation. Nonetheless, we can see evidence that SARS-CoV-2 has made it into the central nervous system, setting up one theory for a mechanism of action in COVID-19-related olfactory (and gustatory) dysfunction. Furthermore, the virus may possibly potentiate the underlying pathophysiology contributing to neurogenerative diseases as suggested in another post-mortem study [15].

However, in a detailed review of mechanisms of anosmia during COVID-19 by Butowt and Bartheld [16], four key mechanisms for entry of SARS-CoV-2 into the central nervous system were proposed (Fig. 11.3):

1. *through the olfactory neurons.*
2. *through the nervus terminalis (cranial nerve 0)*: Support for the nervus terminalis route is embedded in the theory that CN 0 connects to the hypothalamus and that there was evidence of SARS-CoV-1 accumulation in the hypothalamus. Of course, this is somewhat controversial given the CN 0 is considered a vestigial pathway in post-foetal life. In lower mammals, CN 0 is considered to be part of the vomeronasal organ, connected to accessory olfactory bulbs and involved in pheromone signalling.
3. *through the CSF*: CSF drainage through lymphatics in the cribriform plate give some cre-

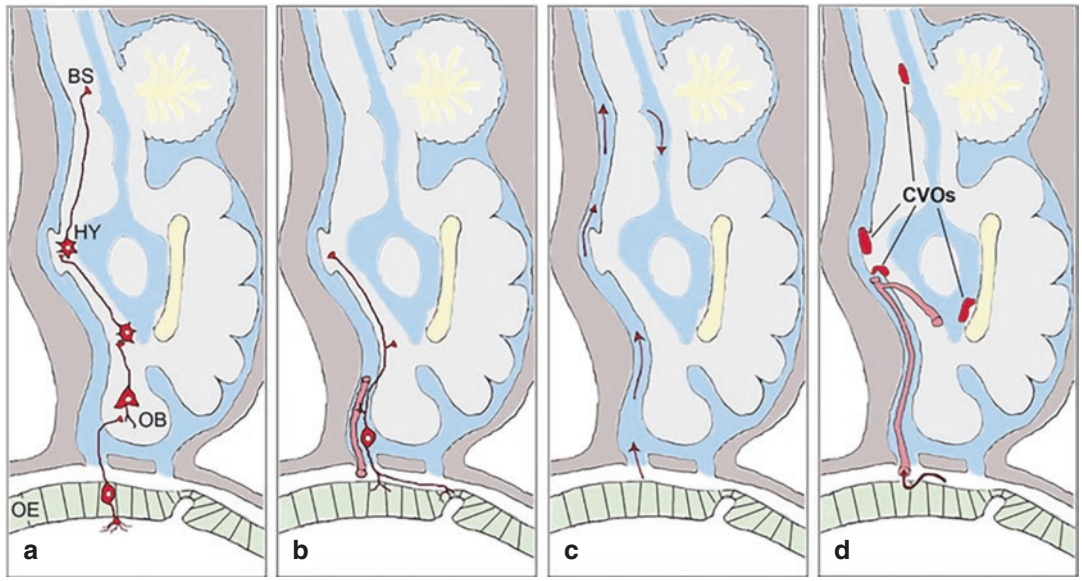

Fig. 11.3 Four potential routes of SARS-CoV-2 virus from the nose to the brain through the cribriform plate: (**a**) olfactory circuits, (**b**) nervus terminalis, (**c**) cerebrospinal fluid, (**d**) vasculature. *BS* Brainstem, *CVOs* Circumventricular organs, *HY* Hypothalamus, *OB* Olfactory bulb, *OE* Olfactory epithelium [16]

dence to this theory but with the direction of CSF flow, this seems less likely.

4. *through a vascular route*: The vascular route is supported by evidence of extracellular bulk flow within cerebral vessel perivascular spaces potentially aided viral transportation [17]. Another group have additionally suggested that as vascular pericytes in the olfactory pathways express ACE2, they provide a further pathway for neuroinvasion of SARS-CoV-2.

Olfactory Epithelium

The above mechanisms suggest a sobering potential for SARS-CoV-2 to access all areas in the central nervous system, but perhaps for many, the problem is confined to the olfactory epithelium?

A leading theory on the key mechanism of action has been that the sustentacular cells, horizontal basal cells, and Bowman's gland cells in the olfactory epithelium express genes that code for both the TMPRSS2 protease and the ACE2 receptor, based on evidence produced by several research groups as summarised by Butowt and Bartheld [16]. This access portal for the virus into these cells may lead to a disruption of the turnover of olfactory receptor neurons (ORNs) as well as their functionality and thus result in the symptom of anosmia.

This viral-induced inflammatory event in the epithelial layer will create an architectural disturbance and may explain why there have been some case reports of imaging showing localised olfactory cleft oedema; it is perhaps the rapidity of the infection at this site that may result in the sudden onset of the anosmia perceived by those affected and also account for why 85–90% experience spontaneous resolution (Fig. 11.4).

Recent cellular research by Brann et al. has analysed data from human and mouse samples to examine the evidence for SARS-CoV-2 in the olfactory epithelial layer and olfactory bulbs [8]. Their work demonstrated that genetic expression of ACE2 and TMPRSS2 in human sustentacular cells was comparable to expression in the lower respiratory tract. In addition, the ORNs and olfactory bulbs (OBs) failed to demonstrate any expression of ACE2, thus lending weight to the theory that it is the non-sensory cells that are becoming infected.

The authors also broke this down into four mechanisms by which the SARS-CoV-2 infection results in olfactory dysfunction:

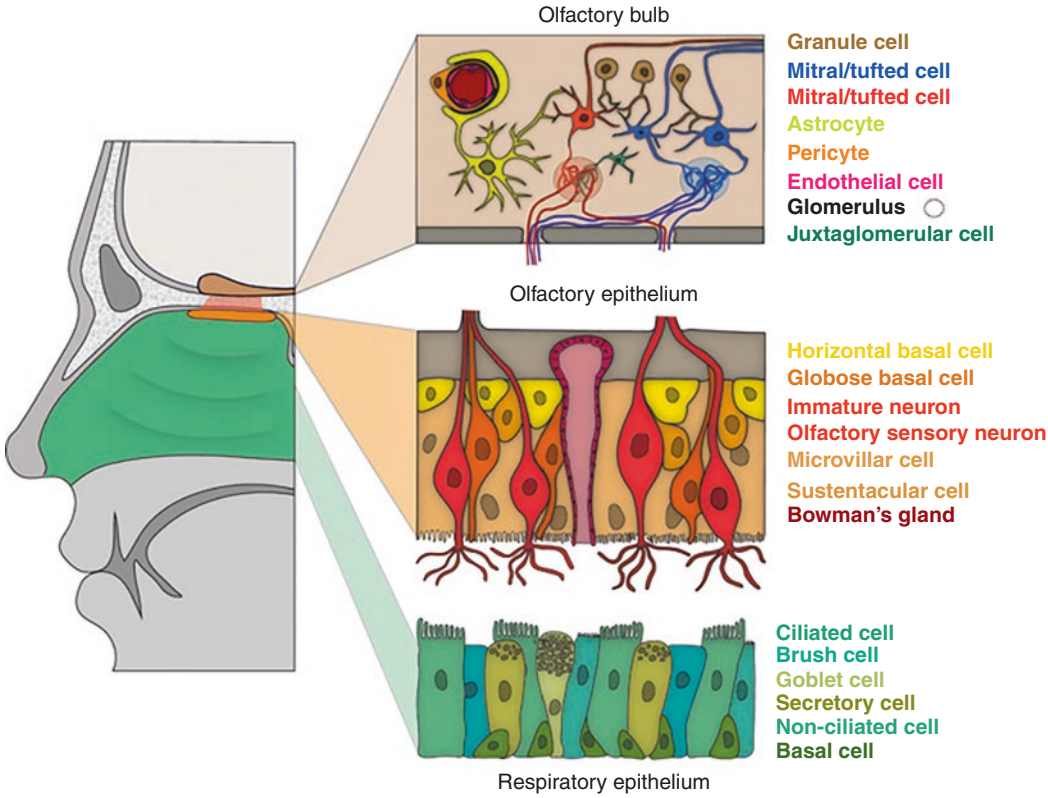

Fig. 11.4 Relevant cell layers in the olfactory neuroepithelium and adjacent respiratory mucosa

(a) Cytokine release in these supporting cells may lead to a conductive block through inflammation or may even change the function of the OBs and ORNs;
(b) given the nutrient function of the supporting cells, there may be an impact on action potential generation in the ORNs;
(c) the mouse model supports the potential for death of the ORNs secondary to the damaged supporting cells;
(d) OB function may be affected by perfusion and inflammatory disruption caused by vascular damage.

Cytokine storms were highlighted as a key systemic response to coronavirus infection with the 'inflammatory soup' considered to include IL-2, IL-7, IL-10, TNF-α, MCP1, G-CSF, MIP1α, CXCL10, CRP, D-dimers and ferritin [9].

The sustentacular cell damage theory for transient anosmia has been given support in an animal model where infection of hamster olfactory epithelium with SARS-CoV-2 led to massive infiltration of immune cells. This immune cell infiltration may have contributed to the desquamation of the epithelial layer; partial restoration of the latter cell layer was found within 14 days of infection [18]. The other consideration is that due to the role of sustentacular cells in the clearance of odour binding proteins, their lack of function will lead to threshold impairment until they are regenerated (Fig. 11.5).

Previous research suggests some local variation in ORN classes, which can affect odour hedonics, thus what may be affected by this pattern of sustentacular cell disruption is a degree of odour processing and perception with evidence to support infected individuals finding certain odours less unpleasant even when apparently asymptomatic [19] (**N.B.**: Odour hedonics is distinct from parosmia, which is discussed below).

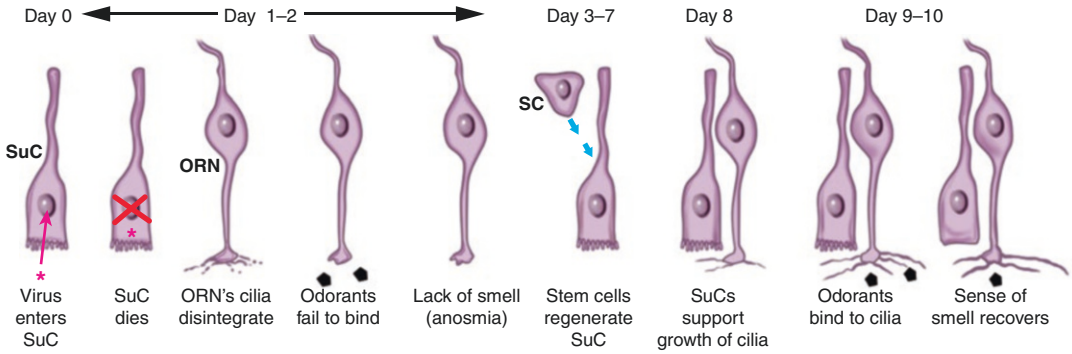

Fig. 11.5 Time course of cellular events that may cause loss of smell and its recovery in COVID-19 patients. Day 0 = day of infection. *SuC* Sustentacular cell, *ORN* Olfactory receptor neuron, *SC* Stem cell [16]

Parosmia

Beyond the initial problem of anosmia, there is then the clinical spectre of parosmia, which often appears a few months later. Parosmia is a common feature of post-infectious olfactory dysfunction, but do we need to question the mechanism of action further in COVID-19? A recent review by Lee et al. proposed that viruses implicated in olfactory dysfunction may target synaptic plasticity and thus affect interneuronal communications [20]. They went on further to propose a "Two-Hit Hypothesis" that in order for persistent olfactory dysfunction to occur, the initial viral insult must indeed be accompanied by this loss of 'synaptic plasticity', citing examples from models in influenza A and respiratory syncytial virus infections and their impact in the central nervous system.

Previous models of parosmia have considered peripheral and central theories. The peripheral theories are favoured by many, as resulting from knockout of individual ORN function and thus disrupting pattern recognition at the level of the OB. This may be further exacerbated or perhaps alternatively explained by incorrect rewiring between the olfactory epithelium and the OB [21].

The insult on synaptic plasticity has fitted previously with the observation that those affected by post-viral olfactory dysfunction are typically over the age of 40 years. What has been very notable in COVID-19 is that the mean age of those affected has been significantly younger [22], and in fact parosmia is now being experienced by teenagers.

SARS-CoV-2 and Taste

Whilst gustation (taste) is not a nasal function, it has a common association with smell and needs discussion here. One of the biggest problems when discussing the issue of "taste" is the general understanding of what true taste really means and how it is used culturally in the English language. Taste buds in glossal and non-glossal locations detect the distinct modalities of salt, sweet, sour, bitter and umami, with some support for the notion that receptors may exist for 'metallic', 'fat' and 'water'. In contrast, retronasal olfaction allows us to detect the odour of food when inside the mouth. Due to the simultaneous nature of these experiences, people find it difficult to separate gustatory sensations from olfactory ones, which is not helped by the colloquial suggestion that we taste food—the French word of degustation is perhaps a little more distinct; other cultures have many more words to apply.

It has long been witnessed by ENT specialists that patients will complain of smell and taste disturbances together; however, specialist smell and taste clinic data show that true gustatory dysfunction typically only accounts for 1% of all presentations. Furthermore, the correlation between subjective assessment of the chemical senses and psychophysical testing is poor.

Set against this, it became evident that complaints of taste loss and disturbance were a feature of COVID-19. The work of the Global Consortium for Chemosensory Research

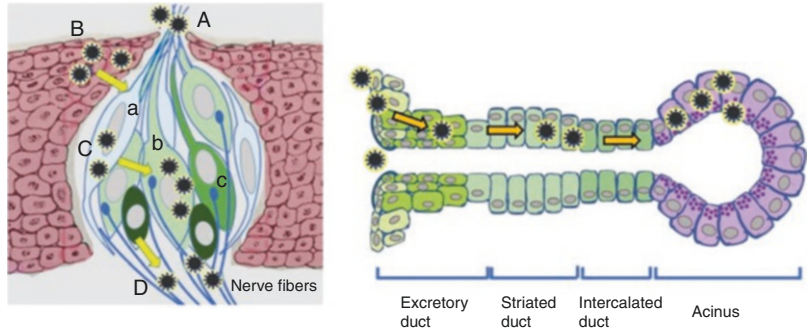

Fig. 11.6 Hypothetical SARS-CoV-2 cell entry mechanism in the taste bud and salivary gland. Taste bud (left). (A) Microvilli of taste sensory cells allow SARS-CoV-2 entry into the cells. (B) Non-ACE2-expressing gustatory cells are infected through ACE2-positive neighbouring cells. (C) SARS-CoV-2 directly invades taste receptor cells via cell surface ACE2 and TMPRSS2 expression. (D) SARS-CoV-2 neuroinvasion can occur at the neural–mucosal interface by transmucosal entry via regional nervous structures. (a) Type I cell, (b) Type II cell, (c) Type III cell, (d) basal cell. Salivary gland (right). SARS-CoV-2 initially enters epithelial cells close to the salivary duct orifice and/or lining salivary gland ducts through ACE2 binding. TMPRSS2 and Furin are also expressed in salivary gland ducts. Secretary cells in acinus are eventually infected with the virus [25]

collected subjective responses from over 4000 international respondents and showed evidence of an overall reduced ability to taste to a magnitude of 69 points (scale of 0–100) with disturbances in salt, sweet and bitter sensations the most frequently reported [6]. But has this been a truly gustatory phenomenon or simply an objective perception?

In a small study published by Huart et al. [23], a comparison was made between olfactory and gustatory function in COVID-19 patients, those with non-COVID viral chemosensory disturbances (post-viral group (PVG)) and healthy controls. The study showed that gustatory functions, most notably for sweet and bitter tastes, were significantly worse in COVID-19 patients compared to PVG cases and controls, suggesting more than just a retronasal olfactory dysfunction. How might the pathophysiology of this phenomenon work in COVID-19? Taste impairment may occur at a peripheral level through alteration of normal taste transduction and cell turnover in taste buds; at least this has been seen in a mouse model [24]. The aforementioned cytokine storm may also lead to induction of damage by pro-inflammatory cytokines resulting in altered transduction. As the receptors for bitter and sweet are G-protein coupled receptors (GPCRs) and are known to play an important role in innate immunity, it may be possible that they either modify the expression of function of these receptors or predispose to COVID-19 infection, with GPCRs as the common portal for both olfactory and gustatory dysfunction. ACE2 is also expressed in the taste buds and oral mucosa and much like the sustentacular cell theory for olfaction, it has been suggested that ACE2-expressing squamous epithelium on the tongue may enable viral access, which then migrates to the taste buds as the next step of invasion [25]. As for olfaction, the potential for CNS invasion may also lead to viral injury to the nucleus solitarius and thus affecting taste centrally [26] (Fig. 11.6).

Clinical Applications

As SARS-CoV-2 is a new virus to contend with, most of the existing evidence for treatment is based on the wider knowledge base for post-infectious olfactory dysfunction. At the opening of 2021, the Clinical Olfactory Working Group published a review of the literature on treatment options and their collective consensus on which treatments they utilise in practice [27]. The review identified 40 relevant citations including 11 randomised controlled trials. Overall, the consensus view was an overwhelming recommendation for

olfactory training with some group members being in favour of vitamin A drops; the British Rhinological Society also supported the view that olfactory training is the key recommendation at this stage [28]; a trial on Vitamin A drops has recently commenced (https://rhinology-group.uea.ac.uk/apollo-trial). A further article by the group ruled against using systemic corticosteroids [29]. The Cochrane ENT group are currently monitoring the emerging evidence through a living review, but substantial evidence is yet to emerge [30]. With parosmia being an increasingly common phenomenon in COVID-19-related PIOD (post-infection olfactory dysfunction), there is certainly a need to see more clinical trials being undertaken; for now treatments for parosmia specifically will be limited to therapeutic agents such as gabapentin [31], albeit that evidence for PIOD-related parosmia is that it will improve with olfactory training and is likely to be self-limiting [32, 33]. So far, it appears that about 10% of those who suffer chemosensory disturbances at the acute stage of infection have persistent symptoms beyond 4 weeks, but we do not yet know the long-term chances of spontaneous recovery; only that prior knowledge of post-infectious olfactory dysfunction suggests that one in three will improve over 3 years [34]. As new variants emerge, this picture may change and we have already seen that the Delta variant causes less olfactory disturbances.

The clinical approach to these patients should explore the timing of onset including proximity to any relevant COVID testing and consider specific questions about the exact nature of what stimuli are missing. Many patients with COVID-19-related chemosensory loss describe a rapid onset. They may then describe a period of apparent recovery before they start to experience parosmia. Careful questioning is needed to ascertain the details of any distortions present and the relationship of those to the presence or absence of any odour stimulus, thus discerning parosmia from phantosmia—start with open questions and then move to closed questions for clarity. On occasion, some patients may describe the parosmia as a heightened sensitivity to an odour source because of the revulsion it induces; this is clarified by the undertaking of psychophysical testing to determine their overall olfactory performance.

In general, patients find it difficult to separate retronasal olfaction that contributes hugely to flavour perception, from true gustatory function such as the detection of the salt, sweet, sour, bitter and umami components of food and careful direct questions are needed to elicit this and to be certain which component is being considered. Ultimately, clinical assessment after the acute phase of infection is needed using standardised psychophysical tests such as the Sniffin' Sticks or UPSIT for olfaction and taste strips for gustation, as the correlation between subjective assessment and pseudo-objective assessment with such tests is generally poor [35].

Conclusion

This chapter has outlined various potential mechanisms for chemosensory dysfunction in COVID-19-affected individuals. It is clearly an evolving area, where new information on the epidemiology and pathophysiology of SARS-CoV-2 is continually forthcoming. It is likely that our outlook on this virus and how to manage its chemosensory consequences will change over time but may hopefully provide an impetus to develop new treatments for post-infectious olfactory dysfunction going forwards.

Key Learning Points

- Although more is to be understood about the pathophysiology of chemosensory dysfunction following COVID-19 infection, it is likely that the process does not involve direct invasion of olfactory sensory neurones.
- It is possible that COVID-19 has a direct impact on true gustatory function but the evidence is uncertain.
- Parosmia is a key symptom experienced by half of those with persistence of olfactory dysfunction at 6 months.
- Smell training is the key therapeutic strategy until further trials are conducted for treatments.

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Section II

The Assessment of the Nose and Sinuses

Clinical Assessment of the Nose and Olfaction

12

Nirmal Kumar and John Rocke

Clinical History

Presenting Complaint

There are five predominant rhinological-presenting complaints that are often associated but can, on occasion, appear in isolation: nasal obstruction or congestion, epistaxis, rhinorrhoea, facial pain and olfactory dysfunction.

Nasal Obstruction

Nasal obstruction may be described in a variety of ways by the patient. They may complain of stuffiness, congestion, partial blockage or complete obstruction and these symptoms may be permanent, fluctuating or progressive.

In patients presenting with nasal obstruction, it is pertinent to determine laterality, timing and associated precipitating features. Whilst unilateral and bilateral nasal obstruction suggest an anatomical or pathological obstruction to airflow, alternating obstruction often indicates inflammation of the sinonasal mucosa however understanding of the normal nasal cycle needs to be appreciated in such patients. Seasonal changes and precipitating factors such as exposure to smoke or pets suggest an association with environmental allergens.

Epistaxis

Epistaxis predominantly presents in the acute or semi-urgent setting. The location of bleeding right/left and anterior/posterior is key in the subsequent management of the condition. Potential precipitants such as digital trauma, recent rhinitis, anticoagulant prescriptions and/or intranasal drug use should be explored.

Rhinorrhoea

Rhinorrhoea or postnasal drip is predominantly made up of water with a small amount of mucin. Symptoms from nasal discharge occur when mucus is produced in excessive amounts or the quality changes to become too viscous or glue-like. It is helpful to ascertain both the consistency and colour of mucus discharge: green-yellow mucus occurs with mucus stasis or infection. Mucus stasis leads to crusts within the nasal cavity.

Discharge may be unilateral or bilateral according to the underlying cause. Acute unilateral discharge in children is commonly a feature of a nasal foreign body.

N. Kumar (✉)
ENT Department, Royal Albert Edward Infirmary, Wigan, Wigan, UK

Wrightington, Wigan & Leigh Teaching NHS FT, Wigan, UK
e-mail: nirmalkumar@doctors.org.uk

J. Rocke
ENT Department, Royal Albert Edward Infirmary, Wigan, UK

Wrightington, Wigan & Leigh Teaching NHS Foundation Trust, Wigan, UK

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Facial Pain

Facial pain possesses numerous aetiologies that are not sinogenic in origin. As such it is important to adopt a holistic approach to patients primarily presenting with this symptom. In acute rhinosinusitis the associated pain, if it is present, is often unilateral, severe and associated with a fever, whereas chronic rhinosinusitis is not frequently associated with facial pain.

Olfactory Dysfunction

Olfactory dysfunction is a broad term that includes anosmia (complete loss of smell), hyposmia (reduced olfactory function), parosmia (qualitative dysfunction in the interpretation of an odour) and phantosmia (sensation of smell without stimuli).

This symptom is often categorised as either conductive (blockage or obstruction of odorant transmission to olfactory epithelium), sensorineural (damage or loss of olfactory neuroepithelium) or central (loss of the central olfactory-processing pathways).

Change in sense of smell is often associated with an alteration in flavour perception. When food enters the oral cavity, the odours are sensed via retronasal olfaction in the nose, which provides depth to its flavour. If there is a defect in the pathway preventing the odours from reaching the olfactory-processing centres, then patients will often complain in changes in flavour. Strictly speaking, change in flavour perception, through retronasal olfaction, is a separate entity to change in taste (ageusia), which is governed by the tongue (sweet, sour, bitter, salty, umami) via the facial and glossopharyngeal nerves.

Triggering Factors

It is important to cover alleviating and precipitating factors when discussing rhinological complaints. The nose and paranasal sinuses are exposed to environmental and occupational irritants, which can trigger or worsen rhinitis or nasal inflammation. Associated allergic symptoms, such as sneezing, epiphora and a seasonal variation may point towards an allergic aetiology. Relationships with weather changes, viral infections, food and drink (especially hot or spicy foods and alcohol), hormonal changes (during menstruation or pregnancy) or gastro-oesophageal reflux disease can also point towards triggers for a non-allergic rhinitis.

Past Medical History

There are numerous associated medical conditions that can exhibit rhinological sequelae and as such it is important to explore these conditions when assessing patients in clinic. Table 12.1 sets out some of the most common systemic medical conditions with their associated rhinological complaints and the pathophysiological pathways behind them.

It is clear from the table that patients often present with a constellation of symptoms which highlights the importance of understanding of other aspects of the disease assessment including timing, associated symptoms and the subsequent examination and investigations [1].

Social History

Due to the inhalational nature of both legal and illegal social drug, it is important to tactfully approach these areas with patients as it often may be the precipitant or significant contributor to their presentation.

Smoking

Significant negative associations have been demonstrated between smoking (pack years) and olfactory function when adjusted for the patients age. There have also been links demonstrated in older age groups (>40 years old), with smoking and CRS.

Pathological changes on histology have been demonstrated on biopsies of the nasal mucosa including loss of cilia, columnar cells, mucosal oedema, reduced goblet cells, hyperplasia of seromucous acini and vascular congestion. However, stopping smoking has been proven to reverse these changes and as such appropriate advice regarding cessation services, including counselling and pharmacological products.

Table 12.1 Presenting features and pathophysiology of associated medical conditions

Condition	Presenting features	Pathophysiology
Respiratory		
Asthma	– Nasal polyps: part of Samter's triad or Aspirin Exacerbated Respiratory Disease (aspirin hypersensitivity, nasal polyposis and asthma)	– Associated with dysregulation of type 2 inflammation (usually functions to defend the body against helminths)
Cystic fibrosis	– Nasal obstruction (80%) – Rhinorrhoea (>50%) – Olfactory dysfunction (25%) – Nasal polyps (7–48%) – Protrusion of lateral nasal wall	– Mutations of the cystic fibrosis transmembrane conductance regulator (CFTR), which leads to viscous secretions of the upper and lower airways
Primary ciliary dyskinesia	– Nasal obstruction (50%) often seen in post-natal period – Polypoidal disease (up to 100%) – Mucopurulent rhinorrhoea	– Several largely autosomal recessive conditions with more than 20 genes described – Abnormality of beating respiratory cilia leading to impaired mucociliary clearance
Mucosal		
Hereditary haemorrhagic telangiectasia (HHT)	– Up to 98% of patients will experience epistaxis – Causes mucocutaneous telangiectasia	– Autosomal dominant condition with variable penetrance – Most common defect in ENG and ACVRL 1 genes
Rheumatological		
Eosinophilic granulomatous polyangiitis (eGPA)	– Often nonspecific; epistaxis, obstruction, crusting, olfactory impairment, rhinorrhoea – Associated asthma	– Pathophysiology of allergic angiitis and granulomatosis unknown, has allergic, eosinophilic and vasculitic phases – Fluctuating (C-) ANCA with predominant (PR)-3 specificity
Granulomatosis with polyangiitis (GPA)	– Nasal mucosa involved in early stage of disease – Nasal obstruction (42%) – Rhinorrhoea (37%) – Olfactory dysfunction (13%)	– Multisystem disease with unknown pathophysiology
Relapsing polychondritis	– External deformities, i.e. saddle-nose – Nasal obstruction – Crusting	– Autoimmune disease with infiltrating T-cells and antigen–antibody complexes within affected cartilage – Associated cartilage involvement in larynx (respiratory tract chondritis) and ears (auricular chondritis) caused by antibodies to type 2 collagen
Sarcoidosis	– 1–4% of patients develop sinonasal problems – Chronic and persistent course – Crusting (up to 90%) – Nasal obstruction (80% of patients) – Anosmia (70%) – Epistaxis (20%)	– Exogenous trigger in genetically susceptible patients of unknown aetiology – Lungs and lymph nodes commonly involved
Trauma		
Nasal/head injury	– Nasal obstruction due to internal or external deformity – Clear rhinorrhoea—CSF leak	– Bony and cartilaginous defects due to trauma

(continued)

Table 12.1 (continued)

Condition	Presenting features	Pathophysiology
Previous surgery		
Septal surgery	– Crusting – Whistling noise on nasal breathing related to iatrogenic perforations – Ongoing obstruction	– Previous septal surgery can result in external aesthetic changes, saddle-deformity and septal perforations
Sinus Surgery	– Recurrence of pre-operative symptoms – Clear rhinorrhoea—CSF leak	– Recurrence of sinonasal disease – Iatrogenic injuries
Dental Surgery	– Unilateral nasal symptoms	– Dental disease closely related to unilateral maxillary sinus disease (impacted roots in upper arches, oroantral fistula)
Head and neck malignancy		
Radiotherapy to head and neck	– Nasal obstruction – Thick mucopurulent rhinorrhoea	– Damage to mucociliary function due to cellular damage with associated mucosal inflammatory reaction

Alcohol

Hyper-responsiveness to alcoholic drinks has been demonstrated in patients with CRS, particularly in those with polyps, with as little as one unit of ingestion when compared to healthy controls. It is therefore useful to ask patients if their symptoms are associated with alcohol use [2].

Medication

Several medications have been linked with precipitating nasal obstruction. Nasal congestion may be induced by sedatives, anti-depressants, beta-blockers, anti-hypertensives, oral contraceptives and drugs used to treat erectile dysfunction.

Non-steroidal anti-inflammatory drugs (NSAIDs) such as aspirin and ibuprofen may cause acute onset severe nasal obstruction, an acute asthmatic attack, urticaria and gastrointestinal symptoms. The effect is due to a specific immunological reaction and is now referred to as Aspirin-Exacerbated Respiratory Disease (AERD) or NSAID-Exacerbated Respiratory Disease (N-ERD).

Intranasal Drugs

Nasal decongestant overuse can precipitate rhinitis medicamentosa (RM). Medications, such as oxymetazoline and phenylephrine, are available over the counter and patients often gain initial symptomatic relief. Prolonged use, outside of that recommended by the manufacturer, can precipitate RM, which is associated with mucosal hyper-reactivity, associated nasal obstruction and discomfort [3].

Use of illicit intranasal drug, most commonly cocaine, can precipitate destructive pathology such as septal perforations and intranasal mucosal appearances that mimic vasculitis. This is partly due to the cutting agents used, such as levamisole that can trigger an acute vasculitis-like reaction in some patients. Other drugs, such as heroin, oxycodone, hydrocodone and acetaminophen, can cause similar features when used intranasally [4].

Clinical Examination

External Nasal Examination

Examination of the external nose and the relationship to facial structures can provide information relating to skin integrity, asymmetry and potential contributors to nasal obstruction. External examination is perhaps most important when assessing the aesthetic appearance of the nose when pursuing both functional and aesthetic septorhinoplasty.

Inspection of the nose during the consultation may demonstrate changes with inspiration and

expiration such as alar collapse. A widened dorsum can indicate nasal polyposis and a horizontal nasal crease suggests allergic rhinitis.

Aesthetics of the Nose and Face

Anthropometrically, the face is divided in to five horizonal and three vertical portions, with the nose occupying the central component in each plane. The nose itself can be divided into vertical thirds; upper (nasal bones), middle (upper lateral cartilages, dorsal septum) and lower (nasal tip, lower lateral cartilages) and each can be assessed for asymmetry, colour, integrity and deformity.

After assessing the nose from anteriorly a lateral view of the patient's nose can provide information relating to tip rotation and nasal projection. The majority of studies related to nasal aesthetic norms are based on Caucasians, but newer studies are investigating a broader multi-racial picture. The nasofrontal and nasolabial angles are largest in Caucasians followed by Asian then African populations in both men and women [5].

Abnormalities of the skin such as prominent blood vessels, superficial lesions, depressions should be appropriately assessed and documented.

Palpation of the Nose

Assess the bony and cartilaginous parts of the nose for integrity through systematic palpation of each area with the fingertips. Particular attention should be attributed to the bony–cartilaginous junction and the integrity of support between these units of the nose. Note the mobility of the nasal skin, which is usually thin and freely mobile over the nasal bones and upper lateral cartilages but is thick and adherent over the alar cartilages.

Nasal Airflow

Nasal airflow can be assessed by performing the cold spatula test in both adults and children. A cold metal spatula is placed horizontally below the nostril during normal respiration. The condensation from moist exhaled air is compared between right and left airways.

Airflow obstruction at the level of the nasal valve may be reassessed after distracting the soft tissues of the alar region laterally to see if this improves the airway (Cottle's test).

Internal Examination

Anterior Rhinoscopy

The anterior nasal airway can be seen well with a head light and nasal speculum to open the nasal entrance and displace nasal vibrissae. Before inserting a speculum, the nasal tip should be elevated with a thumb or finger to open the nasal vestibule. The view is enhanced by gently inserting a Thudichum speculum to spread the skin and external valve to reveal the internal nasal valve. The anterior nasal septum, floor of the nose, inferior turbinate can usually be visualised and assessed for irregularities including mucosal changes, deviations and exophytic components.

Intranasal Endoscopy

Endoscopy of the nasal cavity can be performed with both rigid and flexible endoscopes. A 4 mm diameter 30° or 0° rigid endoscope is recommended but, for diagnostic outpatient assessment, a shorter 3mm diameter rigid endoscopy is an excellent alternative.

Endoscopy is often well tolerated without topical anaesthetic spray but the spray is reassuring to some patients and should be considered before the procedure. Similarly, decongestion is not necessary in all cases but can be a useful adjunct in congested noses or narrow nasal cavities.

All areas of the nasal cavity should be assessed. This can often be done by adjusting the angle of view in the nasal cavity. However, the three-pass technique is frequently quoted (Table 12.2). Its main value is to encourage all areas of the nasal cavity to be examined with the endoscope. Diagnostic endoscopy should be performed according to access and individual nasal anatomy, avoiding unnecessary pain or discomfort. The authors therefore recommend a more pragmatic approach to endoscopic examination where all accessible areas of the nasal cavity are examined whilst ensuring patient comfort and avoiding mucosal trauma.

Table 12.2 Guide to three-pass technique in nasal endoscopy

Procedure	Site	View	Comments
1st pass	Along floor of nose	Inferior turbinate, inferior meatus, Eustachian tube, nasopharynx	Best performed after good decongestion of inferior turbinates
2nd pass	Space between middle and inferior turbinates	Lateral nasal wall, fontanelles, middle meatus, anterior ethmoid (uncinate, ethmoid bulla), sphenoethmoidal recess, sphenoid ostia	Access may be limited by a narrow nose, septal deviation, large concha bullosa, medial displacement of maxillary sinus medial wall
3rd pass	Medial to middle turbinate	Olfactory cleft	Access limited, difficult procedure in clinic setting, best performed with a 30° 2.7 mm endoscope

Investigations

Targeted Assessments [1]

Allergy Testing and Endotyping

Assessment of allergens is an important feature in patients presenting with symptoms of chronic rhinosinusitis (CRS). Identifying seasonal variations or triggers of symptoms, within a patient's history, can point towards an allergic aetiology. Allergy tests assess a variety of common allergens in an attempt to identify causative factors but are not exhaustive.

Skin Prick Testing

Skin prick testing is a common and inexpensive test to identify atopy to aeroallergens. Patients should have stopped antihistamine medications at least 72 h prior to the test.

It is performed after the inner forearm is prepared with soap and water or alcohol. A marker pen is used to separate where allergens will be applied, in a line along the forearm, at least 2 cm apart. A drop of each allergen is placed at each of these marks and a small lancet is placed through this drop and into the skin. A new lancet is required for each allergen to prevent cross-contamination and the excess solution is removed. The patient is monitored for 20 min, and the surrounding skin reaction is assessed as follows.

Weal size (mm)	Interpretation
<5	Negative
5–10	Mildly Sensitive
10	Moderately Sensitive
>15	Very Sensitive

Serological Tests

There are now a wide range of antigens with specific IgE tests that can be performed through venous blood tests. They are particularly useful in small children, or where skin conditions preclude skin prick testing. Food allergen testing is particularly useful as skin prick testing may induce anaphylaxis. Skin prick testing correlates well with Radioallergosorbent testing (RAST), provides an immediate result and is less expensive.

Nasal Allergen Challenges [6]

Challenging the nasal mucosa directly with specific allergens is only performed by specialist allergy units. Indications include patients with persistent allergic rhinitis, intermittent allergic rhinitis, local allergic rhinitis and occupational rhinitis. Contraindications include previous anaphylaxis, severe cardiopulmonary comorbidities, pregnancy, systemic immunotherapy, children under 5 years of age, recent surgery of the nose or sinuses (in the preceding 8 weeks) and recent alcohol or tobacco use (within 48 h of test).

Technique: 0.1 mL of spray is administered per nostril. Nasal obstruction is assessed by a combination of a subjective score on a Likert scale or Total Nasal Symptom Score (TNSS) and an objective assessment by peak nasal inspiratory flow (PNIF) or acoustic rhinometry (AcRh).

Markers of Type 2 Endotype

IgE and eosinophils are the current biomarkers widely used to identify evidence of type 2 disease

in CRS. These investigations should be considered in patients presenting with symptoms of CRS to differentiate between type 2 and non-type 2 disease. Blood eosinophil levels have been shown to positively correlate with endoscopic scoring in patients with nasal polyps, and a serum IgE above 96 kU/L is a poor prognostic indicator in this patient group.

Vasculitic Screen

A combination of blood tests is recommended to identify or exclude vasculitic disorders. These should include a full blood count, renal function, ESR, CRP, ACE, ANCA screen and myeloperoxidase (MPO)/proteinase 3 (PR3) antibodies.

Granulomatosis with polyangiitis (GPA) is linked and positively correlated with c-antineutrophil cytoplasmic antibodies (c-ANCA). However, cANCA may be negative during the early phase of GPA and become positive with disease progression.

Serum angiotensin-converting enzyme (ACE) is the most widely used laboratory test for sarcoidosis but an elevated ACE result is nonspecific and should be interpreted with caution. High ACE levels occur with ACE inhibitor medications and in a range of disorders, such as diabetes mellitus, hepatitis, Hodgkin's disease, asthma and COPD, Addison's disease and hyperthyroidism. IL-2R and lysozyme serum tests are associated with a more aggressive phenotype of sarcoid.

The diagnosis of both GPA and sarcoidosis is confirmed by a combination of clinical features, radiological findings and histology from biopsy of affected areas.

Olfaction

Olfaction disorders can be assessed by olfactory psychophysical tests such as the Zurich Smell Diskettes screening test or the more detailed University of Pennsylvania Smell Identification Test (UPSIT) or Sniffin' Sticks. The UPSIT is a validated supra-threshold smell test that produces a score from a maximum of 40 and is able to discriminate patients with true anosmia from malingerers. Sniffin' Sticks can offer a more detailed analysis of smell that includes smell threshold and discrimination. Threshold tests require the patient to detect minimum concentrations of a tested odorant with increasing concentrations of the smell presented during the test. The olfactory discrimination test provides three odours where two are the same and the patient is asked to identify the third individual smell.

Intracranial causes of smell disturbance or anosmia are rare but should always be considered, and if in doubt, a CT brain or MRI should be considered.

Microbiology

Endonasal swabs are the most widely used adjunct when there is evidence of an infective cause on history or on endonasal assessment. Targeted swabs of mucopus from the middle meatus have shown high concordance with specimens taken from the maxillary sinus, but contamination of the nasal flora may compound the results.

Nasal Patency

Peak nasal inspiratory flowmetry (PNIF), active anterior rhinometry (AAR) and acoustic rhinometry (AR) are all objective measurements of nasal patency. PNIF is the most widely used measure that can be applied to one or both nostrils. It has been demonstrated to show good correlation with quality of life after sinus surgery and subjective nasal patency. It is only able to identify the narrowest part of the nasal airway but not where this obstruction is.

Biopsy

Biopsies of the nose can be performed under local or general anaesthesia. This choice should be based on the location of the area to be sampled, the bulk of tissue required for analysis, risk of general anaesthesia and patient choice. Biopsy is required if there is suspicion of malignancy but can also play a role in diagnosing seronegative vasculitis conditions. Research is ongoing regarding the role that intranasal biopsy holds in identifying endotypes in CRS.

Urinalysis

Cocaine metabolites can be identified in urine. Results may be positive for up to 2 weeks post

drug use and may be useful to confirm that a patient has stopped cocaine prior to undergoing surgery.

Areas of Controversy or Uncertainty

The emergence of SARS-CoV-2 (COVID-19) pandemic has influenced our examination of the nose and sinuses. The most important means of viral spread is by aerosols. If the patient coughs or sneezes, during flexible or rigid nasendoscopy, an aerosol may be generated. The risk of an aerosol-carrying virus particles is determined by the number of covid cases within the community at the time. Wearing adequate PPE is recommended as a precaution but will vary according to the perceived local risk. This is a dynamic situation but it has focused thinking on the safety of clinical examination rooms and the importance of ventilation.

Endotyping is an emerging area and further evidence is required to understand the use of eosinophilia, IgE and mucosal biopsy in this area. Endotyping is likely to provide an avenue for targeted CRS treatment and as such these areas of serological and histological assessment should be considered.

Key Learning Points

- The assessment of the nose and olfaction requires a rounded knowledge of the varied pathology of rhinological disease.
- Targeted history and examination based on the patients presenting complaint will allow a tailored consultation and to formulate an appropriate differential diagnosis.
- Endoscopic examination of the nose is crucial in the diagnosis of disease.
- A wide range of further tests are available to assess nasal function and should be employed when there is diagnostic uncertainty or to demonstrate objective results following treatment.

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13

Outcome Metrics and Measurement Tools for Rhinological Treatment Modalities

Joanne Rimmer

Introduction

History and examination are the first step in the management of all rhinological conditions. Some conditions are diagnosed and treated on clinical assessment alone, but it is becoming ever more important to confirm a diagnosis, formally assess outcomes and provide evidence of treatment efficacy. Standard treatments for even 'simple' conditions, such as septoplasty for a deviated septum, may fail to improve the patient's symptoms. It is therefore vital that we have measurement tools available with which to obtain both subjective and objective measures of symptom severity, for diagnosis and to monitor response to treatments, both medical and surgical [1].

Some of these tools are widely available, while others require more specialist equipment and expertise and are found only in tertiary centres. Some techniques are still primarily research tools, but they are important for evaluating outcomes in clinical trials, and their use may become more widespread with time.

J. Rimmer (✉)
Department of Otolaryngology Head & Neck Surgery, Monash Health, Melbourne, Australia

Department of Otolaryngology Head & Neck Surgery, St Vincent's Hospital, Melbourne, Australia

Department of Surgery, Monash University, Melbourne, Australia
e-mail: joanne.rimmer@monashhealth.org

Subjective Outcome Measures

Patient Reported Outcome Measures (PROMs)

Sinonasal disease has been shown to have a significant impact on quality of life (QOL) as well as general health. Quality of life instruments are therefore used routinely to assess both the impact that a condition has upon a patient's life as well as the benefit gained by treating it. Such tools can assess the impact of different treatments and treatment modalities, which helps patients make decisions about their own management and as such are important for patient-centred care. Quality of life is also a standard outcome measure in many clinical trials.

There are numerous validated QOL instruments. Questionnaires tend to include different domains in which patients are asked to rate the severity of certain symptoms. Some are disease-specific, others measure more generic health-related QOL.

Disease-Specific PROMs

Disease-specific PROMs are subjective by their very nature, but most have been objectively validated and as such can provide clinically useful information regarding symptom severity and control. They are used both clinically and to eval-

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uate outcomes in research. A recent systematic review identified 15 validated PROMs for chronic rhinosinusitis (CRS) alone, and more are constantly being designed and tested. Some are validated specifically for use in children, such as the Sinus and Nasal Quality of Life Survey (SN-5)

22-Item Sinonasal Outcome Test (SNOT-22)

The SNOT-22 (Fig. 13.1) has been reported to be the most reliable of the tools available to measure outcomes in CRS, as well as being easy to use, responsive and valid [2]. It is certainly one of the most widely used, both in clinical practice and trials. Patients rank the severity of 22 symptoms across five domains using a six-point Likert scale; the total score ranges from 0 to 110. Three of the domains are disease-specific, covering rhinologic, extra-rhinologic and ear/facial symptoms. The other two domains (psychological and sleep disturbance) assess general health-related quality of life. The SNOT-22 can be used to assess the response to medical and surgical treatments. When the total SNOT-22 score is used, the minimum clinically important difference (MCID) in CRS is 8.9. The different domains can also be looked at separately to see which symptoms are more or less improved by a treatment. Psychometric validation has shown the SNOT-22 to be reliable and reproducible with excellent discriminant ability.

Nasal Obstruction Symptom Evaluation (NOSE) Scale

The Nasal Obstruction Symptom Evaluation (NOSE) scale (Fig. 13.2) is a validated, reliable and responsive five-item instrument for subjective evaluation of nasal obstruction [3]. It is quick and easy to complete. It has been used to measure improvements in QOL after septoplasty, functional septorhinoplasty and nasal valve surgery.

Skull Base Surgery

The Anterior Skull Base Questionnaire (ASBQ) was designed and validated for the assessment of QOL in patients undergoing resection of anterior skull base tumours. It evaluates 35 items including disease-specific issues such as alterations in smell and taste, epiphora, visual disturbance and appearance.

The Skull Base Inventory (SBI) is an 11 domain, 41-item questionnaire designed to assess disease-specific QOL in patients undergoing endoscopic and open approaches to anterior and central skull base neoplasms. It was shown to be reliable and valid on psychometric testing.

Other Disease-Specific PROMs

The mini-Rhinoconjunctivitis Quality of Life Questionnaire (mini-RQLQ) was adapted from the 28-item RQLQ and is validated for use in allergic rhinitis. It includes 14 questions in five subdomains: activity limitations, practical problems, nose symptoms, eye symptoms and other symptoms.

The Rhinoplasty Outcomes Evaluation (ROE) is a six-item validated questionnaire designed to assess the physical, mental, emotional and social domains of rhinoplasty. It is the only QOL instrument designed specifically for rhinoplasty.

Generic Health-Related PROMs

Generic health-related QOL instruments assess overall physical and mental well-being as well as functional status and how affected patients are by a disease. They can be used to compare health status across different disease states as well as how that changes with treatment. They can also be used to evaluate the cost-effectiveness of treatments. However, such instruments are less discriminatory in mild disease and are less sensitive to changes after some sinonasal procedures such as septoplasty.

Short Form-36 (SF-36)

The SF-36 measures health status across eight domains: vitality, physical functioning, bodily

Sino-Nasal Outcome Test-22 Questionnaire

Below you will find a list of symptoms and social/emotional consequences of your nasal disorder. We would like to know more about these problems and would appreciate you answering the following question to the best of your ability. There are no right or wrong answers, and only you can provide us with this information. Please rate your problems, as they have been over the past two weeks. Thank you for your participation.

A: Considering how severe the problem is when you experience it and how frequently it happens, please rate each item below on how 'bad' it is by circling the number that corresponds with how you feel using this scale ➔	**No problem**	**Very mild problem**	**Mild or slight problem**	**Moderate problem**	**Severe problem**	**Problem as bad as it can be**	
1. Need to blow nose	0	1	2	3	4	5	
2. Sneezing	0	1	2	3	4	5	
3. Runny nose	0	1	2	3	4	5	
4. Cough	0	1	2	3	4	5	
5. Post nasal discharge (dripping at the back of your nose)	0	1	2	3	4	5	
6. Thick nasal discharge	0	1	2	3	4	5	
7. Ear fullness	0	1	2	3	4	5	
8. Dizziness	0	1	2	3	4	5	
9. Ear pain	0	1	2	3	4	5	
10. Facial pain/pressure	0	1	2	3	4	5	
11. Difficulty falling asleep	0	1	2	3	4	5	
12. Waking up at night	0	1	2	3	4	5	
13. Lack of a good night's sleep	0	1	2	3	4	5	
14. Waking up tired	0	1	2	3	4	5	
15. Fatigue	0	1	2	3	4	5	
16. Reduced productivity	0	1	2	3	4	5	
17. Reduced concentration	0	1	2	3	4	5	
18. Frustrated/restless/ irritable	0	1	2	3	4	5	
19. Sad	0	1	2	3	4	5	
20. Embarrassed	0	1	2	3	4	5	
21. Sense of taste/smell	0	1	2	3	4	5	
22. Blockage/congestion of nose	0	1	2	3	4	5	

TOTAL: _____ _____ _____ _____ _____

GRAND TOTAL: _____

Fig. 13.1 The 22-item Sinonasal Outcome Test (SNOT-22). Reproduced with permission from Washington University in St. Louis, Missouri

Nasal Obstruction Symptom Evaluation Scale

Please help us to better understand the impact of nasal obstruction on your quality of life by completing the following survey. Thank you.

Over the past ONE month how much of a problem were the following conditions for you?

	Not a Problem	*Very Mild Problem*	*Moderate problem*	*Fairly Bad Problem*	*Severe Problem*
1. Nasal congestion or stuffiness	0	1	2	3	4
2. Nasal blockage or obstruction	0	1	2	3	4
3. Trouble breathing through nose	0	1	2	3	4
4. Trouble sleeping	0	1	2	3	4
5. Unable to get enough air through nose during exertion	0	1	2	3	4
TOTAL					
TOTAL SCORE /100					

1. Have the patient complete the questionnaire as indicated by circling the response closest to describing their current symptoms

2. Sum the answers the patient circles and multiply by 5 to base the scale out of a possible score of 100 for analysis

Fig. 13.2 The Nasal Obstruction Symptom Evaluation (NOSE) scale. Reproduced from Otolaryngology Head & Neck Surgery with permission [3]

pain, general health perceptions, physical role functioning, emotional role functioning, social role functioning and mental health. When the SF-36 was used to compare CRS to chronic back pain, chronic heart failure and ischaemic heart disease, those with CRS scored significantly worse for both bodily pain and social functioning.

EQ-5D

The Euroqol EQ-5D (www.euroquol.org) is a measure of health-related QOL across five domains: mobility, usual activities, self-care, pain and discomfort, and anxiety and depression. It has been shown to be sensitive to symptom changes in CRS.

Objective Outcome Measures

Olfactory Testing

It is interesting that the subjective evaluation of olfactory function does not correlate well with objective measurements, except in complete anosmia [4]. Formal olfactory testing can therefore be very useful. It is commonly performed by psychophysical methods that are quick and easy. Completely objective measurement of olfactory function, using event related potentials, is more time-consuming and expensive, and is primarily a research tool.

Olfactory Identification

In the most commonly performed test of olfactory function, subjects must identify the suprathreshold concentration odours presented to them. This is a forced choice test, i.e. subjects must choose one of four possible options. This format is used because unprompted odour recognition is difficult. It also detects malingerers, as the likelihood of choosing the correct odour by chance is 25%. There is the potential for cultural bias with any odour identification test, so different versions have been validated for various parts of the world.

Common commercial testing kits include more than 12 odours, as it becomes easier to differentiate between normal smell, hyposmia and anosmia with this number. Such kits include Sniffin' Sticks™ (Burghardt, Wedel, Germany) and the University of Pennsylvania Smell Identification Test (UPSIT™, Sensonics, Haddon Heights, NJ, USA).

Olfactory Threshold Testing

In this test, subjects do not have to identify what the odour is. One odour is presented in gradually increasing concentrations until the subject can detect it. The concentration is then slowly decreased again to confirm the threshold of detection—recorded as the concentration at which 50% of the stimuli are detected and 50% are not. Common commercial kits include Sniffin' Sticks™ and the Connecticut Chemosensory Clinical Research Center Test (CCCRCT).

Olfactory Discrimination

Three suprathreshold odours are presented: two are the same and the subject has to identify which one is different. Accuracy improves as the number of odour triplets increases. Sniffin' Sticks™ is the main commercially available test.

Tests of identification and discrimination assess the more central, cognitive aspects of olfactory function. As such, they are more dependent on memory and executive function than threshold testing, which evaluates the more peripheral changes seen in CRS, where patients often have normal identification but increased thresholds indicating subtle olfactory loss.

Measurement of Nasal Airflow

Nasal obstruction or blockage is perhaps the most common rhinological symptom. Objectively quantifying the degree of obstruction, and the effect of a particular treatment on that obstruction, is often difficult. In many cases these measurement tools remain in the realm of research rather than everyday clinical practice, yet increasingly surgeons are being asked to provide evidence that a specific treatment is effective.

In addition, some patients complain of nasal obstruction in the absence of an obvious cause. An objective measurement of airflow may be useful in such cases, although there is conflicting evidence regarding the correlation between objective measurements and the subjective perception of nasal obstruction [1].

Nasal airflow and volume can be objectively assessed using peak nasal inspiratory flow (PNIF), rhinomanometry, acoustic rhinometry (AR) and rhinospirometry. The latter methods are less commonly used in routine clinical practice, but newer rhinomanometers are becoming available which are easier to use. Such objective measurements can be a useful adjunct to compare with the subjective symptom of obstruction.

Peak Nasal Inspiratory Flow (PNIF)

This quick, simple and inexpensive test of inspiratory nasal airflow is easy to perform. It is highly reproducible, with a correlation coefficient of up to 92%, and gives a direct objective measurement of nasal obstruction [5]. It is correlated with peak expiratory flow, so low values may reflect poor lung function in certain patients.

A standard peak flow meter (Fig. 13.3) is attached to a face mask held over the nose and mouth, with the subject standing upright. Keeping the mouth completely closed, the subject inhales as hard and fast as possible starting from the end of a maximal expiration. The test is repeated three times and the highest result is recorded; PNIF has been shown to improve with practice, especially after the first attempt. PNIF is higher in males than females, increases with height and tends to reduce with age. Normal values have been established in adults and children (Table 13.1). Normal values have also been reported for unilateral PNIF.

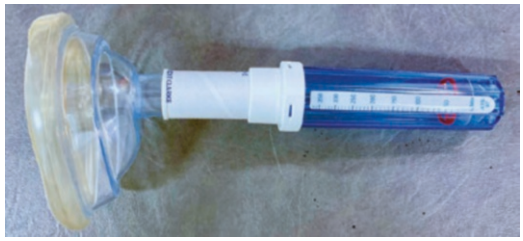

Fig. 13.3 Nasal Inspiratory Flow meter (PNIF)

Table 13.1 Normal values for peak nasal inspiratory flow (PNIF) [6]. Reproduced with permission from *Rhinology*

	Mean PNIF ± SD (L/min)
Adult males	143 ± 48.6
Adult females	121.9 ± 36
Children (over 8 years)	80 ± 25

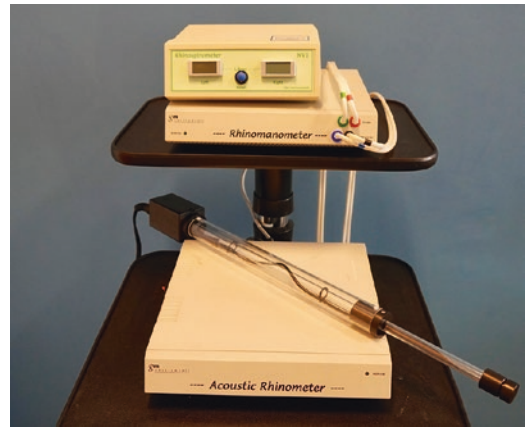

Fig. 13.4 Combination of 3 electronic instruments for assessing nasal obstruction. Rhinospirometer (*top*), Rhinomanometer (*middle*), and Acoustic rhinometer with sonic tube (*bottom*)

Rhinomanometry

Rhinomanometry provides an objective measure of nasal airway resistance (NAR) by measuring nasal airflow and the pressure gradient required to maintain that airflow (Fig. 13.4). Rhinomanometry can be anterior or posterior, active or passive; the most commonly used method is active anterior rhinomanometry (AAR). The subject sits upright with a face mask covering the mouth and nose and a pressure sensor in one nostril. Occlusive tape creates a complete seal of that nostril. The rhinomanometer measures transnasal pressure and flow and NAR is calculated from the pressure-flow curve. Greater pressure is required to generate the same flow rate in the face of increased airway obstruction.

Previous guidelines from the International Committee on Rhinomanometric Standards described using a fixed pressure gradient of 150 Pa to calculate NAR. However, more recent consensus guidelines, established by the International Standardization Committee on the Objective Assessment of the Nasal Airway, recommend the use of four-phase rhinomanometry (4PR) in which NAR is calculated using many hundreds of resistances recorded continuously over several breathing cycles [7]. The four phases of the breathing cycle referred to are the accelerating inspiratory phase, the decelerating inspiratory phase, the accelerating expiratory phase and the decelerating expiratory phase (Fig. 13.5).

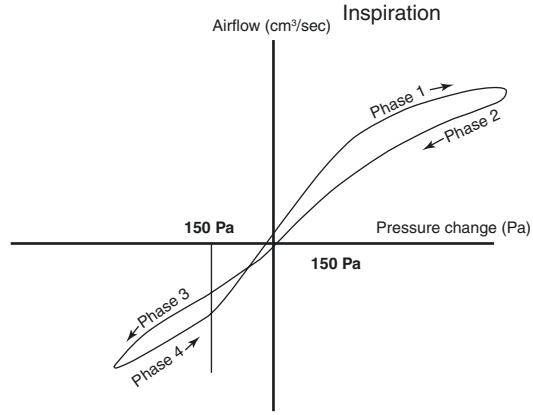

Fig. 13.5 Example of four-phase rhinomanometry (4PR). Adapted from European Archives of Otorhinolaryngology with permission

The basic parameters measured are:

1. the effective resistance of the entire breath (Reff);
2. the effective resistance during inspiration (Reffin);
3. the effective resistance during expiration (Reffex); and
4. the vertex resistance (VR), i.e. the resistance at the highest point of the flow curve during quiet breathing, which can be measured during both inspiration (VRin) and expiration (VRex) [8].

Table 13.2 Normal values for active anterior rhinomanometry (AAR) [1]. (*NAR* Nasal airway resistance). Reproduced with permission from *Rhinology*

	NAR at 150 Pa (Pa/cm³/s)
Adult males	0.24
Adult females	0.26
Children (over 8 years)	0.24 (after decongestion)

Table 13.3 Classification of logarithmic effective resistance [8]. Reproduced with permission from European Archives of Otorhinolaryngology under the terms of the Creative Commons Attribution 4.0 International License (http://creativecommons.org/licenses/by/4.0/)

Class	Unilateral resistance	Total resistance
1: 0–19%	<0.71	<0.42
2: 20–39%	0.71–0.89	0.42–0.57
3: 40–59%	0.89–1.08	0.57–0.70
4: 60–79%	1.09–1.35	0.70–0.90
5: 80–100%	>1.35	>0.90

For clinical purposes and to achieve a normal distribution, the logarithmic values of these parameters are reported (LReff, LReffin, LReffex and LVR). The results of AAR and 4PR testing have been shown to correlate well with each other. Of the different parameters assessed, VR seems to correlate best with subjective nasal obstruction.

Rhinomanometry can be performed in children as well as adults, with normal values available for both AAR (Table 13.2) and 4PR (Table 13.3).

Based on 36,500 4PR measurements, a clinical classification for nasal obstruction is available for Caucasian noses (Table 13.3) [8]. Class 1 represents noses without any obstruction, while class 5 corresponds to total functional blockage.

Acoustic Rhinometry

Acoustic rhinometry (AR) uses the acoustic reflection of a sound wave travelling through the nasal cavity to measure cross-sectional area and volume at different points in the nose. The shape and size of the reflected sound waves is used to calculate the dimensions of the nasal cavity. The time delay reflects the distance travelled by the sound wave from the nostril. These measurements are converted into nasal volume and area.

The subject sits upright and the nosepiece of the sonic tube (Fig. 13.4) is inserted into one nostril where a complete seal is obtained. Measurements are performed during a breath hold, and silence is essential. It is simple to perform, reproducible and can be used in children. Various factors can affect the results and reproducibility of AR, including lack of a complete seal, the angulation of the sonic tube and the presence of a septal perforation. Measurements in the posterior part of the nose may be affected by sinus surgery due to the cavities created.

AR was standardized in 2005 by the Standardization Committee on Objective Assessment of the Nasal Airway. The important parameters are the **minimal cross-sectional area (MCA)** at different 'notches', representing specific areas in the nose, and the **nasal cavity volume (NCV)** [7]. Two notches can be seen on the AR graph, the first being the I-notch (Isthmus nasi) at the nasal valve and the second the C-notch (Concha) at the head of the inferior turbinate (Fig. 13.6). In healthy Caucasians, the absolute MCA usually corresponds to the C-notch. Normal values for MCA in adults are between 1.32 and 1.51 cm^2, and an MCA of less than 0.4 cm^2 has been shown to correlate with subjective nasal obstruction. The C-notch and therefore the MCA will usually change after topical decongestion.

The NCV is defined as the space between the opening plane of the device and a parallel plane at a defined distance from the opening plane. This can be either a fixed distance or the distance to the MCA, and therefore varies between studies. The NCV between 2 and 5 cm is the most sensitive when assessing changes in airflow after nasal mucosal decongestion [1].

Rhinospirometry

Rhinospirometry measures the differences in airflow between the right and left nasal passages, expressed as the nasal partitioning ratio (NPR) (Fig. 13.4). This ranges from −1 (left nasal cavity obstruction) to +1 (right nasal cavity obstruction), with 0 indicating symmetrical airflow. The normal range has been defined as −0.34 to +0.34. When the NPR was measured in 31 patients before and after septoplasty, those with an NPR outside the

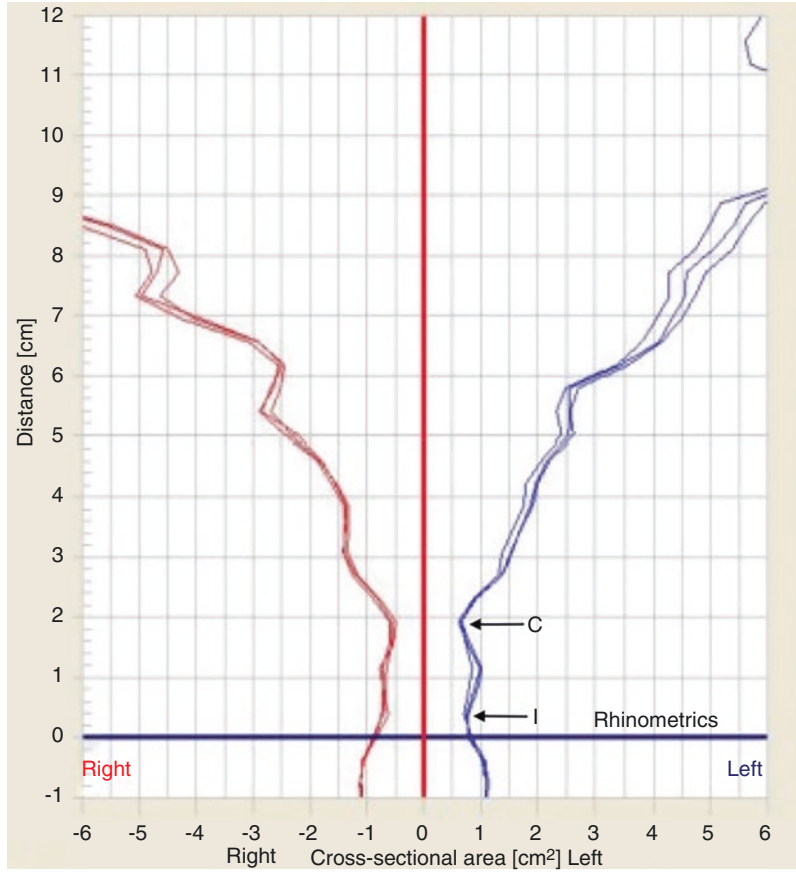

Fig. 13.6 Example of acoustic rhinometry, where I = I-notch and C = C-notch

normal range preoperatively had a greater subjective improvement in nasal obstruction postoperatively [9].

Although the correlation between subjective nasal obstruction and its objective measurement is controversial, these methods can be used to assess the response to medical treatments in chronic sinusitis, nasal polyps and allergic rhinitis. For example, PNIF has been used to monitor the response to intranasal steroid treatment for nasal polyps, when a reduction in nasal polyp score was associated with a significant increase in PNIF as well as a subjective improvement in nasal obstruction [5]. These measurement tools can be employed in aspirin challenge and nasal provocation testing to assess airflow changes related to nasal mucosal congestion. They can also be utilized to evaluate the potential response to treatment. When nasal airway measurements are performed before and after topical decongestion, the change in resistance is presumed to be due to a reduction in mucosal congestion. This provides information on more fixed anatomical factors contributing to nasal obstruction such as septal deviation or nasal valve narrowing. This can help in the selection of appropriate candidates for procedures such as septoplasty or nasal valve surgery. Patients with objective evidence of nasal obstruction prior to surgery have been shown to have significantly better outcomes than those without [1].

Computational Fluid Dynamics

Computational fluid dynamics (CFD) uses numerical methods to simulate fluid flow, and nasal airflow can therefore be simulated using three-dimensional computed tomography (CT) scan modelling. There has been increasing interest in CFD in rhinology in recent years although it currently remains a research tool.

Studies have shown that CFD simulations of nasal airflow correlate moderately well with subjective evaluations [10]. One of the assumptions made in CFD is that the lateral nasal walls are rigid, which means that CFD underestimates nasal resistance compared to in vivo measurements. Correlation between CFD and rhinomanometry is variably reported. Recent evidence shows moderate correlation, more so with unilateral than bilateral measurements. Similar to other objective methods of assessing nasal airflow, correlation was also higher when an intervention such as decongestion or surgery was investigated.

Nasal Nitric Oxide

Nitric oxide (NO) is a colourless reactive gas produced in the sinonasal mucosa from oxygen and L-arginine by nitric oxide synthase (NOS). NOS exists in at least three isoforms in various tissues and is both constitutively expressed and inducible. In the upper airway, high levels of nitric oxide are constitutively produced in the paranasal sinuses rather than the nose itself; in inflammatory conditions including allergic rhinitis, sinusitis and polyposis, additional NO is formed via inducible NOS [11].

The role of NO in the upper airway is complex and incompletely understood. It acts as a vasodilator and has pro-inflammatory effects, but also seems to have anti-infective properties, contributing to non-specific host defences against bacteria, viruses and fungi. It can also increase ciliary beat frequency.

Exhaled NO (eNO) is used in the diagnosis and management of asthma, and the levels of NO produced in the nose and sinuses can also be measured as exhaled nasal NO (nNO). There are standardized procedures to measure eNO, but various methods exist for measuring nNO with no current consensus [11]. Sampling techniques include breath holding and humming. All are easy to perform, can be done in children as well as adults and provide immediate reproducible results.

Healthy control subjects have nNO levels greater than 300 ppb. Nasal NO levels are elevated in allergic rhinitis but not in non-allergic rhinitis, as NO increases in response to eosinophilic inflammation in the airways. Patients with chronic sinusitis generally have lower nNO levels, thought to be due to obstructed sinus ostia preventing the NO produced by the sinus mucosa from passing into the nose; it is therefore not measured. These low levels often improve in response to treatment; the improvement seen after sinus surgery is usually greater than that seen with medical treatment, perhaps due to the widening of sinus ostia and/or creation of sinus neocavities.

Nasal NO is an excellent screening test for primary ciliary dyskinesia. A diagnosis of this congenital disorder of ciliary ultrastructure and/or function is highly likely if nNO levels are below 77 ppb although the diagnosis can still be made if levels are higher. Low nNO levels (70–300 ppb) are also often seen in cystic fibrosis, and tend to be significantly lower if polyps are present. While nNO cannot be easily used to monitor the response to treatment in these congenital disorders, it is sometimes used for that purpose in allergic rhinitis and sinusitis.

Summary of Areas of Controversy and Uncertainty

Subjective outcome measures require patients to complete questionnaires, which requires compliance as well as a minimal degree of literacy. These potential problems can be overcome with patient support and education, and many of the PROMs described above have been validated for different countries and languages.

Some objective measurements require expensive equipment and take time to perform. A more recent problem for those performing objective measurements of nasal physiology was the COVID-19 pandemic, which prevented such testing from being carried out due to the potential risk of aerosolization and droplet transfer. This situation seems to be resolving with time.

There is still conflicting evidence regarding the correlation between objective measurements and the subjective perception of nasal obstruction. Whilst some are still more commonly used in research than everyday clinical practice, it

is important to understand the available measurement tools and to incorporate them into the routine care of rhinology patients where appropriate.

Key Learning Points

- Subjective and objective outcome measures are available for rhinological treatment modalities and should be used where appropriate; they are also increasingly requested by commissioners of healthcare in many countries.
- Patient-reported outcome measures assess health-related and disease-specific quality of life and are able to assess the impact of different treatments and treatment modalities.
- Psychophysical olfactory testing is simple and reliable.
- Objective measurements of nasal airflow can be helpful in evaluating the response to medical and surgical treatments.

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Radiological Imaging in Rhinology

14

Andrew S. McQueen and Joanna K. Dixon

Introduction

The evolution of radiology in the last few decades has revolutionised assessment of the nose and sinuses. The emergence of widely available, high resolution, three-dimensional imaging has established a key role for imaging in the diagnosis and management of sinonasal pathology. In addition to pre-operative planning, modern imaging can be rapidly acquired and is regularly fused with intra-operative endoscopy by navigation software, enabling increasingly accurate image-guided surgery (IGS) to reduce operative time and complications.

This chapter provides a concise overview of nose and paranasal sinus imaging: a foundation to help the reader appreciate the role of radiology within each clinical rhinology chapter. Radiological anatomy is highlighted, with reference to clinically relevant anatomic variants, imaging pitfalls and the communication of findings to enable accurate diagnosis and appropriate management (the radiology report). Sinonasal imaging techniques are described with the strengths and limitations of each different modality discussed in the context of common clinical scenarios. Finally, in an area of constant change and development, future trends in clinical imaging will be considered.

A. S. McQueen (✉) · J. K. Dixon
Department of Radiology, Freeman Hospital, Newcastle upon Tyne Hospitals NHS Foundation Trust, Newcastle upon Tyne, UK
e-mail: andrew.mcqueen1@nhs.net

Clinically Applied Imaging Anatomy

Key Anatomic Findings and Normal Variants

The following section aims to highlight some of the key, surgically relevant anatomical structures of the sinonasal cavity and their common variants, which when present may impair sinus drainage or increase the risk of complication associated with functional endoscopic sinus surgery (FESS) [1–8]. The terminology used within the body of this section is that recommended by the 2014 European Position Paper on Anatomical Terminology of the Internal Nose and Paranasal Sinuses [9], with reference also made to the International Frontal Sinus Anatomy Classification (IFAC) [10].

Basic Anatomy of the Nasal Cavity

The nasal septum divides the nasal cavity in the sagittal plane. Varying degrees of septal deviation, septal spurs and adhesions may be present and posteriorly the septum may be pneumatised from the sphenoid sinuses (Fig. 14.1). The turbinates (inferior, middle, superior and occasionally supreme) divide the nasal cavity in the axial plane into their respective meatus and may be paradoxical or pneumatised (Fig. 14.2a–g).

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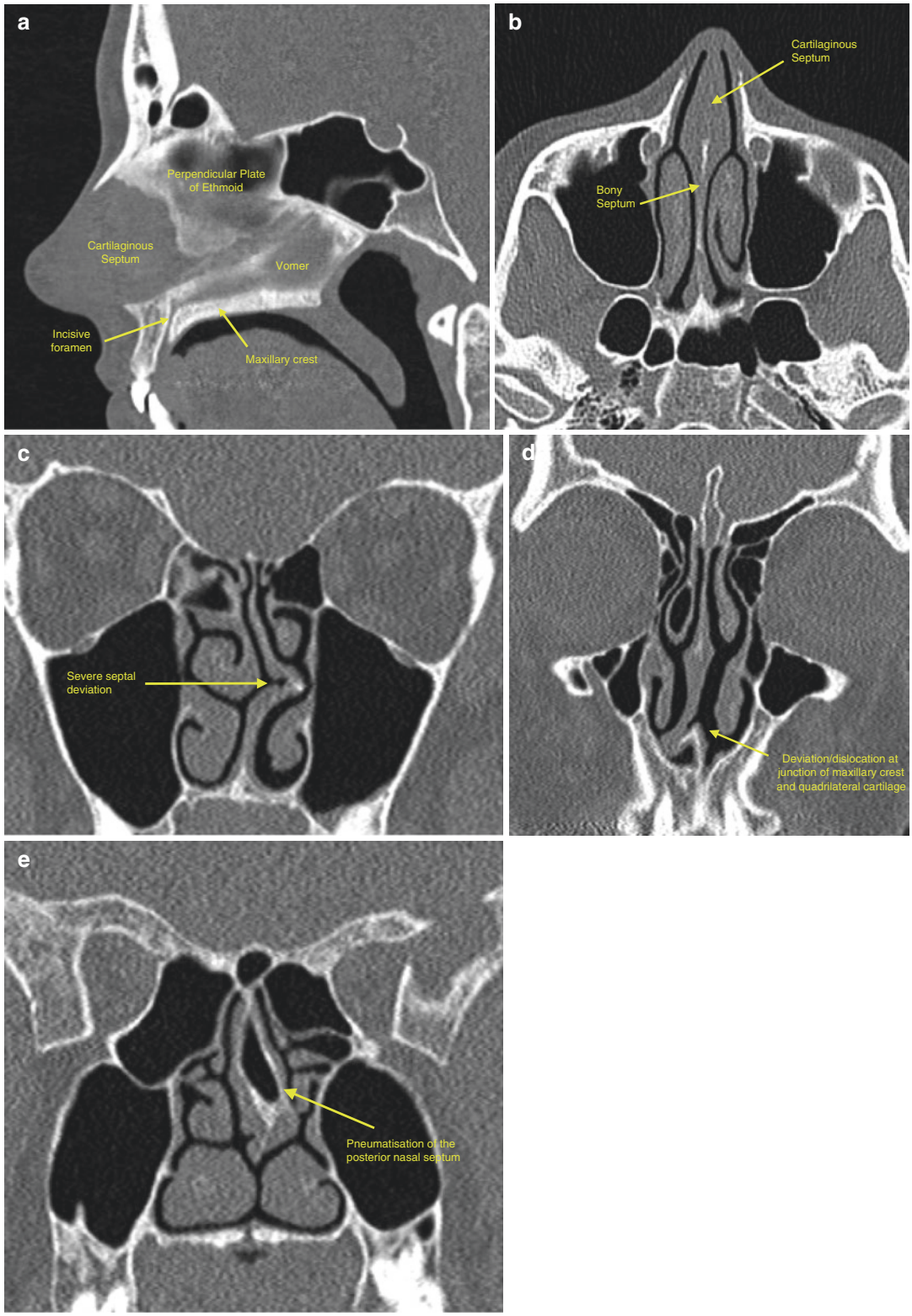

Fig. 14.1 The nasal septum. (**a**, **b**) Sagittal and axial CT images demonstrating the anatomy of the nasal septum. (**c**) Coronal CT showing severe septal deviation to the left. Deviation is often accompanied by enlargement of the contralateral turbinates and ethmoid bulla. (**d**) Deviation/dislocation at the chondrovomeral junction. (**e**) Pneumatisation of the posterior septum, which usually occurs from the sphenoid sinuses

Appreciation of their complex attachments requires image review in multiple planes (Fig. 14.3). The basal lamella of the middle turbinate is an important surgical and radiological landmark as it forms the boundary between anterior and posterior ethmoid cells and therefore separates the anterior from posterior sinus drainage pathways (Fig. 14.4). These pathways will be considered separately below.

The Anterior Paranasal Sinus Drainage Pathway: Maxillary Sinus and Osteomeatal Complex

The maxillary, frontal and anterior ethmoid sinus cells all drain via the osteomeatal complex into the nasopharynx (Fig. 14.5a). The osteomeatal complex is a functional unit comprising bony structures (uncinate process, middle turbinate and ethmoid bulla) and the anatomical spaces that lie between them (maxillary ostium, ethmoid infundibulum, semilunar hiatus and middle meatus). Variations in any of these components may lead to impaired sinus drainage (Fig. 14.5b).

The anterior attachment of the uncinate process is variable, attaching either to the lamina papyracea, anterior skull base or middle turbinate and is of particular interest, as its position alters the drainage pathway of the frontal sinus (Fig. 14.6a–c). It has a free posterior border, which parallels the anterior margin of the ethmoid bulla, usually the largest anterior ethmoid cell. The crescent-shaped opening between the

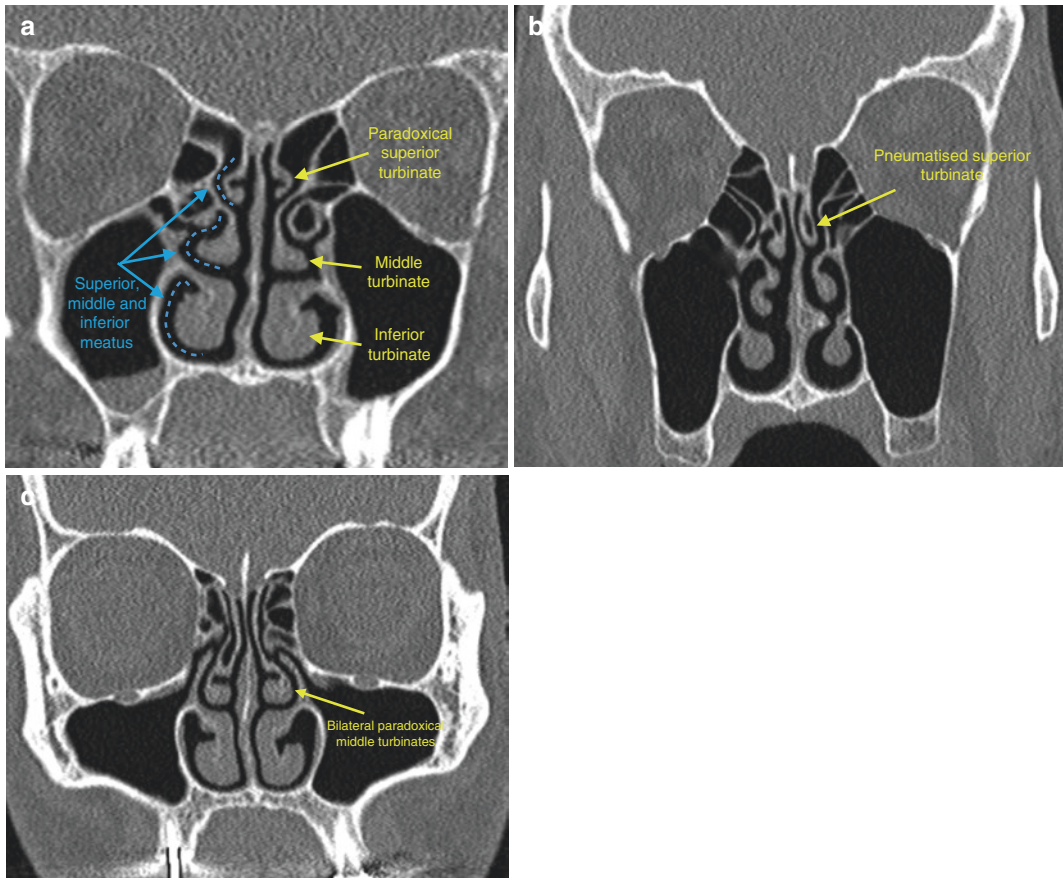

Fig. 14.2 Anatomical variations of the nasal turbinates. (**a**) Paradoxical superior turbinates, (**b**) pneumatised superior turbinates, (**c**) bilateral paradoxical middle turbinates. Pneumatisation of the middle turbinate may involve the turbinate itself (concha bullosa), the lamella only (**d**), or may extend to involve both (**e**). Note that in this final case the pneumatised cell extends to the ethmoid roof

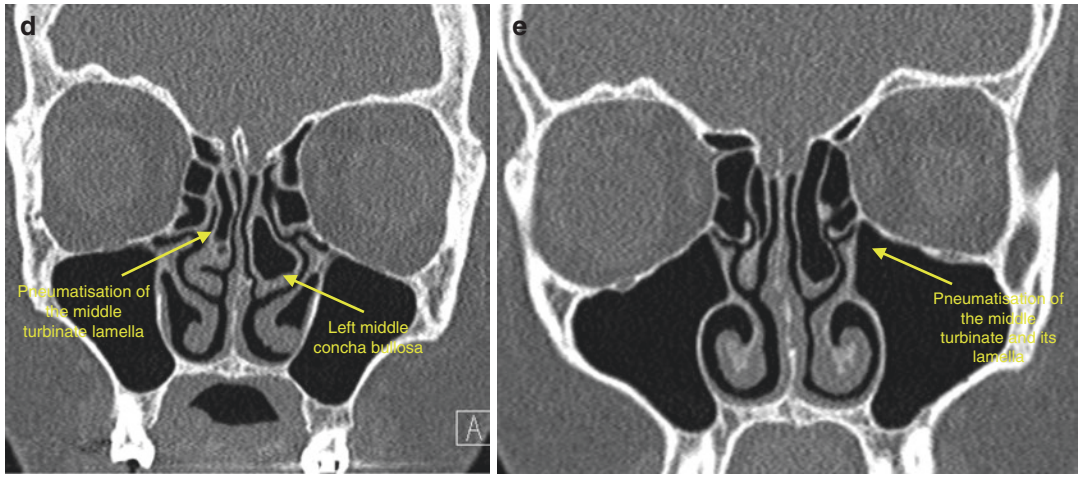

Fig. 14.2 (continued)

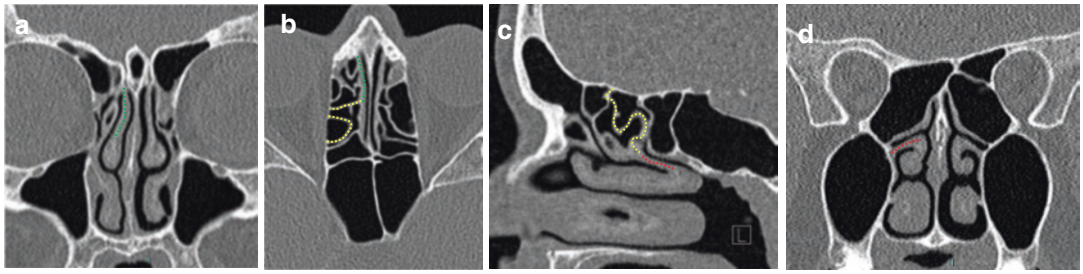

Fig. 14.3 Attachments of the middle turbinate are most easily appreciated in the imaging plane perpendicular to their long axis. Due to the complex configuration and attachments of the middle turbinate, image review in all three planes is required. (**a**–**d**) Anterior coronal, axial, sagittal and posterior coronal images demonstrating the anterior attachment that lies in the sagittal plan (green), the middle attachment (basal lamella) that lies in the coronal plane (yellow), and the posterior attachment that lies in the axial plane (red). In this example, due to the undulating nature of the basal lamella, it is represented several times on this single axial image

two structures is the semilunar hiatus, which forms the superior entrance to the ethmoidal infundibulum. The uncinate process may be pneumatised, everted, paradoxical or lateralised and variations may lead to narrowing of the adjacent ethmoid infundibulum, the space formed between the uncinate process medially and lamina papyracea laterally (Fig. 14.6d–f).

The degree of pneumatisation of the maxillary sinus is variable (Fig. 14.7a). The sinus ostium opens on the medial wall between the attachment of the uncinate process and lamina papyracea and drains into the ethmoid infundibulum. The position of the maxillary ostium is usually aligned with the lamina papyracea on coronal images but can be variable depending on the extent of sinus

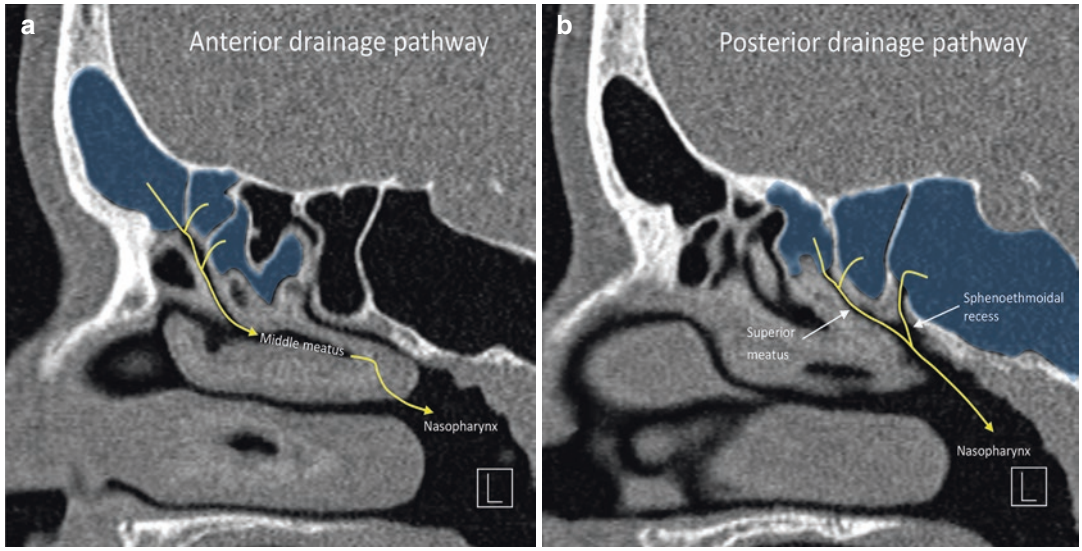

Fig. 14.4 Anterior and posterior paranasal sinus drainage pathways. (**a**) Parasagittal image showing the basal lamella of the middle turbinate separating anterior and posterior ethmoid cells and forming the boundary between anterior and posterior drainage pathways. The anterior drainage pathway is labelled. (**b**) Image from the same patient showing the sphenoid sinus ostium opening into the sphenoethmoidal recess, and posterior ethmoid cells opening into the superior meatus, forming the posterior drainage pathway

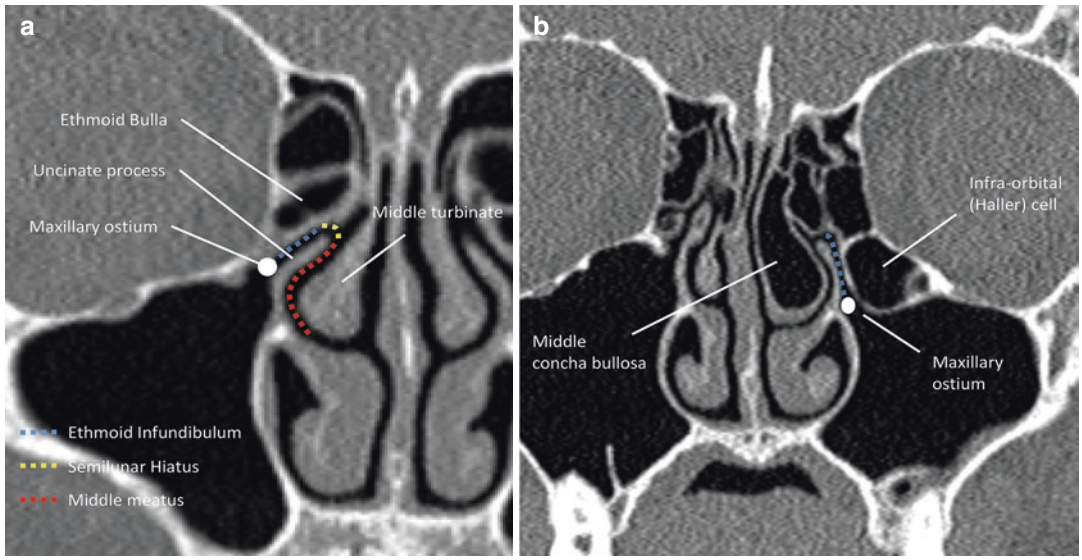

Fig. 14.5 The osteomeatal complex (**a**) is a functional unit that comprises the uncinate process (UP), semilunar hiatus (yellow dotted line), maxillary ostium (white dot), middle meatus (red dotted line), ethmoidal infundibulum (blue dotted line) and ethmoid bulla. (**b**) Pneumatisation of the middle turbinate and a large infraorbital (Haller) cell causes distortion of the left osteomeatal complex, although ethmoidal infundibulum remains patent. Note in this example the maxillary ostium is more medially located than usual in relation to the lamina papyracea

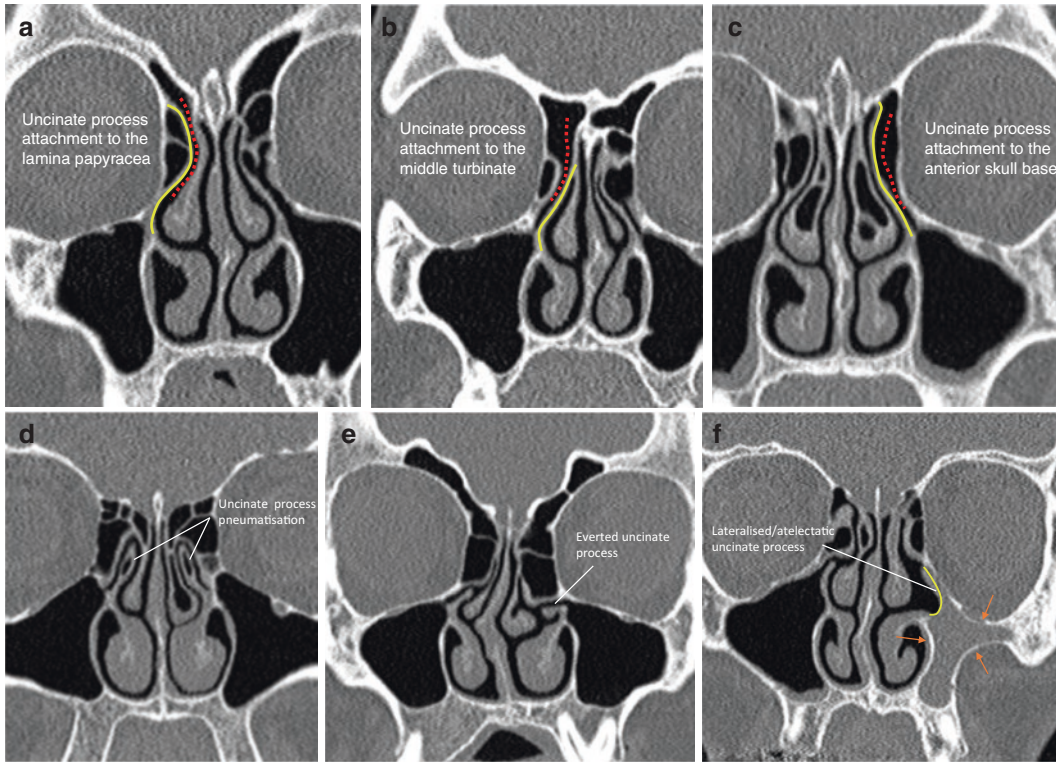

Fig. 14.6 Variations of the uncinate process. The anterior attachment of the uncinate process (yellow line) determines the route of frontal sinus drainage (red dotted line): (**a**) attachment to the lamina papyracea, with frontal sinus drainage directly to the middle meatus, (**b** and **c**) attachment to the middle turbinate and anterior skull base with frontal sinus drainage to the ethmoid infundibulum. The uncinate processes may be pneumatised (**d**), everted (**e**), or laterally displaced (**f**). The lateral displacement results in narrowing or occlusion of the ethmoid infundibulum. Pressure changes within the obstructed maxillary sinus may ultimately result in reduction in volume of the sinus and depression of the orbital floor, known as Silent Sinus Syndrome

pneumatisation (Fig. 14.5b). Haller (infraorbital) cells are anterior ethmoid cells that extend inferior to the orbit, which may contribute to narrowing of the ethmoid infundibulum (Fig. 14.5b). Accessory ostia are often present along the medial wall of the sinus, posterior to the true ostium (Fig. 14.7b). The position of the infraorbital nerve canal may vary from its usual location at the roof of the maxillary sinus, passing through the sinus on a bony mesentery (Fig. 14.7c–d).

The Anterior Paranasal Sinus Drainage Pathway: Frontal Sinus, Frontal Sinus Drainage Pathway (FSDP) and Anterior Ethmoid Cells

The degree of frontal sinus pneumatisation is variable and may directly involve the crista galli. Diploic veins may traverse the sinus and—as they are valveless—can provide a direct route for spread of infection to the cavernous sinuses (Fig. 14.8a–d).

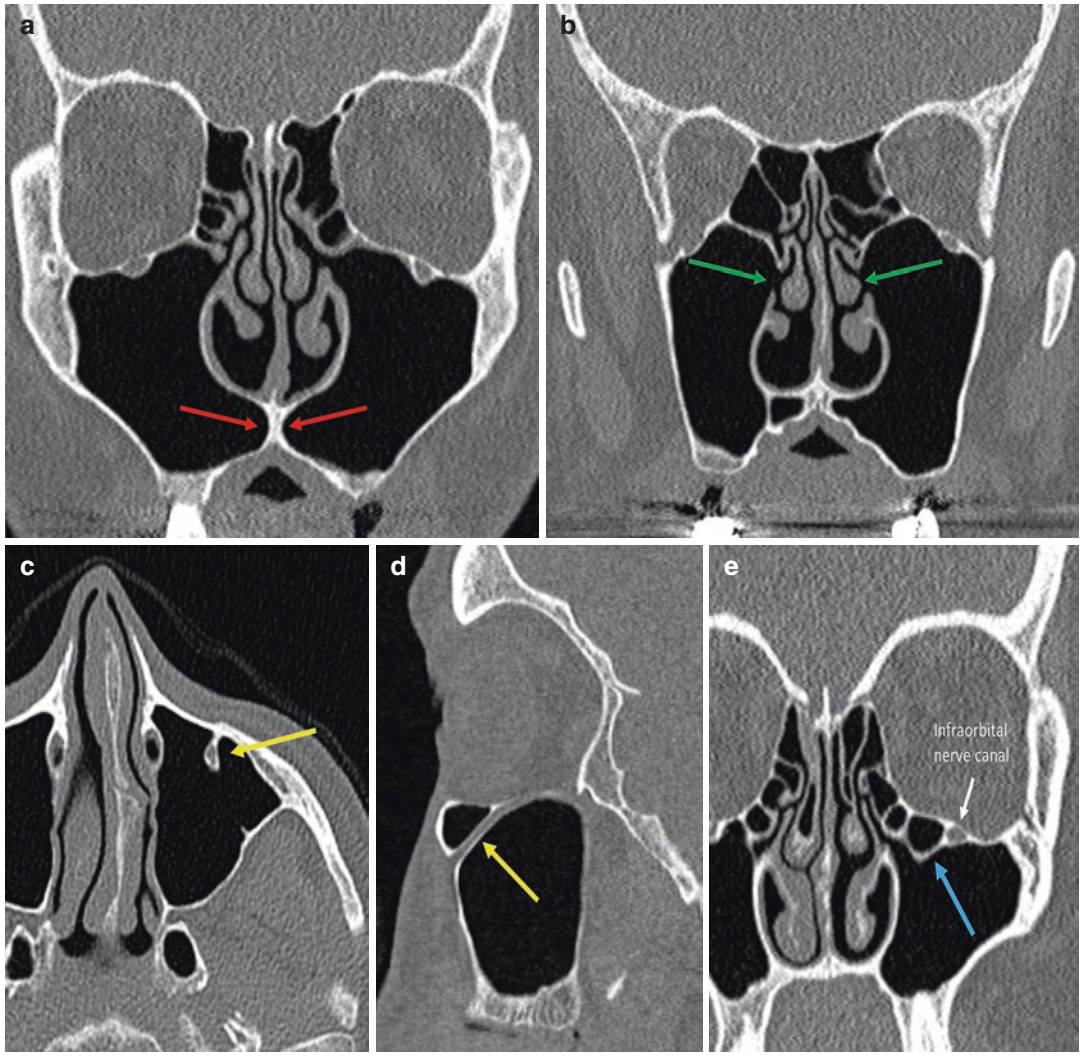

Fig. 14.7 Variations of the maxillary sinus. (**a**) Pneumatisation of the maxillary sinuses is variable, in this case there is pneumatisation medially between the nasal cavity floor and hard palate (red arrows). (**b**) In the same patient, bilateral accessory ostia are noted posterior to the true ostia (green arrows). (**c**, **d**) The infraorbital nerve is suspended within the maxillary sinus on a bony mesentery putting it at risk of iatrogenic injury (yellow arrows). (**e**) Infraorbital (Haller) cells (blue arrows) in this case are seen extending up to the infraorbital nerve canal

The frontal beak indicates the level of the frontal sinus ostium, which separates the sinus above from the FSDP below (Fig. 14.9a). The anatomy of the FSDP is complex as it depends on both the anterior attachment of the uncinate process (as discussed above) and the configuration of the adjacent anterior ethmoid cells, which form its walls. The anterior wall of the FSDP is formed by the agger nasi cell, the most anterior ethmoid cell and first to be encountered on coronal imaging. The ethmoid bulla, usually the largest anterior ethmoid cell, forms the posterior wall (along with suprabullar cells when present). The medial wall is dependent on the uncinate attachment and may comprise the middle turbinate or uncinate itself, whilst the lateral wall is formed by the lamina papyracea or agger nasi cell (Fig. 14.6a–c). Enlargement of any of these cells may lead to displacement and narrowing of the FSDP. To appreciate the complex anatomy in this

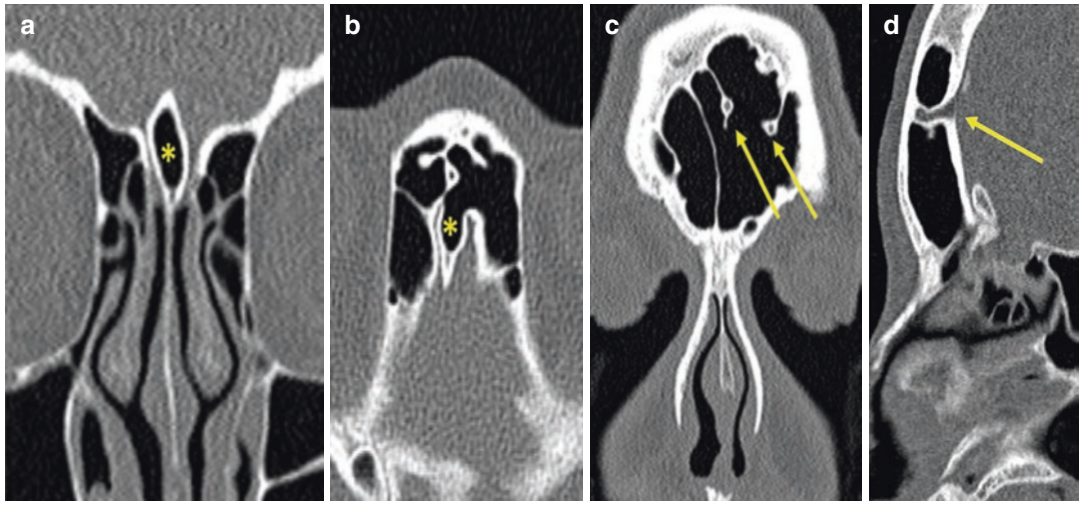

Fig. 14.8 The frontal sinus. (**a**, **b**) The degree of frontal sinus pneumatisation is variable and may involve the crista galli (asterisk). (**c**, **d**) Diploic veins, which can sometimes be seen to traverse the sinus, provide a direct route for the spread of infection to the dural venous sinuses, which puts the patient at risk of cavernous sinus thrombosis (arrows)

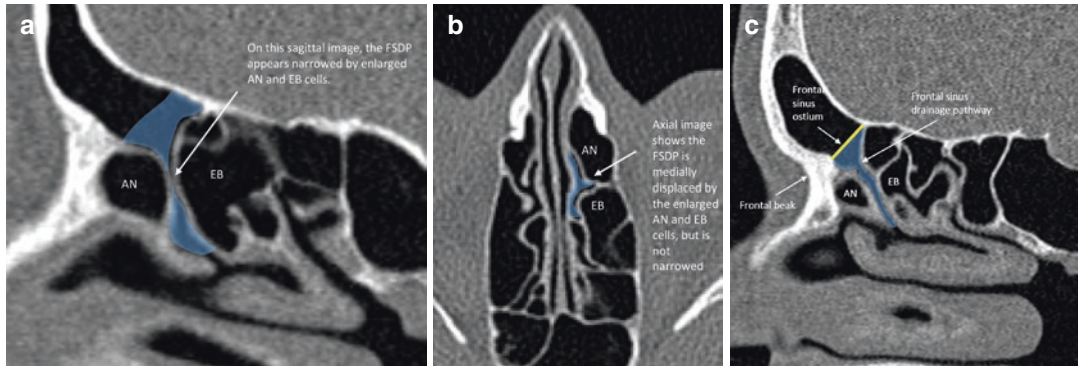

Fig. 14.9 The frontal sinus drainage pathway (FSDP). (**a**) The frontal beak marks the level of the frontal sinus ostium, inferior to which the frontal sinus drainage pathway is formed. (**b**) When enlarged, the agger nasi cell (AN) and ethmoid bulla (EB) can narrow the frontal sinus drainage pathway. Care must be taken to review imaging in all planes, as the FSDP may appear narrowed in one plane, but be displaced and widely patent when reviewed in other planes (**c**)

area, images must be reviewed in all planes (Fig. 14.9b–c).

Frontoethmoid cells are a subset of anterior ethmoid cells that extend superiorly beyond the frontal beak into the frontal sinus, for which classification systems have been described [11]. Inconsistent use of terminology within the literature makes communication of imaging findings relating to the anterior ethmoid cells particularly challenging. In response to this, the 2014 European Position Paper [9] advocates anatomical description of the frontoethmoid cell location relative to the FSDP (anterior, posterior, medial or lateral), rather than the use of other classification systems. Whilst this gives a general idea of the related anatomy, more detail may be preferable in order to accurately define surgical procedures, educate trainees and report outcomes. With this in mind, the International Frontal Sinus Anatomy Classification (IFAC)

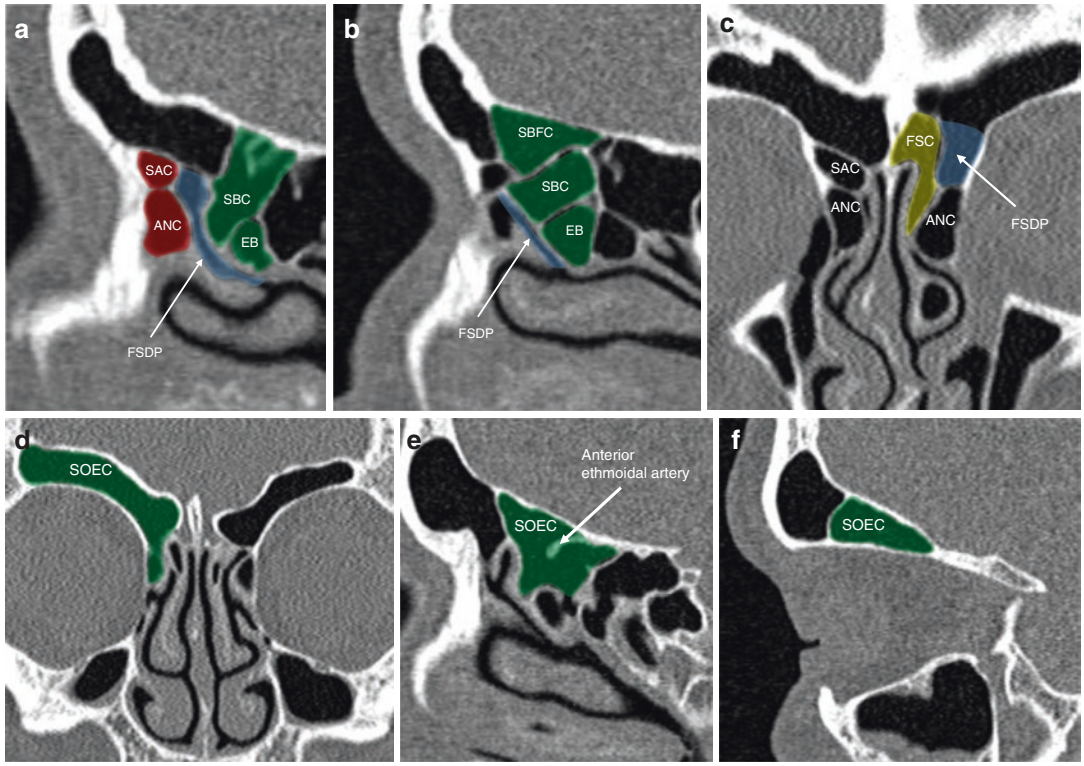

Fig. 14.10 Examples from the International Frontal Sinus Anatomy Classification (IFAC) [10]. This classification system separates the anterior ethmoid cells that surround the FSDP into an anterior group (which push the FSDP medially, posteriorly or posteromedially—highlighted in red), a posterior group (which push the FSDP anteriorly—highlighted in green) and a medial group (which push the FSDP laterally—highlighted in yellow). The anterior group include the agger nasi cell (ANC), supra agger cell (SAC) and the supra agger frontal cell (SAFC). The posterior group includes the suprabullar cell (SBC), suprabullar frontal cell (SBFC) and supraorbital ethmoid cell (SOEC). The medial group comprises frontal septal cells (FSC). Images **a**–**c** show the relationship of these cells to the FSDP. Images **d**–**f** are from the same patient, showing the anatomical relationships of a large supraorbital ethmoid cell, note should be made of the relatively exposed position of the anterior ethmoidal artery as it traverses the cell

was published [10]. Some examples are included below (Fig. 14.10a–f), the reader is directed to the original paper for additional detail.

The anterior ethmoidal artery, a branch of the ophthalmic artery, is located by the presence of a small notch at the superomedial orbital wall on coronal imaging. It may travel along the ethmoid roof or, when there is a pneumatised cell extending above it, be suspended within the sinuses on a bony or fibrous mesentery exposing it to injury during endoscopic surgery (Fig. 14.11a–c). Defects in the lamina papyracea, either traumatic or developmental, are important to recognise as orbital contents may prolapse into the ethmoid sinuses (Fig. 14.11d).

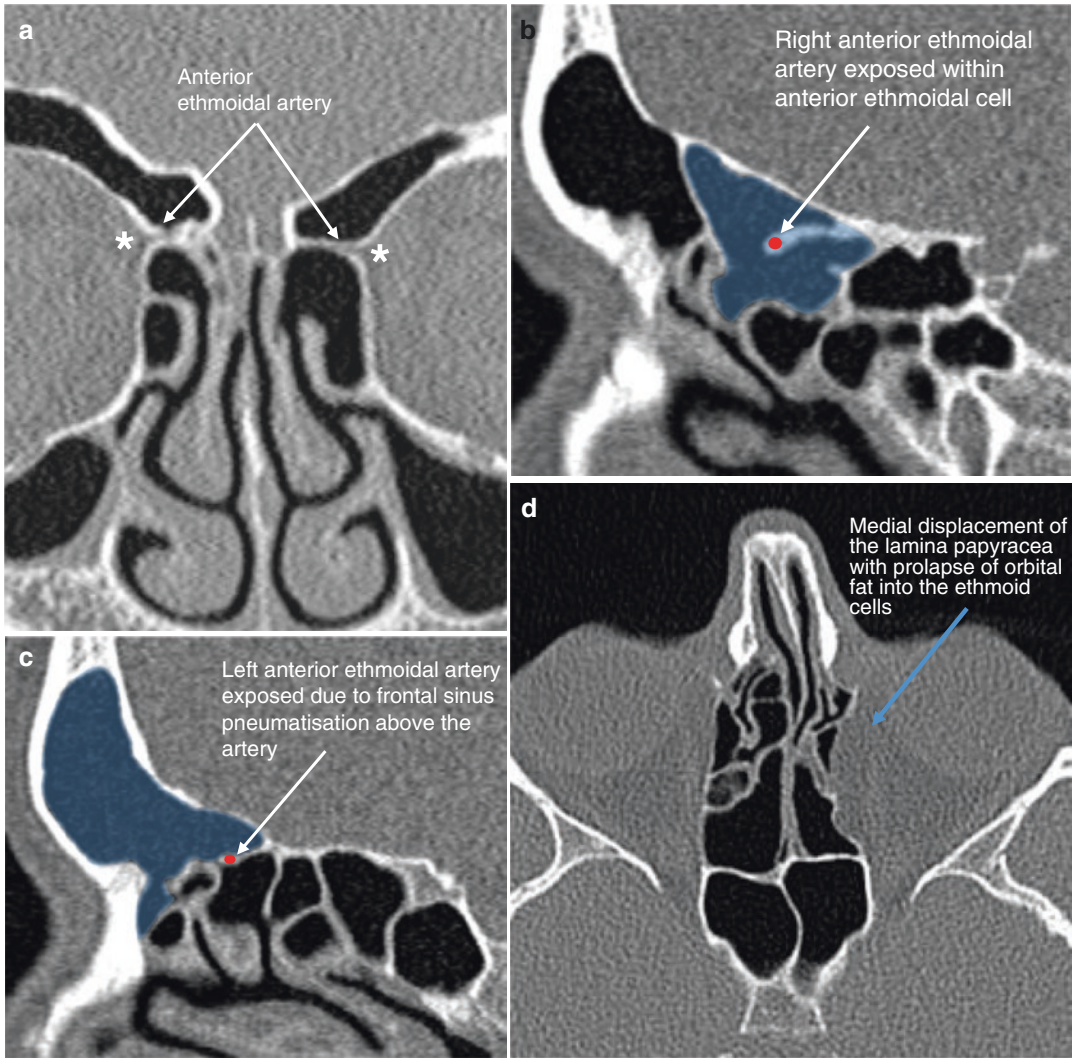

Fig. 14.11 (**a**) The anterior ethmoidal artery is located by the presence of a small notch at the superior aspect of the lamina papyracea (asterisk), which is best appreciated on coronal imaging. Where there is pneumatised sinus extending above the artery it becomes exposed, putting it at increased risk of iatrogenic injury. Pneumatisation is commonly from a supraorbital ethmoid cell (SOEC) (**b**) but can also be due to posterior pneumatisation of the frontal sinus (**c**). As seen in this case, the two cell types cannot be differentiated on a single coronal image. (**d**) Medial displacement or dehiscence of the lamina papyracea, either congenital or relating to previous injury should be recognised

The Anterior Skull Base

The height of the anterior skull base relative to the orbits is variable and a standardised method for measurement has been described [12]. The widely used Keros classification describes the depth of the olfactory fossa (Fig. 14.12a–d), with a deeper fossa leaving the thin lateral lamella exposed to injury. Anterior skull base asymmetry or areas of bone dehiscence at the ethmoid roof are important to communicate.

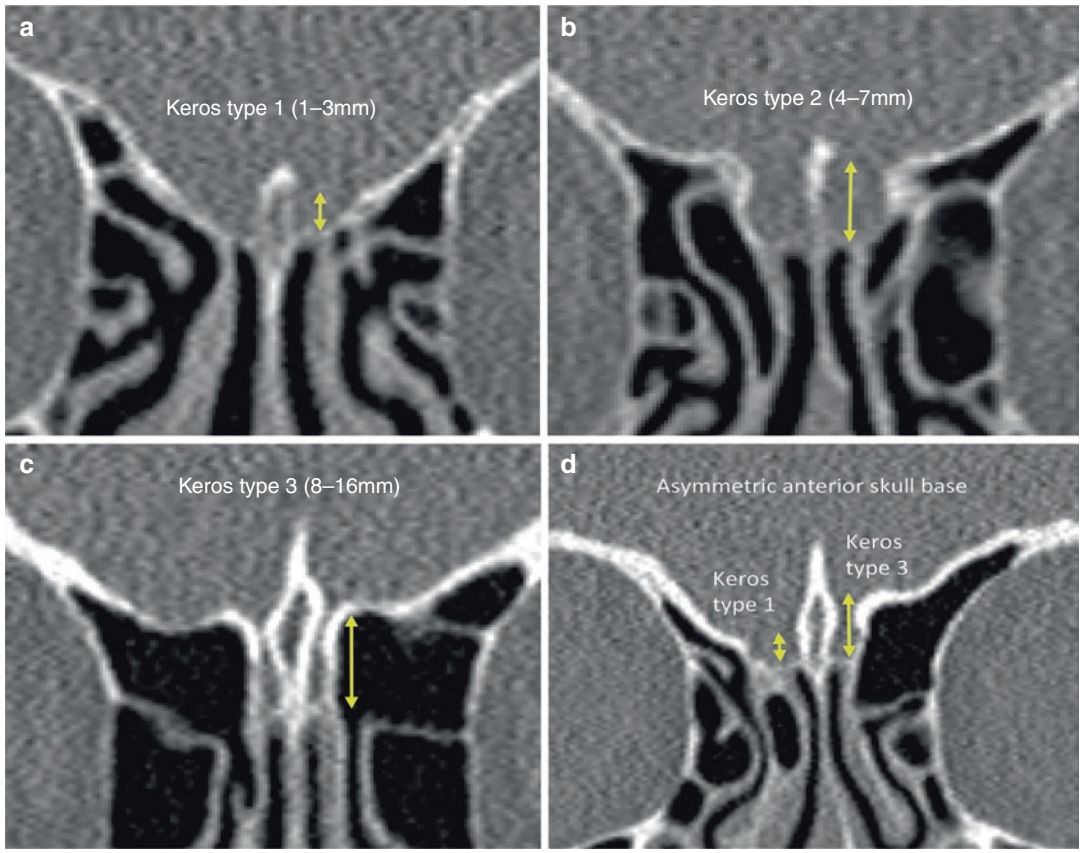

Fig. 14.12 Anterior skull base. Variations in the depth of the olfactory fossa can be described using the Keros classification system (**a**–**d**). The type 3 configuration puts the thin lateral lamella at increased risk of injury during endoscopic surgery

The Posterior Sinus Drainage Pathway: Sphenoid Sinus and Posterior Ethmoid Cells

The posterior ethmoid cells drain via the superior meatus and sphenoid sinus drains via the sphenoethmoidal recess into the nasopharynx (Fig. 14.13a), forming the posterior drainage pathway (Fig. 14.4). Sphenoid sinus pneumatisation is variable and described as conchal (minimal or no pneumatisation), presellar (confined to the anterior sphenoid body with no extension posterior to the anterior wall of the pituitary fossa) or sellar (the commonest type where sphenoid pneumatisation extends below the sphenoid sinus) (Fig. 14.13b–d). Lateral pneumatisation may extend to the pterygoid process, clinoid processes and greater sphenoid wing (Fig. 14.13e–f). Vital neurovascular structures are closely related to the walls of the sphenoid sinus, including the optic nerve (ON), internal carotid artery (ICA), maxillary division of the trigeminal nerve within foramen rotundum (V2) and Vidian nerve. These structures can protrude into the sinus and their bony canal may be dehiscent (Fig. 14.13g). There is often asymmetry in the size of the sphenoid sinuses and attachment of a laterally deviated intersinus septum to one of these bony canals puts the structure at additional risk during surgical manipulation. Sphenoethmoidal (Onodi) cells are posterior ethmoid cells, which extend superior or lateral to the sphenoid sinuses (Fig. 14.13h,i).

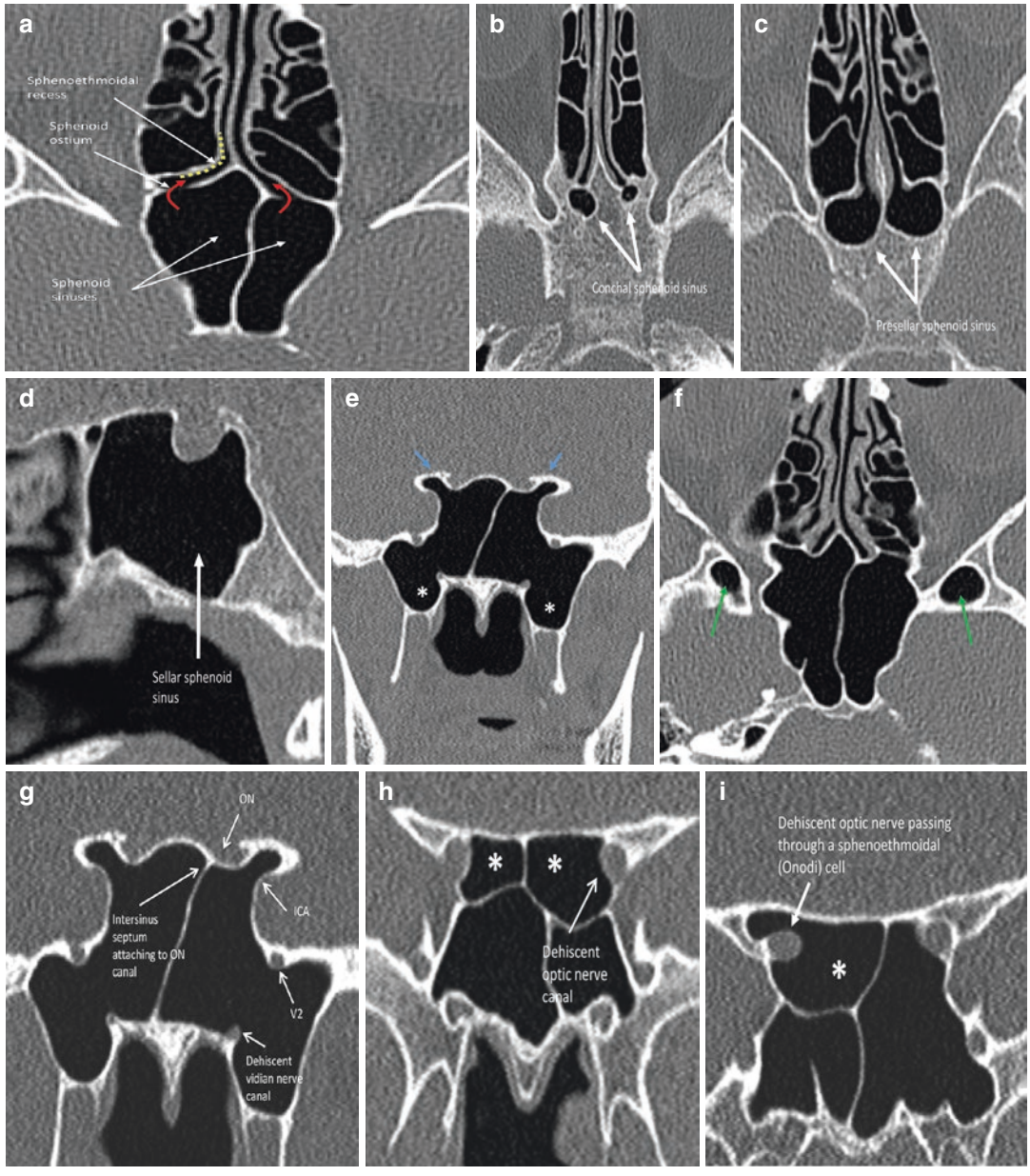

Fig. 14.13 Sphenoid sinus drainage is via the sphenoid ostium, into the sphenoethmoidal recess (**a**). Sphenoid pneumatisation is described as conchal, presellar or sellar (**b**–**d**). (**e**, **f**) Lateral pneumatisation of the sphenoid may involve the pterygoid process (asterisk), and anterior or posterior clinoid processes (blue arrows)

Critical neurovascular structures may protrude into the sinus and their bony canal may be dehiscent. Such structures include the optic nerve (ON), internal carotid artery (ICA), maxillary division of the trigeminal nerve (V2) and the Vidian nerve (**g**). Intersinus septa may attach to these bony canals, putting them at additional risk during surgery. Onodi (sphenoethmoidal) cells are posterior ethmoid cells that extend superior or lateral to the sphenoid sinuses (asterisk) and may be unilateral or bilateral (**h**, **i**)

Structures Outside the Sinonasal Cavity

Evaluation of structures outside the sinonasal cavity such as the orbits, infratemporal fossa and intracranial contents is of particular importance for the reporting radiologist as surgical colleagues may be less familiar in review of these areas. Soft tissue CT reconstructions and MRI are of particular value in this regard.

Pre-operative CT Report

The purpose of the radiology report is timely communication of accurate and clinically relevant information to the referring clinician, such that it adds value to patient care. Sinus CT reports are generated by radiologists with varying levels of experience, the anatomy is relatively complex and important anatomical variations occur with high frequency. It is therefore unsurprising that authors have found inconsistencies in reporting of both critical and non-critical findings [13].

There is growing support globally for the use of standardised radiology reporting, where the radiologist populates predefined fields within a reporting template, rather than traditional narrative reporting [14]. Recently, 'contextual reporting' has also been proposed, which specifically tailors the structured report to the disease process or examination in question [15]. There has been much discussion in the literature about the potential benefits and risks associated with the implementation of standardised reporting [16–20] and these are summarised in Table 14.1.

Table 14.1 Perceived benefits and risks associated with standardised radiology reporting

Benefits	Risks
• Improved consistency • Increased clarity • Reduced grammatical and voice recognition errors • Improved educational benefit for trainees by providing a systematic approach to reporting • Reduces 'satisfaction of search' errors—this is a common source of error in diagnostic radiology, in which the radiologist fails to pick up additional findings after finding an initial abnormality • Increased accessibility to data for research, quality improvement and machine learning/radiomics • May limit second opinion requests or reduce the need for further discussion with the reporting radiologist • Financial benefits in some areas	• Less flexible/restricts autonomy • Less personalisation—it is difficult to produce standard report templates that satisfy all radiologists • Less familiar for radiologists • May not be tailored to the clinical scenario • Too generic/simplistic—for example, it may be difficult to choose which template to use if there is more than one pathological process • May be more time-consuming—initially this is likely, although over time it may increase efficiency • May be too restrictive—there should always be scope to add free text comments • Concern that the radiologist will spend more time looking at the template and less at the imaging, increasing error rates • Technical barriers with current reporting products not having a level of usability to encourage use.

Whilst referrer satisfaction with standardised reporting has been shown to be generally higher than that of their radiology colleagues [21], there is now recognition from international radiological societies that the move to standardised reports should be seen as a positive one [14]. The Radiological Society of North America (RSNA) commenced work on a template report library in 2008 (radreport.org), which is now a common initiative between the European Society of Radiology (ESR) and RSNA. This has a dedicated Template Library Advisory Panel (TLAP), which reviews and edits templates proposed by their members. Successful template design is a balance between comprehensive recording of all findings and a concise, clinically relevant, accessible report. There remains no consensus opinion as to what constitutes the optimal CT sinus report, but an example template is included for reference (Table 14.2). It is likely standardised reports will need to be adapted to suit local practice and level of expertise.

Table 14.2 Example of standardised template for radiology report of CT sinuses

- Technique
- Comparison with
- Findings
  - Paranasal sinuses and their drainage pathways (to include degree of pneumatisation, patterns of inflammatory sinus disease and anatomical variants, where present)
    Anterior sinus drainage pathway
      Frontal sinus and FSDP
      Maxillary sinus and ethmoid infundibulum
      Anterior ethmoid cells
    Posterior sinus drainage pathway
      Sphenoid sinus and sphenoethmoidal recess
      Posterior ethmoid cells
  - Nasal cavity (to include a description of the distribution of polyps/inflammatory mucosal thickening, where present)
    Septal deviation/spurs/perforation
  - Surgically relevant anatomical variants
    Anterior skull base asymmetry/dehiscence/Keros classification
    Anterior ethmoidal artery canal position
    Lamina papyracea
    Infraorbital (Haller) cell
    Turbinate pneumatisation (concha bullosa)
    ICA/ON/V2/Vidian canal position/dehiscence
    Sphenoid septa insertion to neurovascular canal
    Sphenoethmoidal (Onodi) cell
- Other (extra-sinonasal findings)
- Impression

Despite the evidence and growing support from radiological societies, there is still variable uptake across the globe and within different radiology subspecialties. Resolution of complex issues regarding implementation will require ongoing collaboration between the international radiological societies, improved technology solutions and strong leadership to ensure engagement at the local level [22–24].

Radiological Imaging Techniques in the Nose and Sinuses

Forty years ago, radiological imaging of the nose and sinuses consisted primarily of plain radiographs, providing basic anatomic information and minimal diagnostic value to the ENT surgeon. The sequential emergence of computed tomography (CT) and magnetic resonance imaging (MRI) heralded the advent of 3D imaging; vastly increasing the ability to diagnose sinonasal pathology and assist treatment planning. Modern CT (both conventional and cone beam) and MRI are now widely used in the nose and sinuses and are augmented by functional and vascular imaging in specific scenarios (Table 14.3). The rapid growth of multidetector CT (MDCT) has facilitated patient access to imaging within most healthcare systems around the world and MDCT is the most widely performed imaging investigation in the nose and sinuses [25]. The more recent development of cone beam CT (CBCT) offers similar imaging information but with specific differences—CBCT will therefore be considered separately.

Multidetector CT (MDCT)

As demonstrated in the section on imaging anatomy, the nose and sinuses are ideal for *MDCT*: the high attenuation bony walls and very low density air-filled spaces produce natural contrast between adjacent structures, displayed with very high spatial resolution. Mucosal thickening, secretions and neoplasms have similar, intermediate density due to the relatively poor soft tissue contrast of MDCT and are therefore interpreted in the context of clinical history and endoscopic findings. Modern MDCT is fast, using multiple rows of detectors and image reconstruction algorithms to image the nose and paranasal sinuses in seconds [26]. The images are acquired with the patient supine (older CT required prone oblique patient position for coronal images) and are reconstructed in orthogonal planes to enable 3D visualisation of sinonasal anatomy. The dose of ionising radiation that the patient is exposed to has significantly reduced with improvements in MDCT technique and image reconstruction [25, 27]. Dose estimates vary between vendors and institutions; as an example of UK practice, low-dose MDCT in the authors' institution uses a 64 slice scanner, low tube current (40 mAs), 0.6 mm slice collimation and an effective dose of 0.2 mSv to the patient. This equates to approximately 1 month of background radiation (compared with a

Table 14.3 Imaging options for the nose and sinuses

Imaging modality	Advantages	Disadvantages
MDCT	Widely available Quick to perform Low radiation dose Very good bony detail	Poor soft tissue characterisation
CBCT	Very low radiation dose Superb bony detail Compact size ('office based')	Very poor soft tissue characterisation Patient motion can affect images
MRI	Superb soft tissue characterisation No radiation dose	Poor bone detail Slow to perform, degraded by patient movement Patient contraindications (devices, implants)
PET-CT	Metabolic characterisation of sinonasal malignancy Identify distant metastases	Very high radiation dose Slow to perform Poor sinonasal anatomic detail
Plain radiographs	Widely available Very low radiation dose	Very poor sensitivity and specificity No 3D information/navigation

dose range of 2–4 years for body CT) and extremely low patient risk. Other centres report even lower dose techniques [28–30], with recognition of the balance required in reducing radiation dose whilst preserving image quality. From the acquired volume of CT data, image reconstructions are rapidly created and transferred to the Picture Archive and Communication System (PACS). Axial, sagittal and coronal thin slice image reconstructions use windowing and sharpness to emphasise bony detail, whilst many institutions will include at least one set of images created for soft tissue assessment. These high-resolution images can also be exported as Digital Imaging and Communications in Medicine (DICOM) format to surgical navigation applications for intra-operative guidance [31]. For these reasons, MDCT is the first-line imaging investigation for chronic rhinosinusitis (CRS), sinonasal polyps and neoplasms.

The clinical strengths of paranasal sinus MDCT include the elegant demonstration of the varied patterns of sinus obstruction, pre-operative identification of important anatomical variants (described above) and the ability to rapidly recognise complications of CRS (Fig. 14.14). The speed of image acquisition means that children and patients with cognitive impairment (dementia, learning disability) can usually undergo MDCT with adequate image quality (Fig. 14.15). The principal weakness is the limited soft tissue characterisation of MDCT (even with addition of intravascular iodinated contrast); therefore, sinonasal tumour delineation and extrasinal assessment often requires the use of an alternative modality—typically MRI (Fig. 14.16). Streak artefact from dental implants and amalgam historically degraded MDCT quality but are largely avoided now with supine acquisition and enhanced image reconstruction.

Cone Beam CT (CBCT)

CBCT emerged from dental radiography as a technique for obtaining three-dimensional (3D) oral and maxillofacial radiographic assessment. CBCT uses a 'cone' of radiation from an X-ray tube that is moved in an arc around the patient's head, with two-dimensional detectors used to reconstruct 3D images of the imaged volume [32] (Fig. 14.17). The patient remains stationery, hence there is no spiral of the X-ray beam to image large areas (as in MDCT); the field of view is therefore small and CBCT use is limited to specific anatomic subsites (e.g. knee, ankle, petrous temporal bone). The majority of CBCT systems are upright, compact units that use very low radiation doses, enabling point-of-care 'office-based' CBCT to be performed in a man-

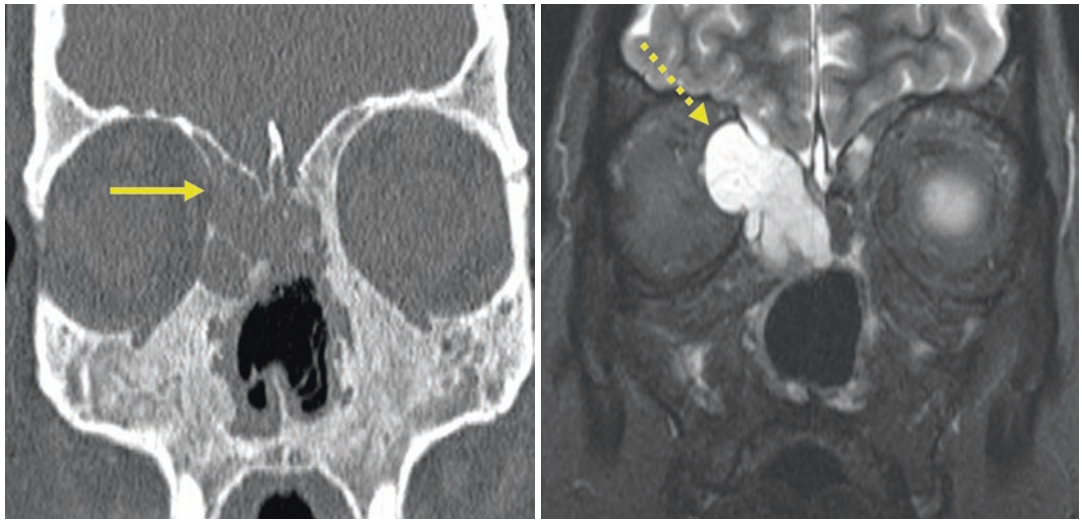

Fig. 14.14 A 52-year-old female with *granulomatous polyangiitis* (GPA). Coronal MDCT (left) demonstrates dehiscence of the right lamina papyracea (arrow), septal destruction and florid hyperostosis. Six months later, the patient developed right proptosis and orbital pain. Coronal fat-suppressed T2 MRI (right) shows fluid expansion of the right ethmoid sinus with herniation through the lamina papyracea, indicating *mucocoele* formation. Note the intact orbital periosteum, seen as a low signal margin (dotted arrow)

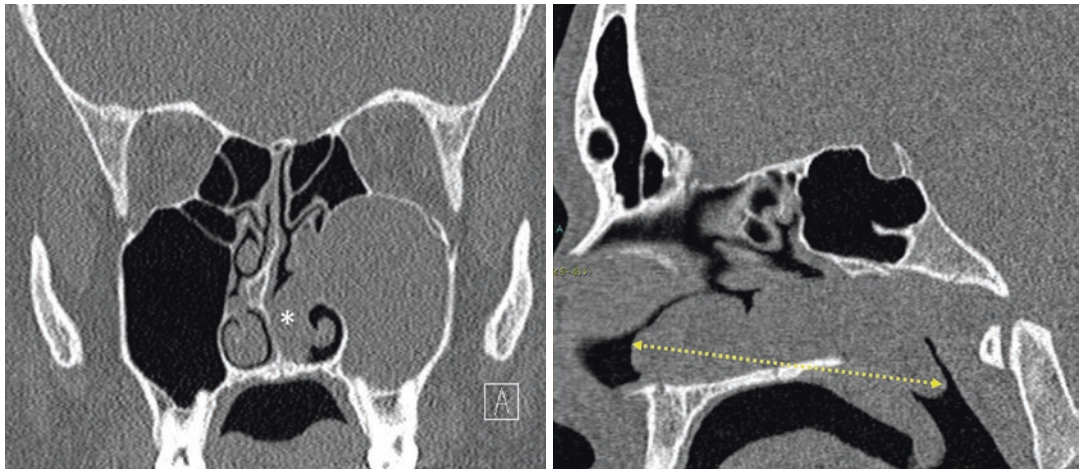

Fig. 14.15 A 15-year-old female with learning disability (limiting clinical examination) and unilateral nasal obstruction. Coronal and sagittal MDCT shows left antral opacification with a solitary poly (asterisk) extending from the antrum to the left posterior choana (dotted arrow). There is no bone erosion and the margins are well defined. The patient proceeded to functional endoscopic sinus surgery (FESS) with resection of a benign *antrochoanal polyp*

ner not feasible with MDCT and MRI—potentially directly accessible to the clinician (Fig. 14.18). CBCT strengths include very low radiation dose, extremely high spatial resolution (detailed bone and dental assessment that is superior to MDCT) and the ability to be exported for intra-operative navigation [33–35]. The increasing use of CBCT in dental imaging has led to its application in the adjacent anatomy of the paranasal sinuses and petrous temporal bones, offering a substitute to MDCT at lower radiation dose (Fig. 14.19). The main limitation of paranasal

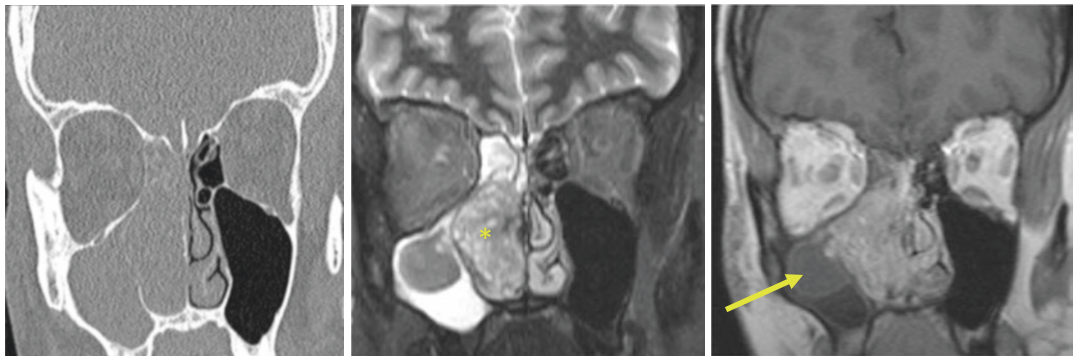

Fig. 14.16 A 44-year-old male with unilateral nasal obstruction, a fleshy polyp on examination and complete opacification of the anterior osteomeatal unit (OMU) on coronal MDCT (left). Fat-suppressed T2 coronal MRI reveals a mass centred on the middle meatus (asterisk) with 'cerebriform' signal intensity and contour, whilst the lesion enhances on the post-contrast T1 coronal MRI (right). Note that non-enhancing secretions in the antrum contain protein-rich material (yellow arrow), indicating mucinous content from chronic obstruction. Diagnosis = *inverted papilloma*

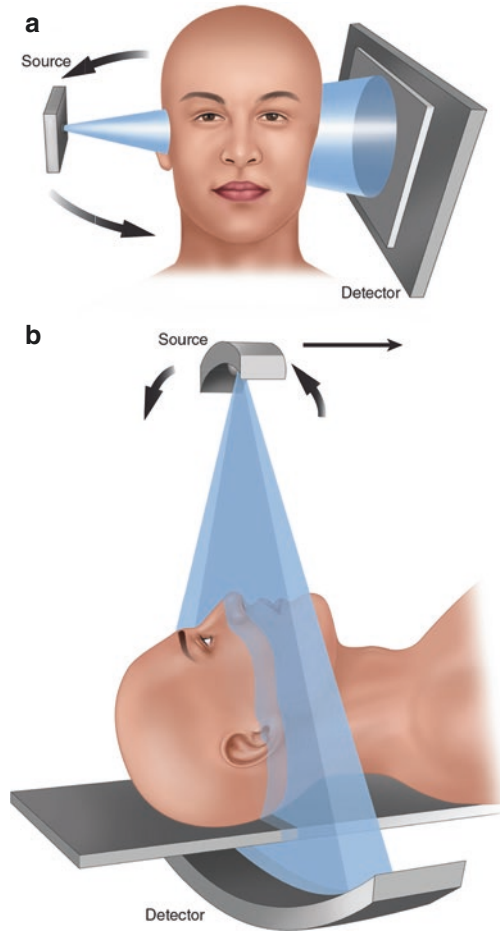

Fig. 14.17 Depiction of CT acquisition geometries. (**a**) Cone beam geometry in a compact office-based system designed for the patient to sit upright. (**b**) Conventional fan-beam geometry as it is used in MDCT scanners with the patient supine. Reproduced with permission of the American Society of Neuroradiology

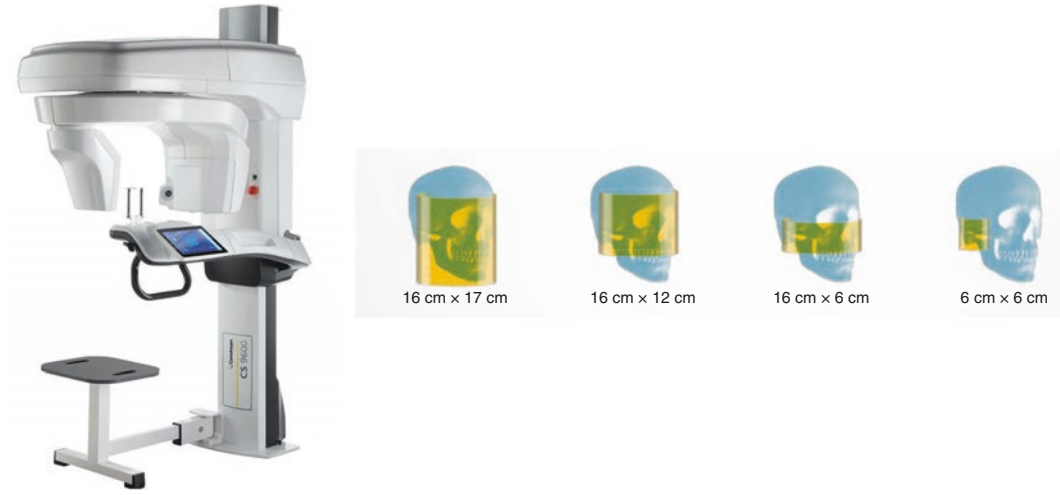

Fig. 14.18 An example of a compact, upright cone beam CT (CBCT) scan system (left). Four different field of view scan ranges are feasible with this system, including full coverage of the paranasal sinuses. *Images courtesy of Hulbert Dental ICT, Worcester, UK*

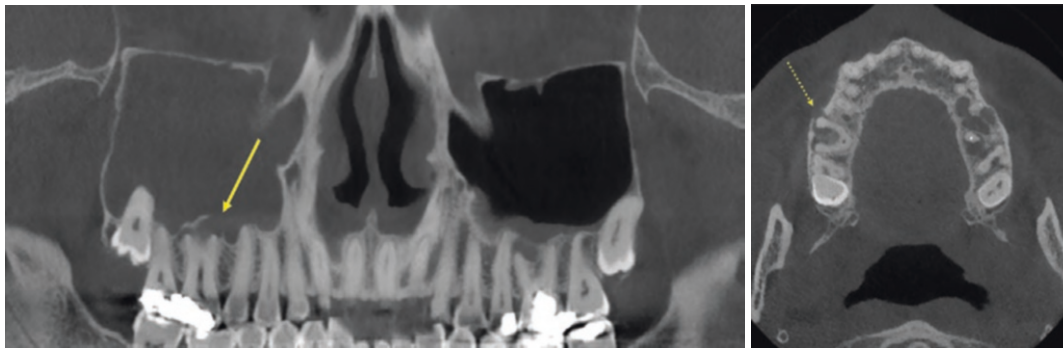

Fig. 14.19 A 42-year-old male with right facial pain and offensive, unilateral nasal discharge. Panoramic reconstruction CBCT demonstrates an opacified right antrum with periapical inflammatory lucency at the restored upper right 6 breaching the antral floor (arrow). The axial images demonstrate localised buccal cortex resorption (dotted arrow). Diagnosis = *odontogenic sinusitis*

sinus CBCT is poor soft tissue assessment—this is improving with the use of higher energy X-ray beams but remains inferior to MDCT and is problematic in patients with sinonasal neoplasia or complications of CRS. Technical factors can also compromise sinonasal CBCT image quality (e.g. patient movement, field of view). Within the last few years, CBCT's excellent bone detail and ease of access have seen this modality emerge as an increasingly attractive and valid alternative to MDCT, particularly for low-complexity sinonasal imaging.

Magnetic Resonance Imaging (MRI)

MRI provides an ideal imaging complement to MDCT/CBCT in the setting of sinonasal disease. The modality offers excellent soft tissue resolution and does not involve ionising radiation, thus addressing two main limitations of CT. Paranasal sinus MRI involves the patient lying supine within the bore of the MRI scanner and using a dedicated head/neck coil (a helmet-like device). The magnetic strength of MR systems varies, but the majority of sinus MRI in the United Kingdom is

performed on 1.5 or 3 Tesla machines using a 60 (standard) or 70 cm (large) bore width. 'Open' MR systems provide more space around the patient but at a significant cost in magnet strength and image quality; therefore, their use in rhinology is uncommon. Contraindications to MRI are well documented (ferromagnetic implants, metal foreign bodies) but a growing number of implanted devices (especially cardiac) are now MRI safe or 'conditional', i.e. the patient can undergo MRI but only under clearly defined conditions. Compared to CT, MRI provides less bone detail and is slower to obtain: a complete paranasal sinus study requires intravenous contrast (gadolinium) and can last 30–45 min, depending on local practice. Each MR sequence lasts several minutes at a time and patient movement during image acquisition can significantly degrade image quality; MR may not be feasible without sedation or general anaesthesia in specific patient groups (e.g. young children, dementia). The benefits of MRI are the superb soft tissue characterisation, which enables complications of CRS to be identified (Fig. 14.20) and sinonasal neoplasms to be characterised and staged, including the delineation of perineural disease spread. Detailed extrasinal assessment of the anterior cranial fossa, orbits and face (Fig. 14.21) are additional MRI benefits, unparalleled by other modalities [36].

In the authors' institution, paranasal sinus MR typically occurs alongside MDCT in patients who require soft tissue characterisation with imaging—particularly sinonasal neoplasia. Standard technique involves multiplanar T1 and T2 weighted sequences with the option of fat suppression to help tumour delineation and diffusion weighted imaging (DWI) to assist detection of malignancy or abscess (Fig. 14.22). The addition of intravenous contrast (gadolinium) enables neoplastic enhancement to be differentiated from secretions and normal mucosa, allowing accurate pre-operative tumour delineation (Fig. 14.16). Tumour relationship to periosteum, dura, orbital contents and skull base are critical in planning safe surgical resection and also facilitate accurate radiotherapy planning in patients where non-surgical treatment is appropriate. In our institution, fat-suppressed post-contrast T1 weighted images are obtained in the coronal plane (2.5 mm thick slices) and as a high-resolution 3D volume (0.8 mm slice thickness), which can be viewed in any plane with isotropic resolution (Fig. 14.23). Additional MRI techniques such as Dynamic Contrast Enhancement and Time Resolved Angiography can provide non-invasive assessment of lesion perfusion and vascularity in specific scenarios, such as juvenile nasopharyngeal angiofibroma.

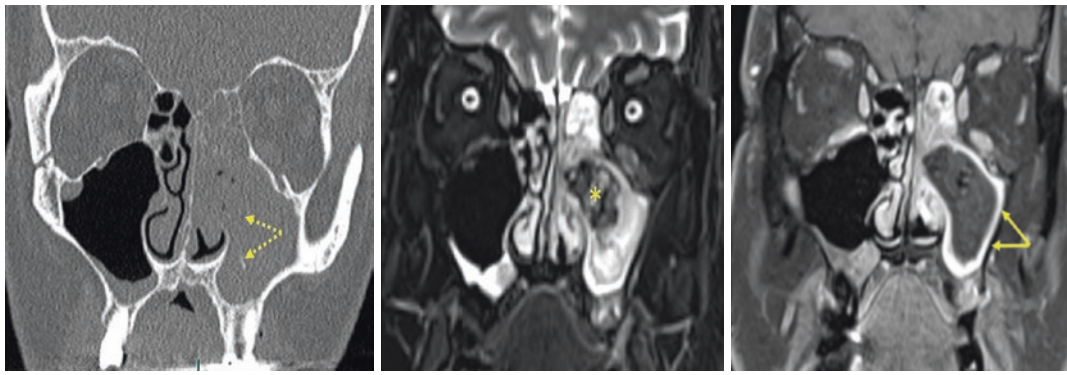

Fig. 14.20 A 47-year-old male with CRS, developed unilateral nasal blockage and bloody discharge. Coronal MDCT shows anterior OMU obstruction with expanded maxillary ostium and calcific foci (dotted arrows) raising suspicion of neoplasia. Coronal fat-suppressed T2 demonstrates absent signal within a mass at the ostium (asterisk). Post-contrast coronal fat-suppressed T1 (right) shows lesion non-enhancement, although the antral walls demonstrate inflammatory thickening and enhancement (arrows). During functional endoscopic sinus surgery (FESS), an obstructing *fungal mycetoma* was removed

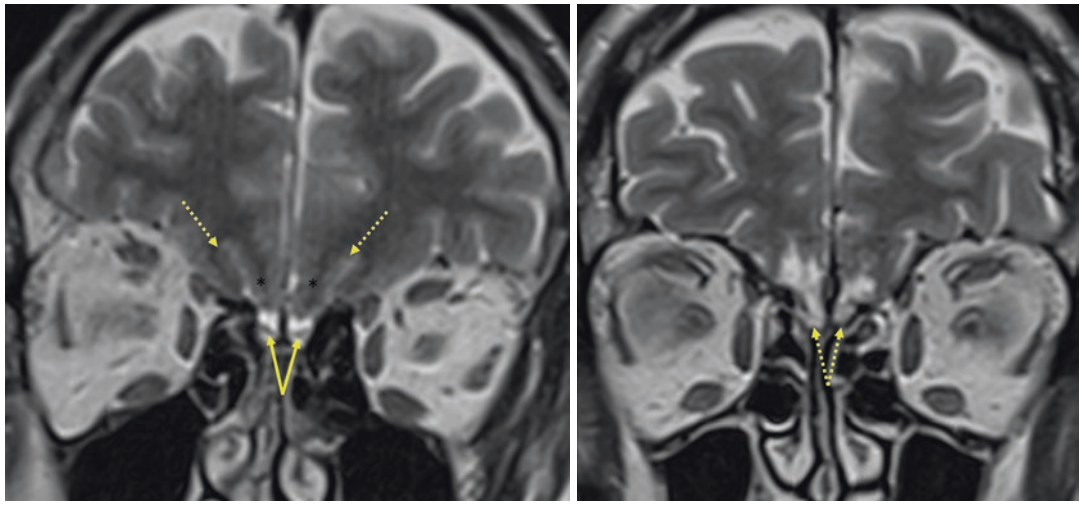

Fig. 14.21 Coronal T2 weighted MRI in a patient with normal olfactory function (left), showing symmetrical olfactory bulbs (arrows), gyrus recti (asterisks) and olfactory sulci (dotted arrows). On the right, a 61-year-old male with anosmia following head injury. MRI shows gliosis of the gyrus recti and widened olfactory sulci—a chronic sequalae of *bifrontal contusions*. Within the olfactory grooves, the olfactory bulbs are not identified (dotted arrows)

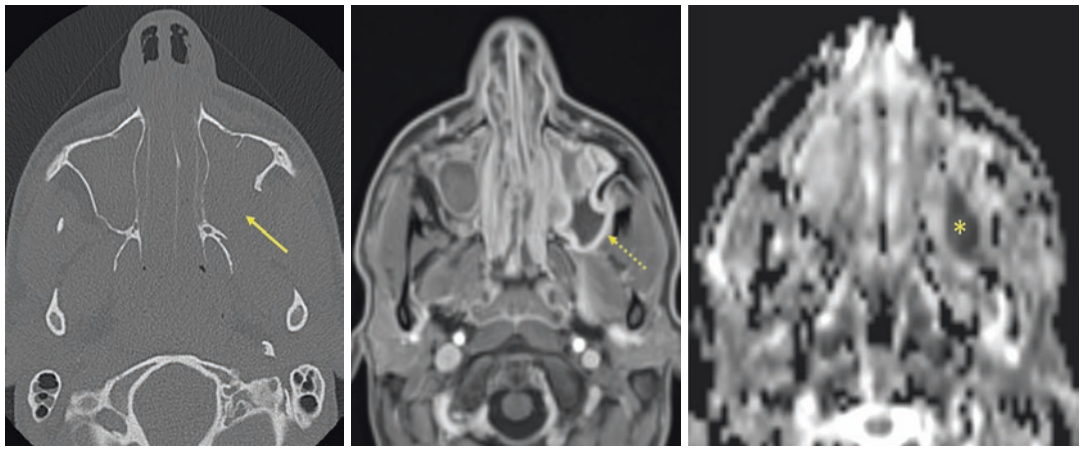

Fig. 14.22 A 27-year-old female, bilateral grade four nasal polyps and facial pain. Axial MDCT (left) shows polyps within the nasal vestibule bilaterally, pansinus obstruction and a bone defect in the lateral wall of the left maxillary antrum (arrow). Axial post-contrast T1 MRI (middle) shows thick rim enhancement in the left antrum (dotted arrow) with low signal (asterisk) on the Apparent Diffusion Coefficient map (right), indicating restricted diffusion. Diagnosis = *infected maxillary mucocoele*

Other Imaging Modalities

Positron emission tomography CT (PET-CT) using ^{18}F-FDG has a supporting role in the setting of sinonasal malignancy, particularly where additional metabolic information is required regarding the presence of nodal or distant metastases at staging or to assess primary tumour viability following treatment [37]. Squamous cell carcinoma demonstrates moderate–high metabolic activity on PET-CT, but less common sinonasal malignancies exhibit a range of FDG uptake from low

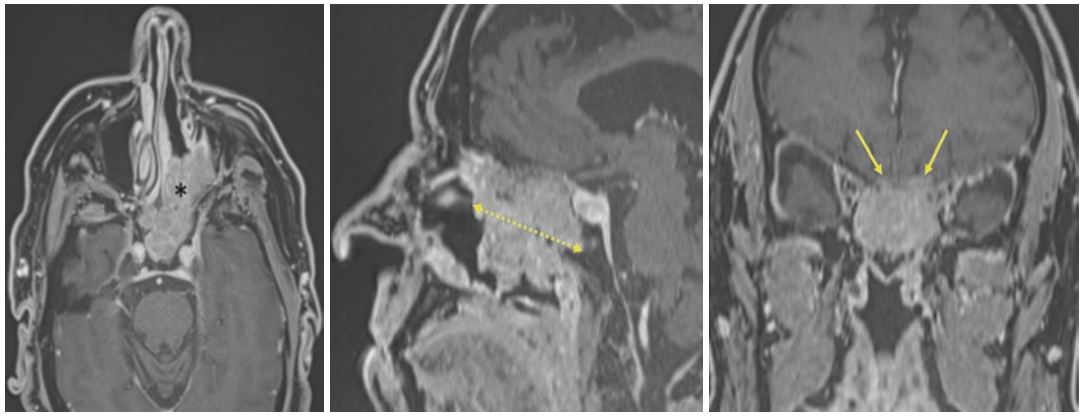

Fig. 14.23 A 56-year-old female with unilateral nasal obstruction and past history of inverted papilloma resection. Thin slice, 3D volume acquisition of post-contrast T1 weighted, fat-suppressed MRI (left) reveals a mass filling the sphenoid sinuses and posterior left nasal cavity (asterisk). The anteroposterior extent of the mass (dotted arrow) and infiltration through the planum sphenoidale to abut the dura (arrows) are delineated using isotropic (equal resolution) sagittal and coronal reconstructions from a single MRI sequence. Diagnosis = *squamous cell carcinoma*

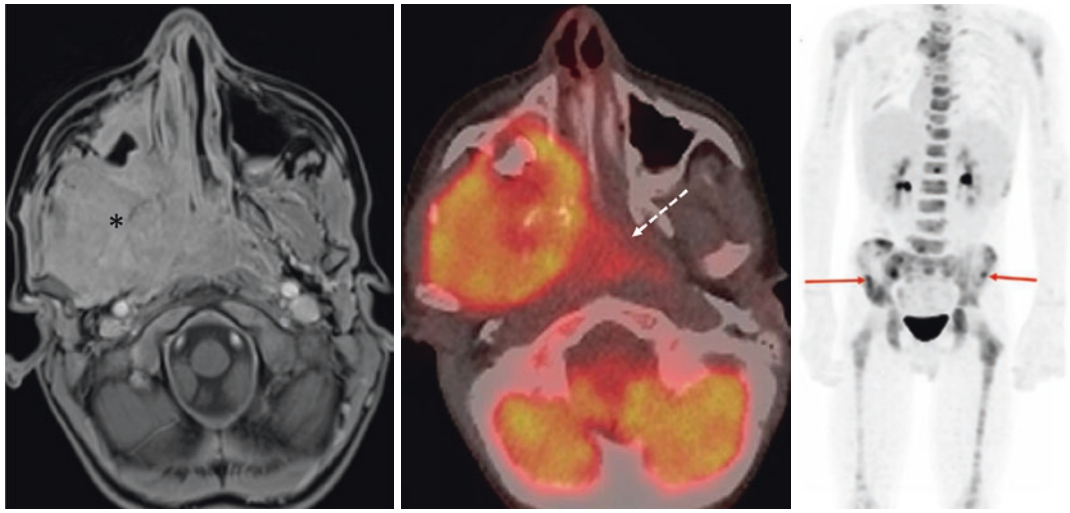

Fig. 14.24 A 9-year-old girl with unilateral nasal obstruction and facial pain. Contrast-enhanced MRI (left) demonstrates an extensive enhancing mass centred on the right masticator space and maxilla (asterisk). ^{18}F-FDG PET/CT (right) shows avid uptake within the mass—note the physiological, lower uptake in the adjacent, benign adenoid lymphoid tissue despite similar MRI enhancement (dotted arrow). PET/CT also revealed multifocal skeletal lesions (red arrows). Diagnosis = *metastatic rhabdomyosarcoma*

grade (adenoid cystic carcinoma) to intense (sinonasal undifferentiated carcinoma, lymphoma). In addition, benign conditions such as inverted papilloma can demonstrate moderate FDG uptake; therefore, the specificity of PET-CT to identify malignancy is limited. In the authors' institution, PET-CT is reserved for specific neoplastic scenarios and interpreted in the context of high-quality anatomic imaging, endoscopic and biopsy findings (Fig. 14.24).

Catheter angiography plays an important role in the scenario of a vascular tumour or malforma-

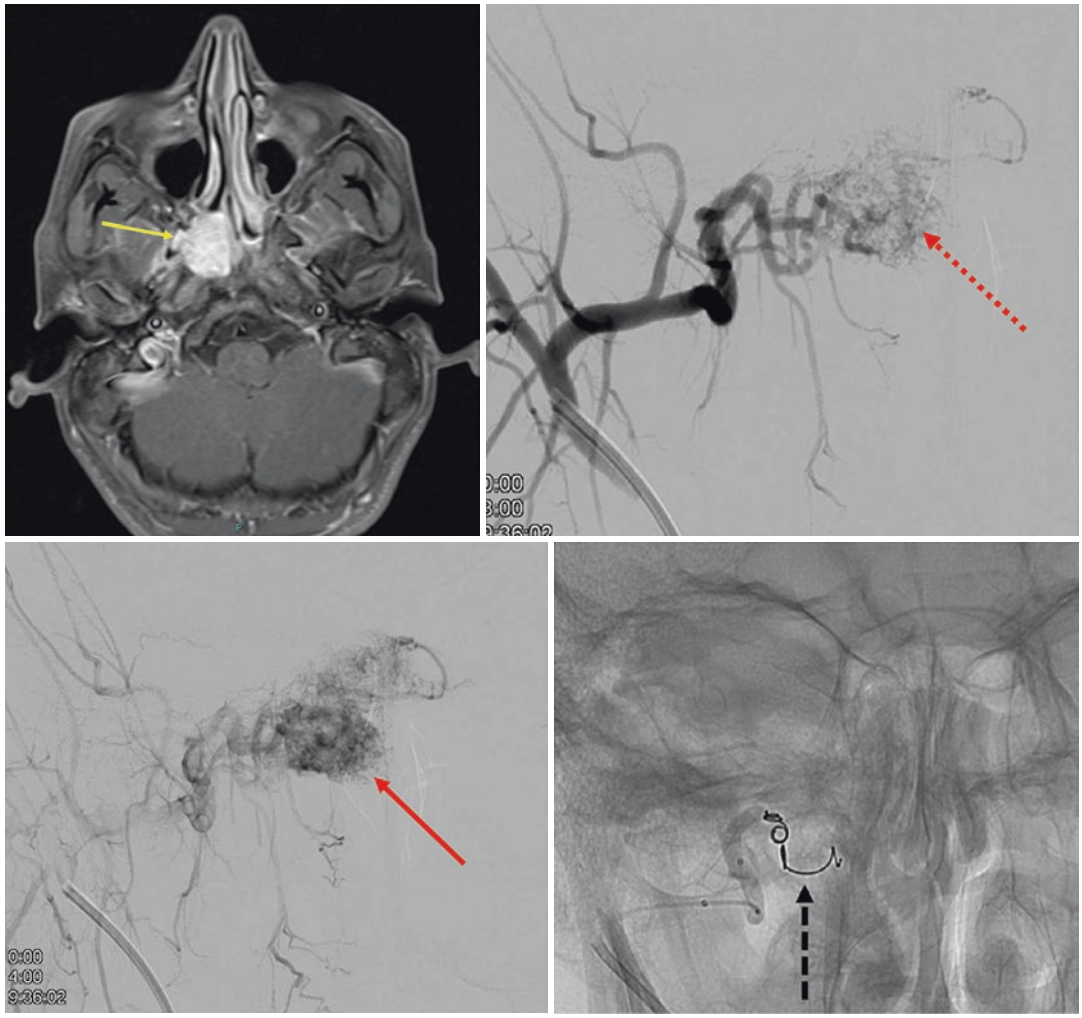

Fig. 14.25 A 14-year-old male, unilateral nasal obstruction and epistaxis. MRI shows an avidly enhancing mass at the right posterior choana with involvement of the pterygoid plates (yellow arrow). Digital subtraction angiography of the right internal maxillary artery shows immediate arteriole filling within the lesion (dotted arrow) and tumour blush (red arrow). Coil embolisation (dotted black arrow) via micro-catheter was performed with subsequent uneventful endoscopic resection. Diagnosis = *juvenile nasopharyngeal angiofibroma*

tion in the nose and sinuses. Angiography of the internal and external carotid arteries is the gold standard for determining feeding vessel origin and vascular outflow and can be combined with pre-operative arterial embolisation to reduce perioperative bleeding (Fig. 14.25).

Plain radiographs for sinonasal disease are now largely obsolete and their use is not recommended [38, 39]. The sensitivity and specificity are poor whilst the evolution of MDCT and CBCT has largely obviated the benefit of plain radiography as easy-access, low-dose imaging.

Future Developments in Rhinology Imaging

Evolution of Image-Guided Surgery (IGS) and Intra-operative Imaging

Image-guided surgery (IGS) for the sinuses and skull base emerged in the late 1980s and is utilised in an expanding range of primary and revision surgical settings [31]. Advances in radiologic imaging have facilitated increasingly accurate and innovative IGS: in particular, high spatial

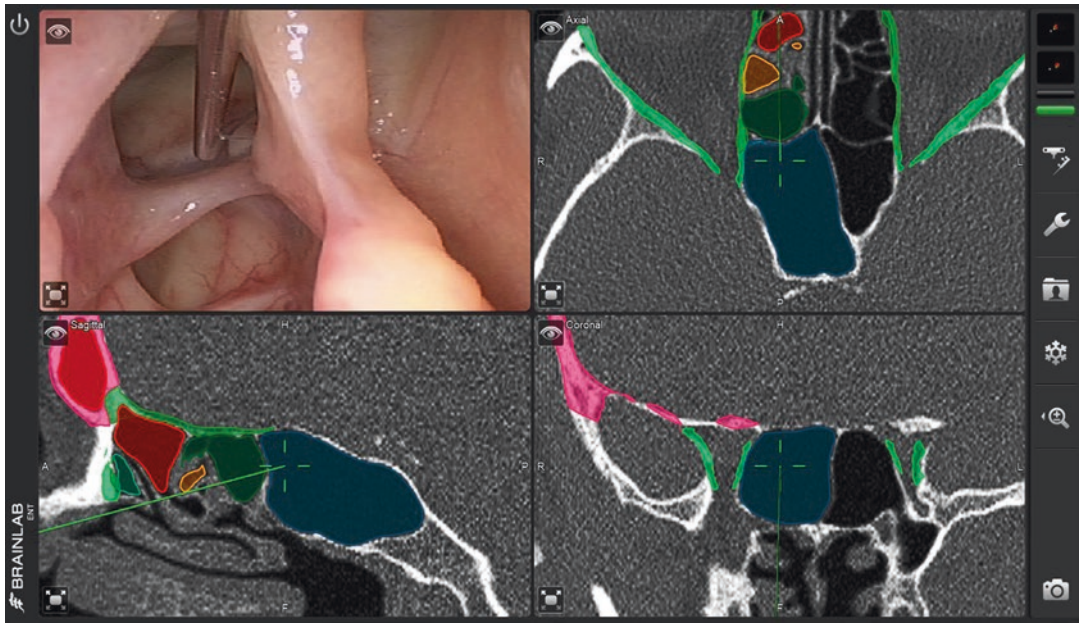

Fig. 14.26 Image-guided FESS using MDCT for real-time navigation. Note the colour-coded display of sinus and bony anatomy, providing virtual reality (VR) feedback to the operating surgeon. *Images courtesy of Brainlab AG, Olof-Palme-Straße 9, 81829 Munich, Germany*

resolution CT (both MDCT and CBCT) and MRI data creates detailed 3D volumes that can be registered with 2D endoscopic imaging with high accuracy (Fig 14.26). As IGS use continues to grow, progressively more personalised pre-operative planning is feasible, desirable to the surgeon and can be utilised in novel ways. Displaying 3D imaging anatomy alongside real-time, operative appearances presents the surgeon with a virtual reality (VR) of detailed diagnostic information regarding key anatomic features and patterns of obstruction to improve surgical efficiency and reduce the risk of complication in endoscopic sinus surgery (ESS) [40]. Recent developments in VR include the fusion of MRI and CT to combine soft tissue and bony detail to assist tumour delineation and surgical decision-making in sinonasal tumour resection; multimodality IGS better harnesses the value of diagnostic imaging in this setting. The more recent innovation of augmented reality (AR) involves the direct overlay of pre-operative imaging volumes onto endoscopic data to fundamentally alter the visual display and integrated surgical experience. The benefits and potential drawbacks of AR ESS are beyond the scope of this chapter, but there is evidence of a positive effect on clinical outcomes, training experience and surgical opinions [41, 42]. The evolution of IGS will continue to build on the strengths of modern radiology with increasingly novel methods of presenting personalised imaging information, to the benefit of both the surgeon and the patient.

A discrete application of IGS is the acquisition of real-time radiology during sinonasal procedures—*intra-operative imaging (IoI)*. The key benefit of IoI is to present imaging anatomy obtained during the surgical procedure rather than from a pre-operative time point, demonstrating temporal and operative changes to the surgeon in real time. IoI use in selected sinonasal procedures is endorsed [43], but practical issues with imaging hardware—particularly time constraints and safety (e.g. MRI)—have limited large-scale use. More recently, technical development of smaller imaging systems with faster acquisition times makes wider IoI use increasingly feasible. As an example, the practical ease of cone beam imaging (either with a CBCT scanner or C arm fluoroscopy) within the operating room environment has been shown to be feasible for complex or revision ESS and skull base sur-

gery [44, 45]. Outside of sinonasal surgery, the safe and effective use of intra-procedural cone beam anatomic imaging in maxillofacial [46] and spinal surgery [47] is further evidence to support the wider use of sinonasal IoI in the future.

Emerging Applications of Artificial Intelligence (AI)

Of all the technical developments in modern imaging considered in this chapter, the integration of *artificial intelligence (AI)* into sinonasal radiology may lead to the greatest changes in clinical practice. The potential for AI to support human image analysis and decision-making within otorhinolaryngology is the subject of extensive research with new applications and clinical tools emerging at a rapid pace [48]. Radiology AI is multifaceted and fast moving; however, automated detection and interpretation of imaging findings are of particular relevance to rhinology. Machine Learning (ML) and Deep Learning (DL) via convolutional neural networks (CNN) are the principal techniques being studied and require large volumes of defined data to train and validate accuracy. The anatomy of the nose and sinuses and the modalities used in rhinology imaging provide an attractive AI environment: detailed, standardised imaging that can be labelled, segmented and categorised to provide the necessary substrate for ML and DL applications.

Several authors have recently described a role for AI in the automated detection of important anatomic findings on paranasal sinus MDCT. Using 675 coronal MDCT images, a CNN (Google Inception-V3) was trained to recognise the position of the anterior ethmoid artery. This DL technique then correctly identified the artery with 82.7% accuracy on a set of validation cases [49]. The presence of middle turbinate pneumatisation was studied with the same CNN and demonstrated 81% accuracy for correct identification of concha bullosa on MDCT [50]. In addition to anatomic variant detection, accurate identification of disease patterns with AI is increasingly reported—in one study, osteomeatal complex occlusion on MDCT was accurately identified using a CNN and subtype of DL called Transfer Learning [51]. The area under the curve of 0.87 demonstrated good to excellent classification of this single finding; however, the authors rightly noted the limitations of AI in this setting; in particular, the results were based on single 2D image interpretation rather than 3D volume (due to current limits of CNN application) and therefore do not directly compare to human analysis in clinical radiology practice. What these early studies do indicate is the strong potential for AI to provide an automated support tool for the reporting radiologist, especially within the template/checklist framework of sinonasal MDCT and CBCT reporting.

The use of AI to characterise pathological imaging findings, assist management planning and even detect prognostic features is referred to as *Radiomics*. Sinonasal neoplasms present a set of clinical challenges (benign vs malignant, optimal management, surgical vs non-surgical therapy) where radiomics might add significant clinical value and this area has been the subject of several recent studies. An example is the detection of squamous cell carcinoma development in patients with inverted papilloma, where analysis of anatomic imaging is challenging. In this setting, radiomic MR image interpretation (texture analysis) produced a similar level of performance to an experienced head-and-neck radiologist in a study of 46 patients [52]. The imaging information used by the ML algorithm in this study goes beyond the human eye, comparing multiple intrinsic quantitative features and identifying patterns to characterise malignant risk. Using imaging from patients with squamous cell carcinoma, characterisation of radiomic MRI features has recently been studied to identify predictors of treatment success and failure [53]. Using multiparametric MR image interrogation (which included diffusion and perfusion parameters, lesion morphology and intratumour image analysis), the ML-based prediction of local control and recurrence was highly accurate, albeit in a small patient group. The potential for radiomics to improve clinical outcomes in patients with sinonasal disease is increasingly apparent and the

future utility of AI to assist—and potentially replace—human roles is both exciting and controversial.

Key Learning Points

- CT (multidetector and cone beam) and MRI are widely used in the nose and sinuses and provide superb detail of bone and soft tissue anatomy, respectively.
- To fully appreciate the complex 3D anatomy of the nose and sinuses, images should routinely be reviewed in all three planes (axial, coronal and sagittal).
- Standardised radiology reporting has perceived benefits and risks but will become more widely used in the future, with the aim of increasing clarity of reporting and reducing error.
- High-resolution imaging enables increasingly accurate image-guided surgery (IGS) to reduce operative time and complications, with wider use of intra-operative imaging (IoI) anticipated.
- There is an emerging role for artificial intelligence (AI) in sinonasal radiology to support human image analysis and assist patient management.

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Section III

Paediatric Sinonasal Disorders

Congenital Sinonasal Disorders

15

Grace C Khong and Raymond W. Clarke

Introduction

Babies are obligate nasal breathers and any obstruction to nasal airflow at birth will cause severe hypoxaemia, only relieved when the baby breathes through the mouth. Nasal obstruction in the newborn is an emergency requiring urgent referral and treatment [1].

Embryology of the Nose and Midface

The skeletal structures of the midface develop by fusion of the frontonasal prominence, the maxillary prominences and the mandibular prominences. Aberrant fusion of these processes can give rise to orofacial clefting, of which the commonest varieties are cleft lip (CL) and cleft palate (CP), often with some nasal involvement.

The nasal cavities and the paranasal sinuses develop from the primitive foregut. Two epithelial elevations (nasal placodes) appear at about the fourth intra-uterine week. They fuse to form the lateral nasal walls, and the midline septum extends dorsally to separate the nose into the two nasal cavities, each closed behind by the 'bucco-nasal membrane'. A persistent bucco-nasal membrane presents as choanal atresia.

Partial or complete agenesis of the nose (arhinia) is a rare neonatal emergency requiring immediate airway support (a Guedel airway, followed in many cases by a tracheostomy) before definitive repair is undertaken.

The developing nose is closely related to the primitive forebrain, from which it becomes separated by the bony structures of the anterior skull base, including the cribriform plate. The developing brain may herniate into the nasal cavity, giving rise to a meningocele or an encephalocele, which can then present as a nasal mass.

Choanal Atresia

Choanal atresia (CA) is a developmental structural anomaly caused by failure of canalization of the posterior nasal apertures (choanae). The incidence is 1 in 5000 to 1 in 8000 live births [2]. The atretic plate may be bony (29%), membranous or mixed (71%) and unilateral or bilateral (ratio 2:1), with the latter presenting as an airway emergency at birth [3, 4].

Clinical Presentation

Unilateral CA is usually an isolated occurrence and can present in older children. In contrast,

G. C Khong · R. W. Clarke (✉)
Department of Ear, Nose and Throat, Alder Hey Children's NHS Foundation Trust, Liverpool, UK
e-mail: grace.khong@alderhey.nhs.uk; Raymond.Clarke@alderhey.nhs.uk

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bilateral CA presents in neonates and may be associated with a series of linked congenital defects, referred to as the CHARGE association. Some or all of the following—**C**oloboma, **H**eart anomalies, **A**tresia of the choanae, **R**enal anomalies, **G**enital hypoplasia, **E**ar anomalies—may accompany choanal atresia, and babies should always be examined and screened by a paediatrician. Some children with CHARGE features are now known to have a specific genetic cause (CHARGE syndrome).

As neonates are obligate nasal breathers, a baby affected by bilateral CA will classically have 'cyclical cyanosis' due to hypoxaemia except during mouth breathing, as occurs when the baby cries. Hence, it becomes almost impossible to feed the child. If the diagnosis is suspected, the midwife or neonatologist will try to gently pass a small suction catheter from the anterior nares into the nasopharynx. If it fails to pass bilaterally, a diagnosis of choanal atresia is suspected, and a good confirmatory test is to place a cold stainless steel spatula or mirror just under the baby's anterior nares during a breath cycle to test for misting and condensation (mirror test) (Fig. 15.1). It is important to note that neonatal rhinitis (see below) and obstruction of the nose due to secretions is commoner than choanal atresia, and in many suspected cases, no true atresia is found.

Fig. 15.1 Nasal misting

Immediate Management

The first step in management is to secure a safe airway. A Guedel tube in the oral cavity may suffice to enable safe transfer to a paediatric centre, but endotracheal intubation may be required, especially as many of these children have associated medical conditions.

Definitive treatment is surgical and should be undertaken as quickly as the baby is stable to facilitate feeding. Delay may compromise breast feeding, and if immediate treatment is not possible, an oro-gastric feeding tube will be needed.

Investigations

Imaging (CT scanning) helps to confirm the diagnosis and plan definitive treatment. A little nasal suction and a few drops of a decongestant such as 0.5% ephedrine help to clear the nares and make for a more helpful image. Classical features of choanal atresia on CT scan in addition to bony and/or membranous obstruction are an air-fluid level in one or both nasal cavities on axial scans, thickening of the vomer and medialization of the pterygoid plates (Fig. 15.2).

As mentioned earlier, a multidisciplinary approach with paediatricians, cardiologists and ophthalmologists is needed to check for any of the features of a possible CHARGE association. Further investigations such as ECHO and ultrasound of the renal tract are undertaken, as dictated by the findings.

Surgical Management

There are now a variety of surgical reconstructive techniques available. Older techniques relied on an open trans-palatal approach but improved modern endoscopes—especially the 120° endoscope that permits a highly detailed view of the posterior nares on a monitor to facilitate transnasal surgery under direct vision—have made

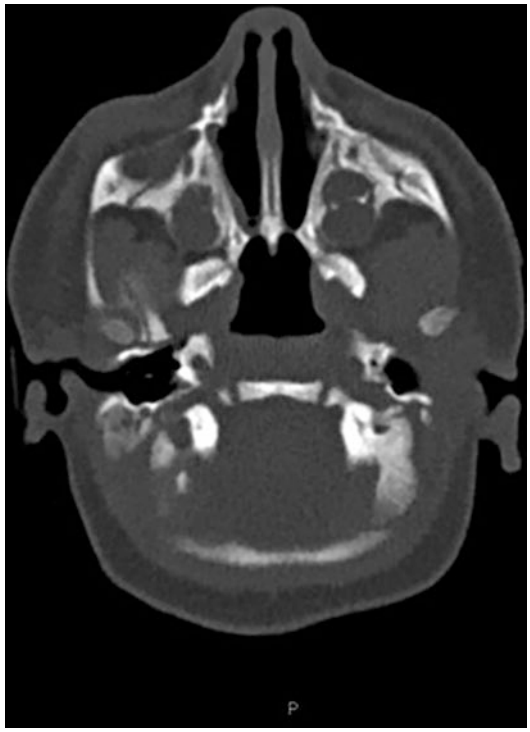

Fig. 15.2 Axial CT scan of bilateral choanal atresia (Courtesy of S De)

this route of access much more popular (Fig. 15.3).

The baby is placed in Rose's position (extension at atlanto-occipital and cervical joints) and a cleft repair mouth gag (Fig. 15.4) is placed with a suspension suture over the base of the uvula to give better visualization with the 120° telescope. Good-sized posterior nasal apertures are usually established with careful serial dilatation using bougies or urethral dilators, keeping the distal ends of the dilators in view at all times and ensuring the direction is inferomedial to avoid the skull base. Bone and soft tissue included in the region of the thickened vomer may be removed with a forward-biting bone forceps or a microdrill. A microdebrider can be used to enlarge the orifices and fashion symmetrical choanae. The baby can soon feed but will need careful follow-up as recurrent stenosis is not uncommon.

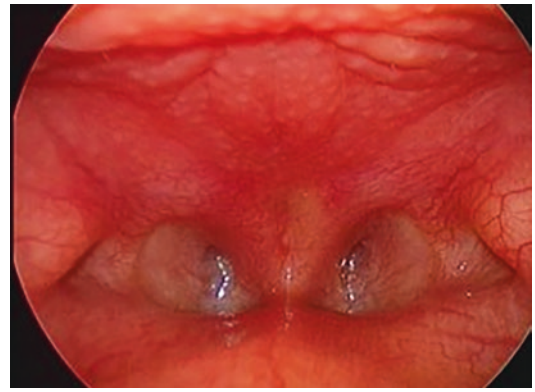

Fig. 15.3 Examination of posterior nares using 120° telescope (Courtesy of S De)

Fig. 15.4 Cleft palate repair mouth gag used in choanal atresia repair

Some surgeons use post-operative stents, but many prefer not to. A recent meta-analysis has shown that stenting does not improve the success rate (around 60% with or without stents) and can cause injury to the ala, columella and nasal vestibule [5]. Nasal flaps have been suggested to reduce scarring and are becoming increasingly popular [6]. In the authors' practice, this is usually reserved for older children with unilateral CA.

Neonatal Rhinitis

Neonatal rhinitis (NR) is a common differential diagnosis and is defined as inflammation of nasal mucosa in an afebrile neonate with mucoid dis-

charge [7]. Clinical presentation is similar to other causes of congenital nasal obstruction, i.e. breathing difficulties particularly when feeding, nasal discharge, stertor, and so on. NR can be confirmed by improvement of nasal airways on gentle suctioning and nasal drops (saline or ephedrine).

Initial management is conservative with saline nasal drops and suctioning using a nasal bulb. If there is no improvement, short-term corticosteroid nasal drops can be given with close monitoring. It is important to keep in mind the possibility of maternal infections, such as chlamydia and syphilis, and if identified they can be treated accordingly.

Pyriform Aperture Stenosis

Clinical Presentation

The bony orifices in the midfacial skeleton on either side of the nasal septum that mark the anterior nares make up the 'pyriform aperture'. It contributes to the internal nasal valve (formed by the anterior end of inferior turbinate, caudal border of upper lateral cartilage and corresponding nasal septum), the narrowest part of the nasal airway that is responsible for the largest component of nasal resistance in the healthy nose. Stenosis of the pyriform aperture is rare and usually caused by excessive prominence of the nasal processes of the maxilla.

There is an association with very significant rare intracranial anomalies, such as holoprosencephaly (a defect in the development of the midline intracranial structures), and a single central incisor tooth. This is also known as the Solitary Median Maxillary Central Incisor (SMMCI) syndrome [8]. Liaison with a paediatrician for screening is essential if this is suspected, as there may be associated cardiac and urogenital anomalies.

Pyriform aperture stenosis mimics choanal atresia and is characterized by inability to pass a 2.2 mm flexible nasendoscope. A CT scan showing a pyriform aperture width of <11 mm on axial views is diagnostic [9] (Fig. 15.5). The CT scan may also reveal a median central incisor, a triangular-shaped palate and a median palatal ridge.

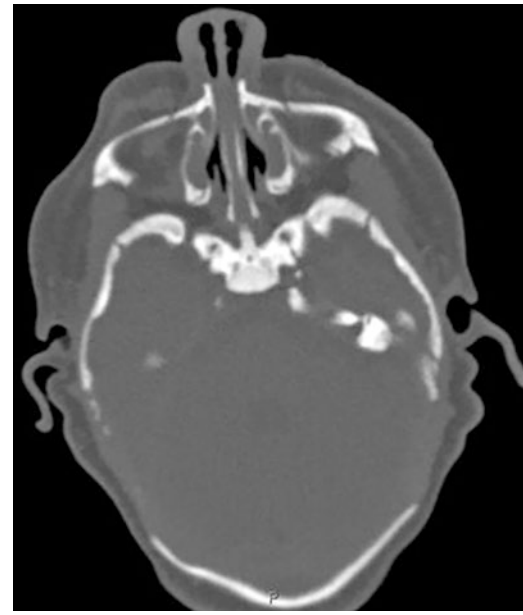

Fig. 15.5 Axial CT scan of pyriform aperture stenosis (Courtesy of S De)

Management

The early management of pyriform aperture stenosis is the same as for choanal atresia, and the prime objective is to establish a safe airway. Decongestant drops and saline irrigation may tide things over and avoid the need for immediate surgery.

Nasal dilatation using urethral or cervical dilators can avoid the more destructive drilling from surgery and its effectiveness is attributed to out-fracture or lateralization of the inferior turbinates.

More recent techniques include balloon dilatation of the stenosis.

Surgical management includes serial dilatation and/or a sub-labial approach followed by drilling of the nasal process to enlarge the apertures. In the sub-labial approach, an incision is made along the gingivobuccal sulcus, the muco-periosteum is elevated and the nasal process is carefully reduced using a drill. Meticulous care is taken to avoid traumatizing the nasolacrimal duct and the dental roots of the central incisors.

Congenital Nasal Masses

Intracranial Masses in the Nasal Cavities

A portion of the developing brain may herniate through the bony skull base and become 'trapped' below the cribriform plate within the nasal cavity to form an encephalocele. The mass contains both meninges and neurological tissue in direct continuity with the intracranial structures. An encephalocele will present as a persistent nasal mass, typically accompanied by nasal obstruction in the newborn.

A meningocele is similar but contains no neurological tissue and consists simply of meninges that contain cerebrospinal fluid.

A glioma is a neural tumour that contains nerve tissue (glial cells, usually with fibrous and vascular tissue), which is discrete from the intracranial contents, i.e. it has become 'pinched off'. Glial heterotopia refers to the presence of a mass of neural tissue in an aberrant site, such as the nasal cavity or the nasopharynx, where neural cells may have migrated some distance from the intracranial origin.

Detailed and skilled imaging is essential in the management of these lesions. Their possible connection to intracranial structures leaves the child at risk of catastrophic intracranial infection, especially following injudicious surgery or biopsy. MRI will confirm the presence of an intracranial connection and is the modality of choice if available. Treatment is surgical for all of these lesions, either by endonasal surgery, craniotomy or a combination of the two. Gliomas are typically removed trans-nasally, but a large encephalocele or meningocele will often need an open combined ENT and neurosurgical approach.

Nasal Cysts

A variety of cysts derived from embryonic tissue can present in and around the nasal structures in children.

Dermoid cysts: The commonest cystic lesion is the dermoid cyst, thought to arise from inclusion of epithelial cells along lines of fusion, hence the tendency for it to occur in the midline.

It typically presents with parents being concerned regarding aesthetic issues, but it may also become infected. Examination typically shows a smooth midline swelling on the dorsum of the nose beneath the skin. There may be an external 'punctum'. The cyst contains thick often viscous fluid, with ectodermal and mesodermal components, sometimes including skin appendages and hair follicles.

Careful evaluation including detailed imaging is essential, not least to exclude an intracranial connection as these lesions can invaginate deeply into the midline nasal cartilages and beyond, making excision very challenging.

The treatment is surgical. Very small discrete lesions can be removed with a single incision on the nasal dorsum, or endoscopically using a small incision remote from the site of the lesion, but an open external rhinoplasty approach can make for a more satisfactory aesthetic result. Larger and more extensive lesions will require liaison with neurosurgical colleagues and may need a fronto-nasal approach via a forehead incision.

Nasolacrimal duct cysts: These may present either to ENT with nasal obstruction or to the ophthalmologist with epiphora. A trans-nasal endoscopic approach is usually possible if they require surgery.

Nasoalveolar and nasolabial cysts: These cysts arise in the floor of the nose or along the nasolabial crease along the lateral nasal wall. They are usually removed by enucleation, taking care not to leave any epithelial remnants behind.

Odontogenic or dentigerous cysts: These occur in association with the development and eruption of the teeth. They may encroach into the maxillary antrum and the floor of the nose. Treatment is in collaboration with maxillofacial surgeons.

Thornwaldt's cyst: This is a midline nasopharyngeal cyst that is often asymptomatic, but increasingly found as an incidental finding dur-

ing endoscopic examination of the nasopharynx whilst performing endoscopic adenoidectomy.

Teratoma: This is a neoplastic cystic lesion that contains all three germinal cell layers, and typically presents as a firm, obstructing nasal mass. Very large teratomas may be diagnosed 'in utero' and may be associated with maternal polyhydramnios. CT and MRI scanning should be performed.

The treatment is surgical. Regular follow-up is recommended and may be assisted by serial alpha-fetoprotein (AFP) measurements.

Haemangiomas and Vascular Malformations

Classification

The International Society for the Study of Vascular Anomalies (ISSVA) classifies vascular anomalies as *vascular tumours* that include haemangiomas and *vascular malformations* (VM). Two-thirds of cutaneous haemangiomas involve the head and neck area. It is important to remember that up to 10% of cutaneous haemangiomas, especially of 'beard' distribution, have a subglottic component that can lead to airway compromise. Highly aggressive cutaneous haemangiomas can encroach on the orbit and cause visual disturbances.

Clinical Presentation

Congenital haemangiomas present at birth as a macular patch and classically have a proliferative stage followed by an involution phase at around 5–7 years old. Large proliferating haemangiomas in and around the nose may cause severe airway compromise as well as the aesthetic effects (Fig. 15.6). The differential diagnosis includes vascular lesions such as capillary and venous malformations, which can be differentiated by ultrasonography or CT/MRI scans.

Treatment

The natural history of haemangiomas is that they almost invariably resolve completely and may need no intervention, other than serial observation. If very extensive they may encroach on important

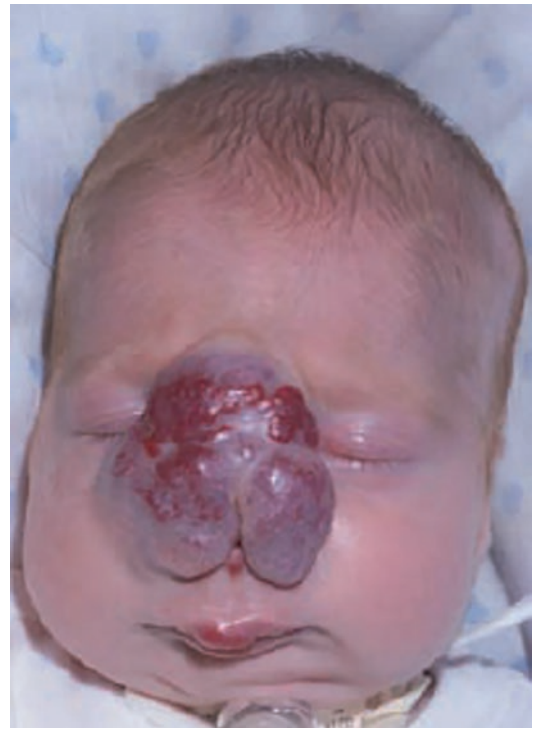

Fig. 15.6 Nasal cutaneous haemangioma (Reproduced with permission from CRC Press)

structures, such as the orbit, the nasal airway or subglottis. This may cause major functional or aesthetic problems and warrant more active intervention. Resolution of haemangiomas may be accelerated by medical treatment with propranolol [10] under the supervision of an experienced team. A typical protocol is to start with 1 mg/kg body weight per day and then to increase to an optimal 2 mg/kg/day in divided doses. Monitoring of blood pressure, heart rate and blood glucose levels is important, especially in the first 24 h. Children who are commenced on this treatment will need to be admitted for observation and monitoring. Baseline ECG and/or ECHO-cardiography is usually done before starting on medications.

Surgical excision of haemangiomas is rarely needed, but large haemangiomas can be reduced in size by serial LASER therapy. Rare, but highly aggressive, histological variants may warrant brief treatment with anti-mitotic agents under the supervision of a paediatric oncologist during periods of rapid proliferation.

Vascular Malformations (VMs)

VM of the head and neck may be slow-flow (venous, capillary and lymphatic malformations) or fast-flow (arterial). CT or MRI scans or Doppler are useful for differentiation and to know the extent of the lesion. Nasal VMs are very rare but cause significant disfigurement. They typically grow with the child and do not involute. Investigations should include cardiac assessment for high output failure, especially with a fast-flow malformation. Management depends on symptoms and the type of VM. Slow-flow VMs can be managed with LASER and sclerotherapy. Fast-flow VMs are challenging due to their high vascularity. Therapeutic options include embolization and surgical excision.

The Nasal Septum

Some degree of deviation of the nasal septum is so common as to be normal. Deviation can occur due to compression of the facial skeleton at birth, particularly following a difficult instrumental delivery. Usually no intervention is needed, but a grossly deviated septum can be repositioned in the midline using Ashe's forceps. Unless there is a very troublesome aesthetic deformity or severe airway obstruction, nasal septal surgery is usually discouraged before the mid to late teens due to the risk of a poor long-term result following growth of the midface to adulthood. Interference with nasal growth may result in lack of nasal projection and a saddle nose deformity.

Nasal Problems in Craniofacial Deformities

Congenital structural deformities of the craniofacial skeleton may occur as part of a recognized syndrome (syndromic craniofacial disorders) or as an isolated event (non-syndromic craniofacial conditions). Both functional and aesthetic nasal problems may be prominent in these disorders. Features of some of the commoner syndromic craniofacial anomalies are shown in Table 15.1.

Table 15.1 Common craniofacial syndromes

Common syndromes	Salient ENT features
Treacher Collins syndrome	Downward-slanting palpebral fissures Maxillary and mandibular hypoplasia Retrognathia Microtia with abnormal middle ear structures Conductive hearing loss Choanal atresia Cleft palate
Apert syndrome	Craniosynostosis—brachycephaly Syndactyly Maxillary hypoplasia Proptosis and hypertelorism
Pfeiffer syndrome	Similar to Apert syndrome Broad thumbs and first toe

Children with these conditions require complex multi-disciplinary care by a dedicated team that includes an otolaryngologist with a specialist interest and expertise in these conditions. Newborn babies with craniofacial anomalies may require immediate airway support due to the architecture of the midface, and narrowing of the nasal passages compounded by a crowded nasopharynx and oropharynx, prolapse of the tongue base, micrognathia and, in some cases, laryngotracheal stenosis.

A Guedel airway may tide things over until more definitive arrangements can be made, but some children will need the support of a judiciously place nasopharyngeal airway (NPA) (Fig. 15.7). In extreme cases, a tracheostomy will be required. The child may be tracheostomy-dependent for some time and, in rare cases, indefinitely.

Children with craniofacial disorders need careful surveillance and follow-up to screen for obstructive sleep apnoea (OSA). They may need early intervention to manage this disorder, such as adenotonsillectomy or continuous positive airway pressure (CPAP).

Airway obstruction, associated with these conditions, is due to the skeletal structure of the midface and may require staged orthognathic surgery (midface advancement by osteotomies with bone grafting and fixation). Such surgery may

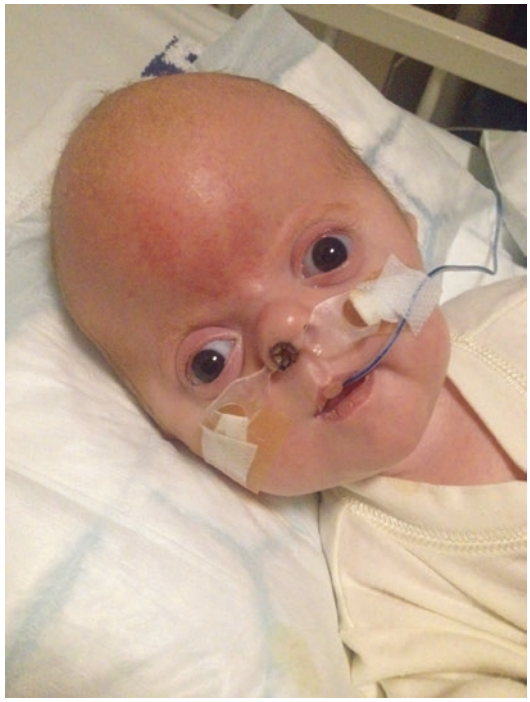

Fig. 15.7 Child with NPA in situ

ensure a safe airway and, in some cases, permit tracheal decannulation.

In recent years, distraction osteogenesis with implantation of external or internal devices, or 'frames' that can facilitate serial elongation of the facial bones over a prolonged period has been greatly refined, and may facilitate not only greatly improved aesthetic results but tracheal decannulation in some previously recalcitrant cases as well.

Trisomy 21 (Down syndrome): This is a chromosomal abnormality associated with several nasal manifestations. Absence or severe hypoplasia of the nasal bones, demonstrated by ultrasound scanning in the second trimester, is an important prenatal marker for Down syndrome [11]. Narrow nasal apertures, with flattening of the nasal profile, and hypoplasia of the maxilla all contribute to the very high prevalence of OSA in this group of children.

Cleft Lip and Palate

Clefts of the lip and palate, alone or in combination, make up the commonest congenital facial anomaly, with an incidence of about 1 in 700 live births. Maternal factors such as anti-convulsant medication (phenytoin, phenobarbital), systemic steroids, alcohol, tobacco, smoking and perhaps folic acid deficiency may be implicated.

Some cases are associated with chromosomal abnormalities, and some cases with specific syndromes and sequences such as Treacher Collins syndrome, Apert syndrome and Pierre Robin sequence. Airway obstruction may be severe in Pierre Robin sequence but can usually be managed with careful placement of a nasopharyngeal airway (NPA) (Fig. 15.7).

Clefting of the lip and/or palate may be unilateral or bilateral (Figs. 15.8 and 15.9). Rhinological involvement is variable. Even mild cases of cleft lip will be associated with abnormal insertion of the orbicularis oris muscle with splaying of the lower lateral nasal cartilage. Anomalies include shortening of the columella, distortion of the septum, functional nasal obstruction and aesthetic issues that need to be addressed as part of the overall management strategy for these children.

Some surgeons undertake some form of primary nose repair at the time of lip repair, but

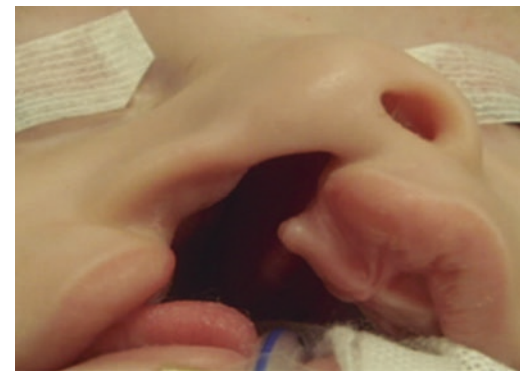

Fig. 15.8 Unilateral cleft lip and palate (Reproduced with permission from Springer)

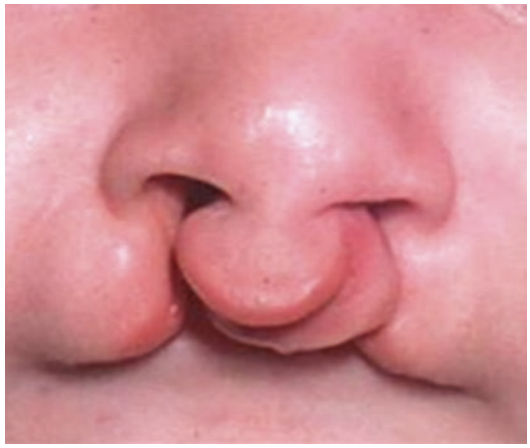

Fig. 15.9 Bilateral cleft lip and palate (Reproduced with permission from Springer)

definitive septorhinoplasty surgery is best deferred until facial growth is complete.

Key Learning Points

- Neonates are obligate nasal breathers and nasal obstruction in a newborn can present as an airway emergency.
- Careful head to toe examination is important to look for other clinical features keeping in mind possible syndromic presentations.
- Nasal obstruction can lead to significant problems with feeding that may require urgent management.
- The diagnosis of bony deformities, such as choanal atresia and pyriform aperture stenosis, can be confirmed by flexible nasendoscopy and CT scans.
- MRI scan is needed for all nasal masses to look for intracranial extension.
- The management of nasal obstruction in patients with craniofacial syndromes is complex and will need a multidisciplinary approach, including and not limited to input from maxillofacial, plastic and neurosurgical teams.

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Paediatric Rhinosinusitis

16

Peter George Deutsch
and Ann-Louise McDermott

Background

Rhinosinusitis is an inflammatory condition of the nose and paranasal sinuses and is a common condition across most of the world.

Acute rhinosinusitis (ARS) is reported to have a 1-year prevalence of 6–15% and although it is generally a self-limiting condition, it has the potential for life-threatening complications. In children and young adults, the diagnosis and treatment are challenging because of the symptom overlap with adenoidal hypertrophy and allergic rhinitis (AR) (Table 16.1) [1–4].

Chronic rhinosinusitis (CRS) is less common than ARS in children. It is, however, a significant health problem; the true prevalence of this in the UK paediatric population is unclear from the literature, but US studies suggest that it affects 2–4% of the population with significant impact on daily activities, education and quality of life.

Table 16.1 Key features to aid clinical differentiation between allergic rhinitis, non-allergic rhinitis and chronic rhinosinusitis in children [5]

	Allergic/non-allergic rhinitis	Chronic rhinosinusitis
Signs and symptoms	Itchy eyes, mouth, palate and nose	Nasal obstruction
	Sneezing bouts	Cough
	Nasal obstruction	Facial pain/pressure
	Watery rhinorrhoea	Rhinorrhoea—may be purulent
	Seasonal or specific triggers	
Clinical findings	Oedema of the nasal mucosa Mucosal hypersensitivity on endoscopy	Pus, polyps and mucosal oedema in the middle meatus
Skin prick test/specific IgE test	Positive (allergic) or negative (non-allergic)	Negative
Imaging	None required	Sinus opacification may be seen if imaging has been requested

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Development of the Paranasal Sinuses

Knowledge of the development of the paranasal sinuses at various stages of childhood is crucial for diagnosis and management of inflammatory sinus disorders. (Please refer to Chap. 1 for embryol-

P. G. Deutsch (✉)
Department of Otolaryngology, Birmingham Women's and Children's Hospital NHS Foundation Trust, Birmingham, UK
e-mail: peter.deutsch@nhs.net

A.-L. McDermott
Department of Otolaryngology, Birmingham Childrens Hospital, Birmingham Womens and Childrens Hospital NHS Foundation Trust, Birmingham, UK
e-mail: ann-louise.mcdermott@nhs.net

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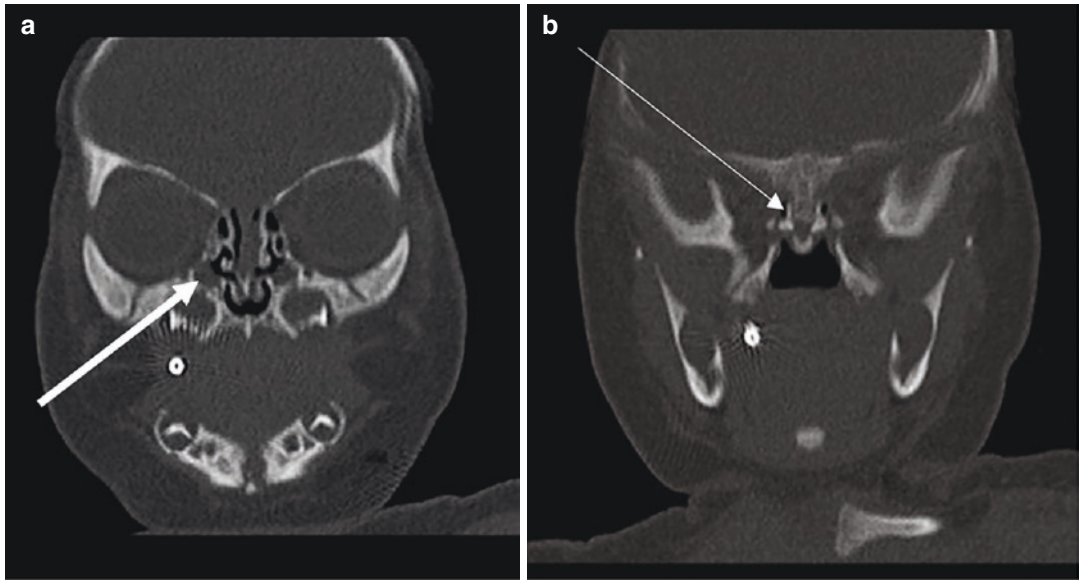

Fig. 16.1 (**a**) Axial CT scan of a newborn demonstrating the small maxillary sinuses (*large white arrow*) and their relationship with the orbital floor, ethmoidal bulla and tooth germs. (**b**) Coronal CT images of a neonate demonstrating rudimentary sphenoid sinuses

ogy.) The majority of paranasal sinuses will reach full adult size by the age of 15 years, but there is much variation in sinus anatomy during their developmental years that must be appreciated.

The ethmoidal bulla is present at birth, together with one to two other small ethmoidal air cells. Ethmoidal growth is relatively slow during the early years, but the sinus complex reaches adult size somewhere between 7 and 10 years of age.

The maxillary sinus gradually enlarges and the floor descends, becoming level with the nasal cavity floor, also at the age of 7–10 years (Fig. 16.1a, b).

The sphenoid sinus generally becomes visible on imaging after the age of 6 months. The air cells remain relatively small until the age of 4–5 years, when pneumatisation and growth occur, which continues until the teenage years [1].

The frontal sinuses are absent at birth. Anterior ethmoidal cells extend superiorly to form the frontal recess and frontal sinuses. The cells extend into the anterior cranium, and once the superior edge of the air cell reaches the level of the orbital roof, they are considered as frontal sinuses. The frontal sinus development typically occurs from the age of 5 years onwards [2].

Acute Rhinosinusitis (ARS) in Children

Definition

The clinical definition of acute rhinosinusitis in children has recently been clarified within the European Position Paper on Rhinosinusitis and Nasal Polyps in 2020 [5].

Acute inflammation of the nose and paranasal sinuses characterised by two or more symptoms as seen in Table 16.2. *Symptoms persist for a period of less than 12 weeks.*

Table 16.2 Definition of paediatric acute rhinosinusitis as defined in the European Position Paper on Rhinosinusitis and Nasal Polyps 2020 [5]

Two or more symptoms, one of which should be from the following: • Nasal blockage • Nasal obstruction • Nasal congestion • Nasal discharge (anterior/posterior) Additional symptoms: +/− Facial pain +/− Cough (day or night) [*specific to paediatric symptoms*]

Aetiology

Viruses, and particularly the 'common cold' viruses, are accepted as the most frequent causative organisms in ARS.

It is estimated that children attending school, nursery and other childcare establishments suffer between 7 and 10 episodes of ARS per year [6, 7]. Once symptoms persist beyond 5–10 days, the child is considered to have acute post-viral rhinosinusitis and that can last up to 12 weeks [1].

Whilst acute viral rhinosinusitis predominates in children, it may be followed by acute bacterial sinusitis. The incidence of bacterial infection is higher in children compared to adults and is reported to complicate 5–10% of paediatric viral ARS [2, 5, 8–10].

However, this may be underestimated due to the non-specific clinical features and underdeveloped sinuses during early childhood [2–4]. Whilst most children will recover, occasionally infection escalates to present as a serious complication.

Microbiology of ARS

The major pathogens in uncomplicated bacterial ARS in otherwise healthy children are *Haemophilus influenzae* (non-typeable), *Streptococcus pneumoniae* and *Moraxella catarrhalis*.

Diagnosis of ARS in Children

The diagnosis of ARS in children can be challenging. Symptoms are non-specific and may include irritability, halitosis, poor appetite and hyponasal speech.

The diagnosis is reliant on the history and examination may be limited. Endoscopy is not always possible, but children have round nostrils that facilitate a reasonable view within the nasal cavity by an otoscope, thus displaying details of the nasal mucosa, inferior turbinates and any nasal discharge (Table 16.2).

The tonsils, adenoids and cervical lymph nodes should be examined, and large adenoids, polyps, masses and nasal foreign bodies excluded.

Table 16.3 Symptoms of acute bacterial rhinosinusitis as defined in the European Position Paper on Rhinosinusitis and Nasal Polyps 2020 [5]

Defined by three or more of the following symptoms:
• Discoloured mucus
• Localised pain (often unilateral)
• Fever >38 °C
• Raised CRP/ESR
• 'Double' sickening

Occasionally, children may require general anaesthesia to assess the nose to aid in diagnosis and rule out differential diagnoses.

Management of ARS in Children

In the majority of episodes of viral ARS, the illness is short-lived and self-limiting, typically being less than 10 days. Treatment is mostly conservative and managed by over-the-counter medications and/or primary care practitioner support.

There is no evidence to support antibiotics in the management of ARS unless a secondary bacterial ARS is present, but this distinction is always not easy to make (Table 16.3).

The role of topical nasal corticosteroids has been shown to reduce the severity of ARS symptoms, but compliance in young children is poor, and licensing rules will make some medications prohibitive on the grounds of age.

Recurrent Acute Rhinosinusitis (RARS) in Children

Recurrent acute rhinosinusitis is defined as ≥4 episodes per year with symptom-free intervals [5].

Predisposing factors in children include active and passive smoking and anatomical anomalies. The prevalence of ARS among children exposed to passive smoking was reported as 68% compared to 1.2% who were not exposed [11]. Allergic rhinitis and gastro-oesophageal reflux disease (GORD) have been considered but there is little evidence to support them as true risk factors [5, 12, 13]. Several studies have demonstrated a variety of humoral immune deficiencies in children with RARS as well as CRS. Children

Table 16.4 Definition of chronic rhinosinusitis in children as defined in the European Position Paper on Rhinosinusitis and Nasal Polyps 2020 [5]

Defined by two or more symptoms:
At least one from:
- Nasal blockage
- Nasal obstruction
- Nasal congestion
- Nasal discharge (Anterior/Posterior)

Additional symptoms:
- Facial pain or pressure
- Cough (day or night) [*specific to paediatric symptoms*]

And at least one from:
- Endoscopic signs of CRS:
  - Nasal polyps and/or
  - Mucopurulent discharge primarily from middle meatus and/or
  - Oedema/mucosal obstruction primarily in middle meatus
- CT changes—mucosal changes within the sinus or osteomeatal complex

with RARS have a higher incidence of low IgA and IgG levels as well as a reduced response to pneumococcal titres [14].

Chronic Rhinosinusitis in Children

Definition of Chronic Rhinosinusitis in Children

The current definition of CRS is described in the European Position Paper on Rhinosinusitis and Nasal Polyps from 2020 [5].

Inflammation of the nose and paranasal sinuses characterised by two or more of the symptoms as seen in Table 16.4 *along with either radiological or endoscopic findings* [5]. *Symptoms persist for a period of greater than 12 weeks.*

CRS is typically a sinus inflammation with low-grade symptoms that persist for longer than 3 months despite the use of standard medical treatment. Viral infections, allergies and anatomic differences in children can lead to chronic obstruction of the sinus drainage pathways, most commonly the osteomeatal complex.

Prevalence of CRS

The prevalence of CRS in children has been estimated to be 2–4% and data from the United States reports CRS in 63.9 of children and young adults below 18 years of age per 1000 population [6]. The true prevalence of CRS is unknown because of the diagnostic difficulties in children, such as possible allergic rhinitis and adenoidal hypertrophy. Nasal endoscopy may be of limited value and imaging may be avoided because of concerns regarding radiation dose. There is also a misconception that young children do not suffer from ‘sinus disease’.

Predisposing Factors Associated with CRS in Children

In adults with CRS, 25% have concomitant asthma, and other predisposing factors include smoking, gastroesophageal reflux and hypogammaglobulinaemia [15–17].

There is no evidence of these environmental and host factors playing a role in children with CRS [5]. However, evidence for potential risk factors for CRS specific to children have been considered.

Significant Effect

Adenoid Biofilms and Bacterial Reservoir

The adenoids are very important in the pathophysiology of paediatric CRS, and contribute in two ways:

Anatomical obstruction of the posterior nose/postnasal space
Acting as a bacterial reservoir [18–20]

A biofilm covering the adenoidal surface has been demonstrated in nearly 95% of children with CRS compared to 1.9% in non-CRS children [16].

The most isolated bacteria include *Haemophilus influenzae*, *Streptococcus pneumoniae* and *Streptococcus pyogenes*, and the bacterial isolation correlates with the severity of CRS.

There is strong evidence showing the benefit of adenoidectomy in children with CRS [21–23].

Immune Deficiency

It is important to consider immune deficiency in any child who is not responding to appropriate medical management. A variety of humoral immune system deficiencies have been reported in at least 1 in 10 children with CRS [5].

Specific immune function investigations are best discussed with an immunologist but may include IgG subclasses, immunoglobulin levels and functional antibodies to pneumococcus serotypes, *Haemophilus influenzae* and tetanus.

Inflammatory Mechanisms in Paediatric CRS

Traditionally, it has been accepted that eosinophils and CD4-positive lymphocytes play a significant role in tissue inflammation in older children with CRS.

However, this is currently an area of great interest and recent knowledge has now shown that children display more neutrophils and lymphocytes than adults, higher numbers of CD8-positive cells but fewer eosinophils [24].

The nasal lavage of children with CRS shows higher levels of pro-inflammatory factors, especially cytokines (TNF-α), human β-defensin 2 and neutrophil-released calprotectin [37]. These inflammatory factors are even higher if the child has concomitant asthma.

The characteristic phenotype in paediatric CRS is submucosal glandular hyperplasia and the predominant glandular mucin is MUC5B [5, 37].

Moderate Effect

Age

The prevalence of CRS in children is lower than in adults but the impact on daily activity, education, concentration, sleep and quality of life is equally important.

It has been reported that in UK secondary school children, 31.5% had symptoms of rhinitis, and 15% of these reported symptoms of sinusitis [25]. CRS causes a significant effect on the schooling and quality of life in the paediatric population [26].

Atopy–Allergic Rhinitis–Asthma

The prevalence of allergic rhinitis (AR) in children has been reported to be as high as 40% [27]. The incidence of AR and atopy in children with CRS is higher than in the general population [27, 28]. Children older than 6 years with CRS have the highest rate of positive atopy results (elevated serum IgE/positive skin prick test), whereas younger children (<3-year olds) have the lowest risk. Quality-of-life outcomes in children are worst in those with atopy and CRS.

Concomitant asthma has been reported in 18% of children with CRS [29]. The concept of the unified airway is important in the management of CRS and it is important to address both the nose and the chest.

The nature of the relationship between paediatric CRS, allergic rhinitis and asthma remains unclear, but allergy testing should be considered in all older children with CRS.

Low Effect

Ethnic and Socioeconomic Factors

An ethnic and socioeconomic study in children showed the highest rate of a primary diagnosis of CRS to be in Caucasian children with private medical insurance [8]. The findings were most likely due to better access to tertiary care and heightened parental perceptions of their child's disease severity rather than a true difference between different groups.

Passive/Active Smoking

There is no evidence to show a causal effect between tobacco exposure (passive and active) and paediatric CRS. However, tobacco smoke exposure worsens disease scores, and revision surgery rates are higher [5].

Genetics

Children with CRS are more likely to have parents with CRS. A similar risk has been identified in first cousins and to a lesser extent in second cousins.

CRS and nasal polyps in monozygotic twins may differ, confirming that environmental factors are also involved [30].

No Proven Effect

Nose and Paranasal Sinus Anatomy

Whilst anatomical sinus variations are more commonly seen in older children, no causal effect has been demonstrated in the development of CRS [31].

Viral Infection in Children

There is little evidence to show that viral infections contribute to the development of paediatric CRS [32].

Gastroesophageal Reflux Disease

Whilst it has been suggested that gastric acid reflux into the pharynx and nasopharynx induces mucosal inflammation of the sinus ostia, impaired mucociliary clearance and rhinosinusitis, the evidence remains unclear and medication for GORD is not routinely recommended in the absence of reflux symptoms [5, 33].

Rare Genetic Disease in Children

Cystic Fibrosis (CF)

This is an autosomal recessive disease caused by mutations in the CFTR gene. Characteristics include thick viscous secretions that predispose to chronic infections in the upper respiratory tract. Newborn screening has reduced the age of diagnosis. The diagnosis of CF is confirmed by the classical method of a sweat test demonstrating elevated sweat chloride levels, or genetic testing that is becoming more widely available and superseding the sweat test.

All children with CF have been shown to have CRS, but some will be more affected than others and some will develop obstructing and sometimes recurrent nasal polyps [15] (Fig. 16.2a). However, the evidence shows that CRS in children with CF appears to have a low impact on their quality of life [5, 34].

Typically, children with CF develop chronic colonisation of the chest and paranasal sinuses, most commonly with *Pseudomonas aeruginosa* and *Staphylococcus aureus*, and require long-term antibiotic management to maintain good health. These patients are also prone to fungal sinus colonisation and chronic fungal sinusitis (Fig. 16.2b).

The presence of nasal polyps, mucoceles, hypoplasia of the frontal and sphenoid sinuses and the absence of any bony erosion in the paediatric population are highly suspicious of CF and should prompt further investigation (Fig. 16.2c).

Primary Ciliary Dyskinesia (PCD)/ Ciliopathy

This is a rare autosomal recessive disorder due to genetic mutations that affect the structure and function of cilia. The true incidence is unknown, but it is estimated to affect 1:15,000–20,000 live births affecting boys and girls equally.

Cilia may be immotile, dyskinetic or aplastic, leading to abnormal mucociliary clearance from the lungs, paranasal sinuses and middle ears.

Children typically develop frequent upper and lower airway infections, but the presentation is very heterogenous.

The clinical features of PCD include partial or complete situs inversus, situs ambiguous and infertility. Symptoms of CRS and recurrent cough are common problems that can be debilitating and compromise lung function. Nasal polyposis is reported in 18–30% of children with PCD [5, 35].

PCD should be suspected in children with refractory CRS and pulmonary disease, especially in those with uncommon microorganisms such as Gram-negative bacteria, concomitant bronchiectasis, situs inversus or spermatozoid abnormalities.

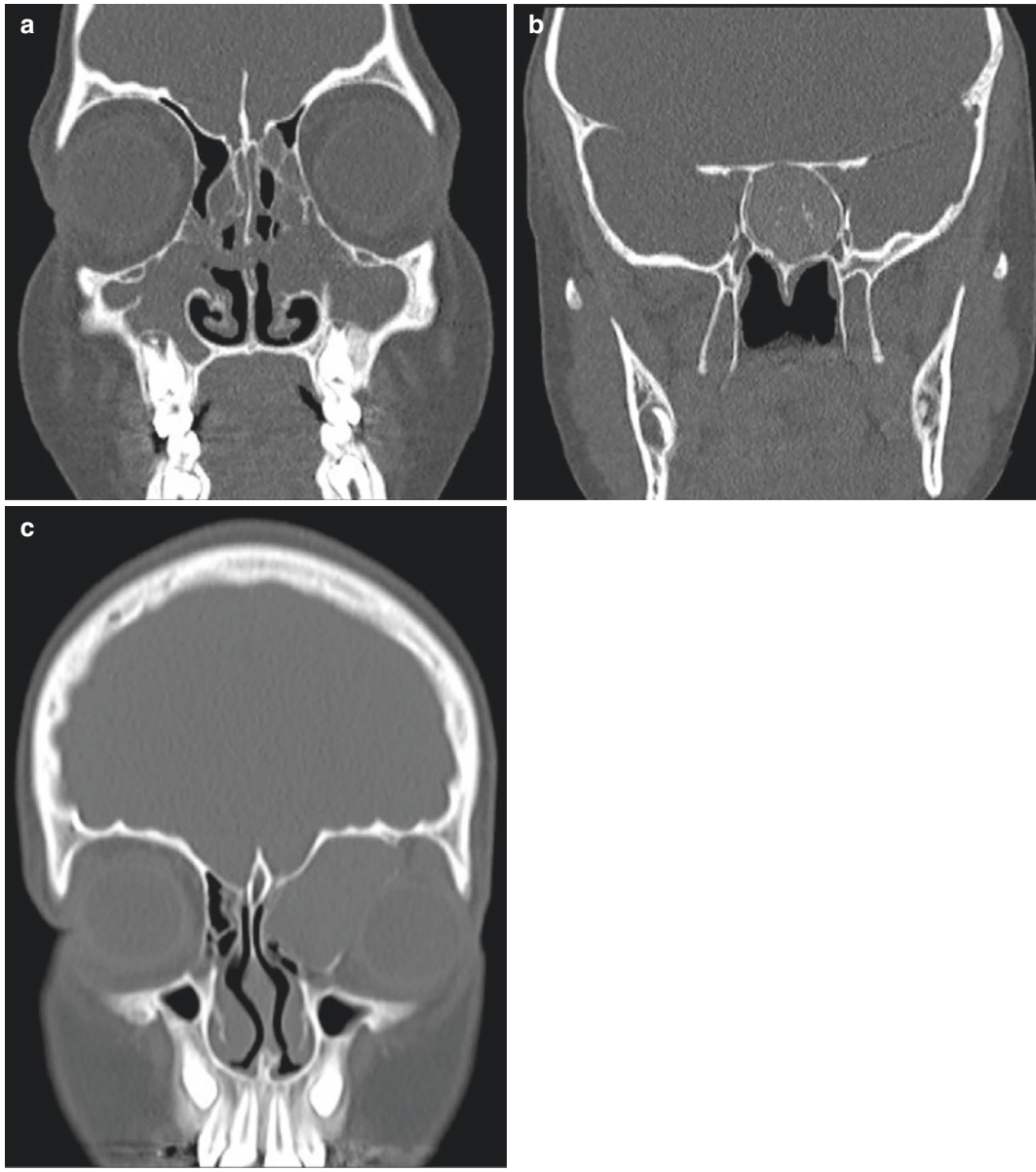

Fig. 16.2 (**a**) Extensive (recurrent) nasal polyps and osteitis in a patient with known CF. (**b**) Coronal CT imaging demonstrating chronic sphenoid sinusitis with evidence of a fungal ball in a patient known to have CF. (**c**) Coronal CT imaging demonstrating a left-sided fronto-orbital mucocele in a patient later diagnosed with CF

The diagnosis of PCD is difficult. Nasal nitric oxide levels are low; mucociliary transit time is prolonged (saccharin test) but not standardised; genetic testing is not always available and is expensive; ciliary brushing and evaluation by transmission electron microscopy (TEM) and high-speed photography is highly specialised and may not be accessible.

The triad of CRS, chronic bronchiectasis and situs inversus (Kartagener's syndrome) is commonly found in PCD patients [5] (Fig. 16.3).

The treatment of PCD is similar to CF. Sinus surgery should include all affected sinuses and may induce long-term improvement in lung cultures. A working team relationship is needed

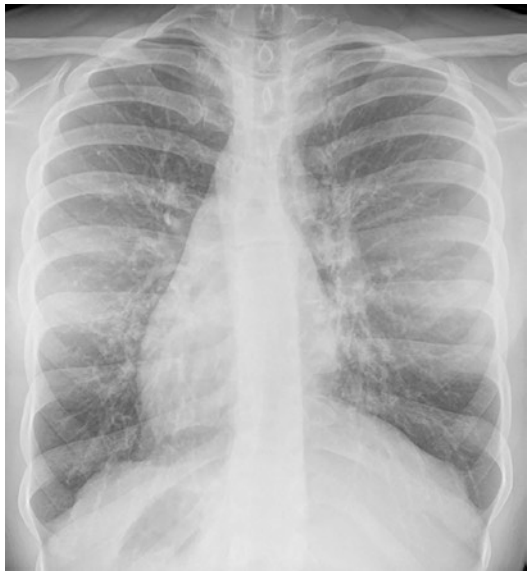

Fig. 16.3 Chest radiograph demonstrating situs inversus and bronchiectasis in a patient with CRS and PCD (Kartagener's syndrome)

when treating children with chronic chest pathology such as PCD and CF.

Diagnosis of CRS in Children

History

The diagnostic criteria are shown in Table 16.4.

Important supporting information includes details of environmental factors such as parental smoking, household pets, swimming and family history of atopy. A history of symptoms of GORD should be sought as this is an important differential to CRS in paediatric patients presenting with a chronic cough. Details of previous treatments should be sought.

In contrast to adults, chronic cough is a really important question in the assessment of paediatric CRS.

Complaints of olfactory dysfunction are unusual in children, and they do not seem to be aware of such symptoms until well into their teenage years [36]. Acquired olfactory dysfunction in children is predominantly due to CRS [38]. Congenital anosmia, as seen in Kallmann syndrome, is rare. Healthy newborns, babies and toddlers have an extremely sensitive olfactory function, but they lack the ability to interpret this and articulate a dysfunction in the olfactory system [39].

Early reports of COVID-19 suggest that olfactory dysfunction in children is more prominent than previously believed, but this needs to be appreciated in the current situation.

Examination

Examination should include assessment of the ears for middle ear effusions, the oropharynx for tonsillar hypertrophy and the neck for cervical lymphadenopathy. Ideally, the nose should be examined with a narrow endoscope, looking specifically for polyps, inflammatory mucosa or discharge. The procedure should be performed after topical anaesthesia, with carer support, utilising a narrow rigid or flexible nasendoscope, which may afford a better view of the adenoids. Nasal endoscopy may not always be possible, and consideration should be given to examination under general anaesthesia.

Patient (Carer) Reported Outcome Measures (PROMs)

Patient reported outcomes measures are important for evaluating CRS and the effects of interventions. Whilst the SNOT-22 questionnaire is well-established, the Sinus and Nasal Quality of Life Survey (SN-5) is more suitable for younger children (aged 2–12 years) [40].

Allergy Testing

Whilst skin prick testing can be performed at any age, the serum radioallergosorbent test (RAST) may be more suited for younger children or those with significant eczema. A raised IgE alone is unhelpful: it can be a normal finding in young children, may not be clinically relevant and often returns to normal during the child's development.

Smell Assessment

Smell tests are not usually performed in children whilst assessing their sinuses for CRS.

If a smell test is thought to be appropriate, Sniffin' Sticks offer a very acceptable, effective means of assessment in paediatric practice [38]. Children must be able to recognise the correct

odour from a list of descriptors, have familiarity with the odour, have associative and verbal capacities and have sufficient concentration to be able to perform this test. Interpretation can be challenging in children younger than 5 years of age.

Upper Airways Physiological Tests

Physiological respiratory investigations are not routinely performed but may be helpful in children with associated respiratory symptoms. They are, however, difficult to perform accurately with children due to compliance.

- *Peak nasal inspiratory flow (PNIF)*: This is a relatively quick, inexpensive, assessment of nasal obstruction, suitable for use in children over 5 years old. However, PNIF correlates poorly with symptoms of obstruction.
- *Acoustic rhinometry*: This test evaluates nasal obstruction by analysing nasal cross-sectional area from reflections of a sound pulse introduced via the nostrils. It can be used in young children (3-year olds).
- *Rhinomanometry*. Anterior rhinomanometry objectively assesses respiratory function of the nose by measuring pressure and flow during nasal inspiration and expiration.

Acoustic rhinometry and rhinomanometry were both used more in rhinological research than routine clinical practice, but since COVID-19, the tests have been difficult to reintroduce into clinical practice.

Miscellaneous Specialist Diagnostic Testing

The following investigations should be considered in patients where an underlying predisposing diagnosis is suspected. These tests are specifically relevant to the paediatric population.

Assessments of Ciliary Function

Saccharin mucociliary transit time—This test involved placing a saccharin source in the anterior nasal cavity and measuring the time to perception of a sweet taste. This is however not frequently used in the paediatric population due to compliance, tolerance and understanding. The senior author uses a tiny spot of Bonney's blue dye (a mix of green and crystal violet dissolved in ethanol) placed on the head of the inferior turbinate with a Jobson Horne probe. The dye is typically seen in the oropharynx in less than 20 min. This is easier to perform in clinic where both the child and parents can identify the blue dye in the mouth.

Ciliary nasal brushings—collection of nasal cilia for microscopic examination. This can form part of the diagnostic work up for primary ciliary dyskinesia.

Immunological Tests

Humoral immune response (IgG subclasses) as well as functional antibodies.

Tests for cystic fibrosis (sweat test or genetic testing)—Must be performed in any child with nasal polyposis.

Miscellaneous

Exhaled nasal nitric oxide levels (age 5 onwards): Often only available in highly specialised units but has been suggested as a screening tool for PCD and cystic fibrosis, which are associated with lower nasal nitric oxide levels.

Imaging

Imaging is always controversial in children because of the radiation dose. It is however mandatory when contemplating endoscopic sinus surgery (ESS) or managing suspected or untoward complications.

Computerised tomography (CT) of the sinuses is the scan of choice prior to ESS, where sinus anatomy and sinus disease need accurate delineation.

Magnetic resonance imaging (MRI) with contrast offers superior and supplementary information in evaluating complications of sinusitis such as intracranial infection or cavernous sinus pathology. MRI has also been suggested as the modality of choice in diagnostic surveillance of sinusitis in young children with CRS [5].

Isolation sinus opacification in children should be interpreted with caution since sinus opacities in this age group are relatively common incidental findings and in one report, only one in five children without rhinological symptoms had a normal scan.

Management of Paediatric CRS

The therapeutic goals of the treatment of paediatric CRS are symptom relief, improving quality of life, preventing both negative effects on education complications of infection.

Nasal Saline Rinses

Evidence shows that saline nasal rinses, used as an adjunct or as a single modality, are beneficial in the treatment of paediatric CRS.

Significant improvement in CRS symptoms occurs with hypertonic and isotonic saline, but hypertonic saline significantly reduces cough and superior overall symptom relief. There is no additional benefit from the addition of antibiotics to this saline regime [5].

Medical Therapy

Antibiotics

There is no strong evidence for the use of antibiotics in the management of paediatric CRS. However, it is still a common practice to use antibiotics in children with very symptomatic CRS.

In very symptomatic children and those with reduced immunity, such as Down syndrome, low-dose macrolides can be beneficial during the worst periods of the year. Such antibiotic regimes probably work by preventing acute exacerbation rather than treating CRS. Also, low-dose macrolides are thought to have anti-inflammatory immunomodulatory effects. Some studies of low-dose clarithromycin over 8–15 weeks report two-thirds of children being disease-free at the end of treatment.

Intranasal Steroids

There is little evidence to support the use of intranasal steroids in children with CRS, but they are recommended as first-line therapy in children with CRS, especially where there is coexisting allergic rhinitis [5]. The majority of intranasal corticosteroids only have doses recommended for children over the age of 4 years. A low systemic absorption steroid should be used to minimise any potential systemic effects (i.e. fluticasone or mometasone which have minimal systemic absorption). Mode of application is also an important consideration in paediatrics and delivery, with a fine mist spray is preferable and better accepted than traditional 'pump' sprays.

Systemic Steroids

Systemic steroids are associated with significant improvement in cough, nasal obstruction and postnasal discharge in children with CRS, and CT scan scores also improve.

However, their use is limited because of concerns about side effects, especially the impact on long bone growth. Special situations where their use may be justified include times of important school examinations or when CRS significantly interferes with quality of life.

Adjunctive Therapies for Paediatric CRS

There is no evidence to support the use of antihistamines, leukotrienes modifiers, decongestants or mucolytics in paediatric CRS, unless there are concomitant symptoms of significant AR.

Routine anti-reflux treatment is not warranted unless there are symptoms of GORD or diagnostic uncertainty [5].

Biologics in Paediatric CRS

Whilst medical therapies for CRS may be effective, long-term compliance can pose a significant challenge, and biologics may offer a targeted effective alternative.

Biologics are currently only available for children who have failed all appropriate medical and surgical treatments. Omalizumab is the only such medication licensed for children under the age of 12 years, but anaphylaxis is a potential risk, and the cost is considerable [41].

Instructions: Please help us understand the impact of sinus and/or nasal problems on your child's quality of life by checking one box [x] for each question below. Thank you.

SINUS INFECTION: Nasal discharge, bad breath, daytime cough, post-nasal drip, headache, facial pain or head banging. How often a problem for your during the past 4 weeks?

[ ] None of the time
[ ] Hardly any time at all
[ ] A small part of the time
[ ] Some of the time
[ ] A good part of the time
[ ] Most of the time
[ ] All of the time

NASAL OBSTRUCTION: Stuffy or blocked nose, nasal congestion, reduced sense of smell,trouble breathing with mouth closed. How often a problem for you child during the past 4 weeks?

[ ] None of the time
[ ] Hardly any time at all
[ ] A small part of the time
[ ] Some of the time
[ ] A good part of the time
[ ] Most of the time
[ ] All of the time

ALLERGY SYMPTOMS: Sneezing, itchy nose/eyes, need to rub nose/eyes, or watery eyes. How often a problem for your child during the past 4 weeks?

[ ] None of the time
[ ] Hardly any time at all
[ ] A small part of the time
[ ] Some of the time
[ ] A good part of the time
[ ] Most of the time
[ ] All of the time

EMOTIONAL DISTRESS: Irritable, frustrated, sad, restless, or trouble sleeping. How often a problem for your child during the past 4 weeks because of nose or sinus illness?

[ ] None of the time
[ ] Hardly any time at all
[ ] A small part of the time
[ ] Some of the time
[ ] A good part of the time
[ ] Most of the time
[ ] All of the time

ACTIVITY LIMITATION: Missed school/daycare, lost time with, family/friends, unable to do projects, How often a problem for your child during the past 4 weeks because of sinus illness?

[ ] None of the time
[ ] Hardly any time at all
[ ] A small part of the time
[ ] Some of the time
[ ] A good part of the time
[ ] Most of the time
[ ] All of the time

OVERALL, HOW WOULD YOU RATE YOUR CHILD'S QUALITY OF LIFE AS A RESULT OF NOSE OR SINUS PROBLEMS?
(Circle one number)

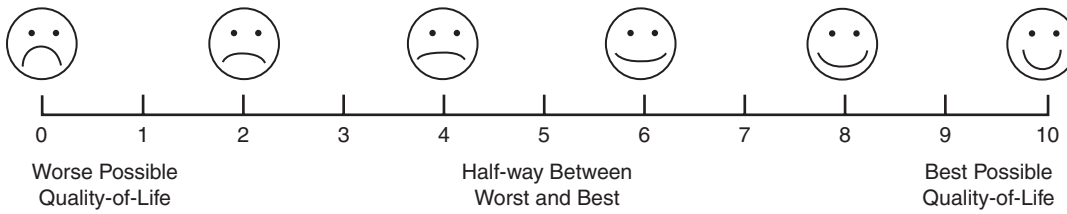

Fig. 16.4 SN-5 questionnaire [40]. As published in Kay DJ et al. in *Otolaryngology—Head and Neck Surgery* in 2003

Surgery

Surgery is indicated in children with CRS who have complied and failed to improve on medical therapy (intranasal corticosteroids/antibiotics).

Adenoidectomy is a first-line surgical option reported to have success rates of symptom resolution in 69% of children [33]. Alleviation of mechanical obstruction and removal of the bacterial reservoir are the rationales for surgery. Children below the age of 7 years and those with asthma and AR are more likely to require further revision adenoidectomy or sinus surgery [42]. The quality of life, as assessed by the SN-5 questionnaire, has been shown to significantly improve after adenoidectomy (Fig. 16.4) [5].

Balloon sinuplasty is a safe technique in children although there is no evidence to show clini-

cal benefit over adenoidectomy, or to demonstrate improved efficacy or cost-effectiveness.

Endoscopic sinus surgery (ESS) is recommended in children where the child has failed appropriate medical treatment and adenoidectomy. However, intervention should be conservative with mucosal preservation. Endoscopic surgery should address the removal of obvious obstructive polyps or mucosal lesions, drainage of the ethmoid bulla, perform limited ethmoidectomy, and limit enlargement of maxillary ostia.

Previous concerns regarding adverse effects of ESS on facial growth have been allayed. The long-term evidence is that ESS has no impact on qualitative and quantitative parameters of paediatric facial growth, as assessed over 10 years [42].

Additional indications for ESS include orbital and intracranial complications of ARS, children with CF and obstructing nasal polyposis and patients with fungal rhinosinusitis.

Complications of Rhinosinusitis in Children

Complications of bacterial rhinosinusitis in children are uncommon but can cause significant morbidity and possibly death. Fortunately, treatment with high-dose effective antibiotics and surgery where indicated is normally successful, but bacterial resistance to antibiotics is now a serious issue.

The main complications of paediatric rhinosinusitis are either intracranial or extracranial.

Intracranial

Meningitis

Meningitis is one of the more likely intracranial complications of sinusitis. Direct spread of infection from the ethmoid air cells, sphenoid or frontal sinuses is relatively easier than in adults, due to the arachnoid membrane being more permeable in children.

Investigation includes a CT scan or MRI of the head, followed by a lumbar puncture. It is sometimes difficult to exclude an intracranial collection.

The clinical management should include a paediatrician, and appropriate intravenous antibiotics should be commenced as soon as possible. Prompt drainage of the infected sinus should be considered at presentation in the presence of intracranial complications.

Intracranial Abscesses

Intracranial abscesses may be subdural, intracerebral and epidural, all of which are serious, and prompt recognition and management is crucial for recovery. It is important to appreciate that a CT scan of the head may not show evidence of an early abscess, and a combination of CT and MRI is ideally required for diagnosis and surgical planning. Intracranial abscesses are an uncommon complication of paediatric rhinosinusitis and should be managed jointly with paediatricians and neurosurgeons. Prompt drainage of pus from the infected paranasal sinus is required either via an external or endoscopic approach. Frequently, a combination of approaches may be required. These procedures are usually undertaken at the same time as any neurosurgical intervention.

Extracranial

Periorbital Infections

Periorbital infection is the most common infective complication of acute rhinosinusitis in children. Infection is more likely to spread from the ethmoid sinuses and occasionally from the frontal sinus.

There are several different presentations, and some are now rarely seen. The historical classification by Chandler separates the different presentations in a clinically useful manner, but the stages do not necessarily reflect the severity or the progression of the infection (Table 16.5).

The principles of management are to include the expertise of colleagues in paediatrics, ophthalmology and neurosurgery when appropriate, treat quickly and maintain close observation on vision and disease progression. Appropriate

Table 16.5 Chandler's stages of orbital infection

	Diagnosis	Clinical details	
Stage 1	Preseptal cellulitis	Inflammation of eyelid, anterior to tarsal place	Oral antibiotics or IV if response is minimal
Stage 2	Postseptal or orbital cellulitis (without abscess)	Inflammation of orbital tissues	IV antibiotics
Stage 3	Subperiosteal abscess + orbital cellulitis	Abscess/pus in subperiosteal plane adjacent to lamina papyracea or +/− frontal sinus floor	IV antibiotics + surgical drainage External or endoscopic approach
Stage 4	Orbital abscess + orbital cellulitis	Abscess/pus within orbital tissues	IV antibiotics + surgical drainage
Stage 5	Cavernous sinus thrombosis + orbital cellulitis	Extension of infection to cavernous sinus	Prolonged IV antibiotics Surgical drainage of sinus pus or abscess No consensus on anticoagulation

scans of the head, orbit and sinuses should be considered at an early stage.

Early recognition of a periorbital abscess is important, and drainage of pus considered. There is some evidence to suggest small medial abscesses (<1 cm) can be managed initially conservatively. However, many surgeons will still opt for prompt surgical management due to the challenges in regular assessment of the child's vision [43].

Frontal Bone Osteomyelitis

Frontal sinusitis can progress to cause osteomyelitis and destruction of the frontal bone, progressing to either an intracranial or extracranially abscess (Pott's puffy tumour).

Treatment necessitates initial intravenous antibiotics, continued as a long-term course, typically for 6–8 weeks, with local microbiology guidance. Pus within the frontal sinus and any associated abscess may require surgical drainage, but some do respond to antibiotic treatment.

Mucoceles

Mucoceles are epithelial-lined mucus-filled cysts that develop over many years following inflammation and obstruction of a sinus ostia. They are uncommon in children, especially if young, but should raise suspicion of a possible diagnosis of cystic fibrosis.

Mucoceles typically induce bony remodelling and bone erosion that can lead to complications such as visual disturbances, nasal obstruction or facial swelling.

Conclusions

There is still much to be investigated in pathogenesis and management of paediatric rhinosinusitis. Current best clinical practice involves a thorough history and examination and an awareness of the difficulties this poses in children.

Appropriate investigations and maximal medical management remain the first-line treatment. It is clear that initial adenoidectomy with/without sinus irrigation provides excellent symptom relief and is very effective.

Biologics are an exciting treatment modality that may have a future role in the management of paediatric CRS.

Controversies

- Currently, there is no justification for GORD treatment in children with CRS.
- The addition of antibiotics to saline irrigations is not recommended.
- There is now evidence that ESS does not have long-term effects on facial growth.
- Balloon sinuplasty has no proven role in the management of CRS.

Key Learning Points

- Acute viral rhinosinusitis is more common in children and has a higher incidence of secondary bacterial rhinosinusitis than adults.
- CRS *does* exist in children but is less common than ARS and does not frequently require endoscopic sinus surgery.
- CRS has a negative impact on quality of life similar to adults.
- Allergy testing should be considered in older children with CRS.
- Any child not responding to appropriate medical management should have their humoral immunity evaluated.
- The presence of nasal polyps, mucoceles, hypoplasia of the frontal and sphenoid sinuses on CT imaging in the absence of any bony erosion are highly suspicious of CF.
- PCD should be suspected in children with refractory CRS and pulmonary diseases, especially in those with concomitant bronchiectasis, situs inversus or spermatozoid abnormalities.
- Saline nasal irrigation is recommended for the treatment of CRS in children.
- Intranasal steroids are recommended for use in children with CRS.
- Adenoids are very important in the pathophysiology of paediatric CRS, so adenoidectomy with/without antral irrigation is a simple and safe first procedure to consider in younger children with symptoms of CRS.
- Endoscopic sinus surgery (ESS) is a safe and effective surgical modality for children with CRS following failure of adenoidectomy or those refractory to medical therapy.

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Further Reading

European Position Paper on Rhinosinusitis and Nasal Polyps 2020.Rhinology 2020;58 (suppl S29):1-464.

Paediatric Nasal Masses

17

Michelle Wyatt and Claire Frauenfelder

Introduction

Masses in the nose, nasal cavity, nasopharynx or sinus of a child represent a very broad spectrum of pathology (Table 17.1) and most commonly present with nasal obstruction.

M. Wyatt
Department of Paediatric Otolaryngology, Great Ormond Street Hospital for Children NHS Foundation Trust, London, UK
e-mail: michelle.wyatt@gosh.nhs.uk

C. Frauenfelder (✉)
Department of Paediatric Otolaryngology, Great Ormond Street Hospital for Children NHS Foundation Trust, London, UK

University of Adelaide,
Adelaide, South Australia, Australia

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Table 17.1 Differential diagnosis of paediatric nasal masses

	Pathology	Chapter
Congenital		
	Nasal dermoid	Nasal Masses Congenital Sinonasal Disorders
	Nasolacrimal duct mucocele	Congenital Sinonasal Disorders
	Nasolabial cyst	Congenital Sinonasal Disorders
	Glioma	Congenital Sinonasal Disorders
	Meningoencephalocele	Congenital Sinonasal Disorders
	Hairy polyp	
Non-neoplastic		
	Pyogenic granuloma	
	Haemangiomas	
	Tornwaldt cyst	
	Dentigerous cyst	
	Nasal polyposis	Paediatric Rhinosinusitis
Benign neoplastic		
	Juvenile angiofibroma	Juvenile angiofibroma
	Teratoma	
	Fibrous dysplasia	
	Juvenile ossifying fibroma	
Malignant neoplastic		
	Rhabdomyosarcoma	
	Olfactory neuroblastoma	
	Nasopharyngeal carcinoma	
	Lymphoma	

Imaging in Paediatric Nasal Masses

Thorough physical examination of the nasal cavity and postnasal space can be challenging in small children, so imaging plays an important role in diagnosis and treatment planning as many pathologies have characteristic features (Table 17.2). Congenital abnormalities (see Chap. 15), juvenile angiofibroma (previously known as juvenile nasopharyngeal angiofibroma) (see Chap. 33), paediatric rhinosinusitis including polyposis (see Chap. 16) and sinonasal malignancies (see Chap. 31) have all been expertly discussed elsewhere in this text; however, their imaging characteristics are included here for a complete reference guide to paediatric nasal masses.

Table 17.2 Characteristic imaging findings for paediatric nasal masses [1–5]

		Imaging modality	
Pathology	CT	MRI	Other
Nasal dermoid	Bone detail can indicate intracranial extension: widened foramen caecum (>3 mm), bifid crista galli	Well-circumscribes lesion, bright on T2, variable intensity T1, high intensity on DWI	–
Nasolacrimal duct mucocele	Low-attenuating, well-circumscribed cyst	T1 hypointensity of lesion. T2 hyperintensity of fluid-filled structure from medial canthus to inferior meatus	–
Nasolabial cyst	Well-circumscribed cystic lesion with mild rim enhancement with some attenuation of serous or mucoid cyst contents. Occasional local bone erosion	T1 hypointense cystic lesion. T2 hyperintense with minimal rim enhancement	–
Glioma	Well-defined, non-enhancing soft tissue lesion	T2 non-enhancing mass iso- or hyperintense to brain with a diffusion restriction	–
Meningoencephalocele	Extension of intracranial soft tissue. Bony defect in anterior skull base may include patent foramen caecum, bifid crista galli or local fontal bone deficit	Soft tissue connection from mass to cranial cavity. T1 isointense to intracranial grey matter. T2 iso- or hyperintense to grey matter	MR or CT angiography useful for preoperative planning
Nasal polyposis	Soft tissue opacity in the nasal cavity and affected sinuses	T1 hypointense tissue. T2 hyperintensity with thin peripheral contrast rim enhancement	–
Hairy polyp	Well-circumscribed, fat-filled mass with stalk	Both T1 and T2 hyperintense lesion with hypointense core	–
Tornwaldt cyst	Well-defined, cystic lesion	T1 hypointense, T2 hyperintense	–
Haemangioma: *Infantile*	Well-circumscribed, lobulated hypervascular mass. Intralesional flow-voids with contrast, decreases during involution	T1 isointense to muscle, T2 hyperintense. Intralesional flow-voids with contrast, decreases during involution	US Doppler: High vessel density during proliferation without evidence of arteriovenous shunt. Involution shows decreasing vessel density and increased resistive index
Haemangioma: *Congenital*	Heterogenous, lobulated vascular mass with foci of calcification, haemorrhage and necrosis	T1 isointense to muscle, T2 hyperintense. More heterogenous than infantile haemangioma variants	–
Pyogenic granuloma	Well-circumscribed, homogenous mass without calcification and diffuse contrast-enhancement	T1 isointense to grey matter, marked enhancement with contrast (with no rim). T2 heterogeneously hyperintense	–
Dentigerous cyst	Unilocular well-defined pericoronal lucency around unerupted tooth, thin sclerotic margin. No cortical breach	T1 hypointense lesion. T1 with contrast—no solid component, no enhancement. T2 hyperintense lesion	OPG: Unilocular radiolucent cystic lesion with sclerotic boarder associated with crown of unerupted tooth

(continued)

Table 17.2 (continued)

		Imaging modality	
Pathology	CT	MRI	Other
Juvenile angiofibroma	Well-defined soft tissue mass with characteristic lobulation at sphenopalatine foramen and other key anatomical sites. Intense contrast enhancement. Bowing and erosion of adjacent bone	T1 hypo- or isointense to surrounding muscle. T2 irregular hyperintensity with isointense areas due to fibrous foci within lesion. Diffuse contrast intensity with flow voids. Mucinous secretions trapped around lesion appear homogenous and hyperintense	Digital subtraction angiography: Indicative of vascular recruitment by tumour and highlights preoperative embolization targets
Teratoma	Well-defined margin around heterogenous and variable lesions due to mixture of tissues in each lesion. Mixed solid and cystic components. Multiple calcified intralesional foci	T1 mixed signal with hyperintensity of fat and proteinaceous fluids, hypointensity of calcium and blood product, contrast enhancement of solid soft tissues. T2 mixed signal	–
Fibrous dysplasia	Characteristic ill-defined, ground-glass intramedullary bony lesion(s). Expansile and thinned overlying bony cortex. Erosion rare	Aggressive appearance on MR, mimicking malignancy. T1 low intensity, T2 variable, internal heterogenicity with contrast	–
Juvenile ossifying fibroma	Sharply defined, unifocal lesion with sclerotic rim and internal lucency	T1 low-intermediate intensity. T2 variable, heterogenous intensity, often with hypointense cystic areas	–
Rhabdomyosarcoma	Invasive soft tissue mass with surrounding bony erosion and variable contrast enhancement due to focal intratumoral necrosis	Facilitates assessment of meningeal involvement and intracranial extension. T1 isointense lesion. T2 variable lesion iso- and hypointensity with irregular contrast enhancement	FDG-PET scan: Primary RMS and metastatic disease give bright signal with increased FDG avidity
Olfactory neuroblastoma	Dumbbell of soft tissue arising high in nasal cavity, extending through cribriform plate. Macrocalcifications and intralesional necrosis. Local bone destruction and remodelling at skull base	T1 low to intermediate intensity. T2 intermediate to high intensity. Intralesional variability due to focal necrosis and cystic areas	–
Nasopharyngeal carcinoma	Aggressive, asymmetrical mass of lateral nasopharynx/fossa of Rosenmuller. Associated bone erosion, intracranial invasion. Cervical lymphadenopathy common. Heterogenous contrast enhancement	T1 isointense lesion. T2 isointense lesion. Contrast enhancement variable, usually heterogenous. Diffusion-weighted images demonstrate decreased diffusivity	FDG-PET scan: Metastatic disease detection and post-treatment surveillance
Lymphoma	Soft tissue mass with mild to moderate contrast enhancement. Local bone destruction and remodelling is common	T1 lesion isointense to muscle, T2 mild hyperintensity. Mild to moderate contrast enhancement. Key for assessment for dural involvement when cribriform plate erosion present	–

DWI Diffusion-weighted imaging

Congenital Lesions

Dermoids

Nasal dermoids affect 1:20,000 live births and are the most common midline congenital lesion. They can present as a cyst, sinus tract or fistula.

Dermoid lesions form after failed neuroectodermal involution in the prenasal space between the developing nasal bones and septum. A remnant tract of both mesoderm and ectoderm is characteristically lined with stratified squamous epithelium and follows the path of the dural diverticulum through the foramen caecum.

Clinically, a midline mass or punctum is seen between the nasal tip and the glabella, most commonly at the rhinion. The typical appendages of skin are embedded within the lesion and hair, or a sebaceous discharge may extrude from a sinus or be contained within a cyst. Persistent attachment to the intracranial dura along this tract is common and is associated with the risk of serious complications: the intracranial component increases the risk of meningitis, cavernous sinus thrombosis and intracranial abscess. The depth of extension has been classified and is key for preoperative planning (Fig. 17.1, [6]): superficial (most common), intraosseous, intracranial extradural and intracranial intradural.

Both MRI and CT of the skull base give complementary information regarding soft tissue and intracranial extension, and bony anatomy, respectively (Fig. 17.2).

Management is surgical excision via an external rhinoplasty approach for superficial lesions with or without burring the nasal bones to prevent recurrence if the lesion is adherent to periosteum. Larger lesions with intracranial extension require collaboration with neurosurgical colleagues and either endoscopic-assisted or open excision (via coronal flap elevation) and may require local reconstruction of a dura defect where the tract extends intracranially. Failure to address the entire lesion results in high post-operative recurrence.

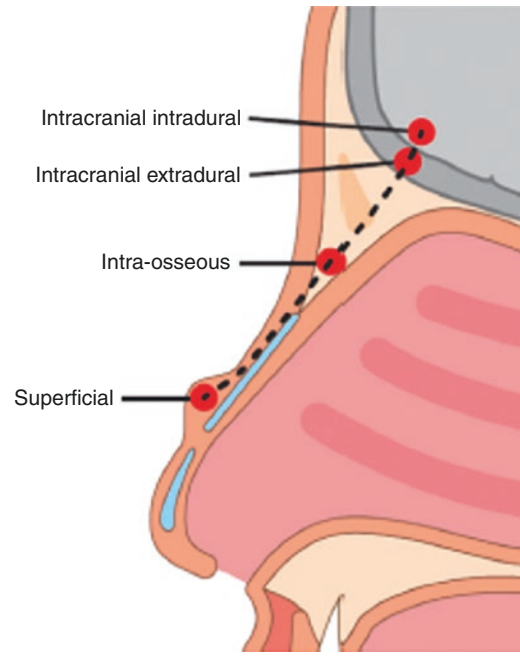

Fig. 17.1 Nasal dermoid classification is based on extent of intracranial extension and is important for pre-operative evaluation of the patient [6]

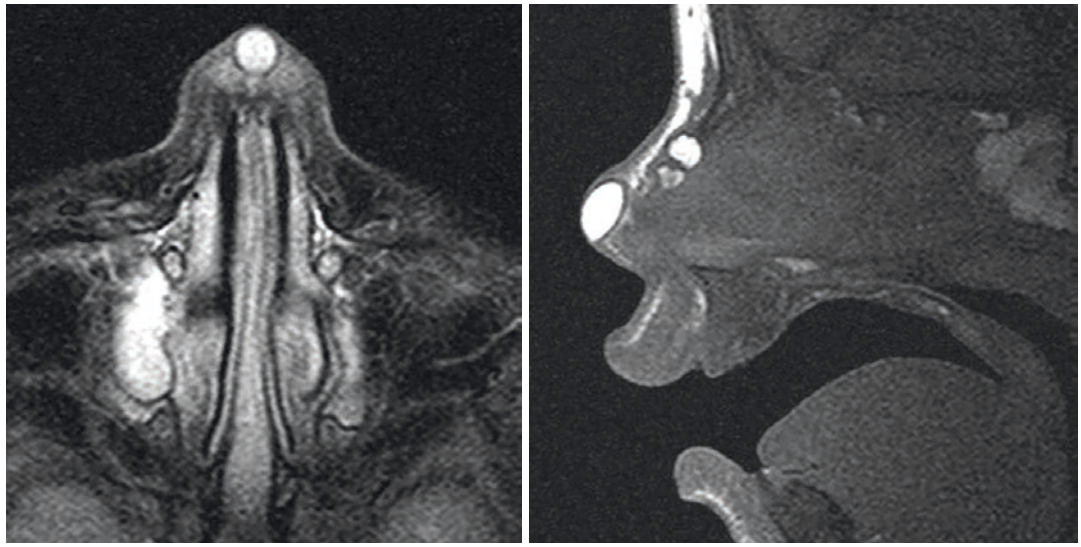

Fig. 17.2 MRI axial and sagittal—Nasal dermoid with superficial and intra-osseus components

Hairy Polyp

Hairy polyp, or naso-oropharyngeal choristoma, are a form of congenital cyst found in the upper airway of neonates, and contain matured ectoderm and mesoderm. They are found in approximately 1/4000 live births and are more common in females. They are pedunculated ectopic foci of tissue originating from the first or second branchial arches (please refer to Chap. 1) and present with a clinical picture dependent on size, location and mobility of the lesion in the upper airway. Whilst the diagnosis is often clinical, they have a classical appearance on MRI with a hyperintense ring of fatty tissue surrounding a hypointense core, and an associated fatty stalk sometimes hard to distinguish from surrounding tissues. These lesions are surgically excised using either cold steel or coblation and have low recurrence rates.

Non-neoplastic Lesions

Pyogenic Granuloma

Nasal pyogenic granuloma arises from mucosa or skin of the nose and oral cavity and was previously referred to as lobular capillary haemangioma. It is a friable red or purple polypoid mass and characteristically presents with recurrent epistaxis, nasal obstruction, nasal discharge and pain. It is slightly more common in male children, differing from adults where women are more frequently affected, particularly if using hormonal contraception, and especially during pregnancy, typically involuting after birth. It is most commonly found on the anterior septum, turbinates or nasal cavity roof and the appearance on imaging is of a localised but vascular lesion. These lesions are treated surgically via excision by a range of methods including cold steel, electrocautery, laser and electrocoagulation. Rarely are the lesions vascular enough to warrant preoperative embolization. Reports of recurrence vary but repeated surgery is uncommon.

Haemangioma

Haemangioma in childhood involves several separate entities as classified by the International Society for Study of Vascular Anomalies [7]. The two most common and that affect the airway are infantile haemangioma and congenital haemangioma.

Infantile haemangioma is the most common tumour of childhood, affecting up to 10% of children, and mostly females. Characteristically, it appears during the first weeks of life and proliferates for months, before spontaneously involuting. More than 30% of lesions affect the head and neck, and large lesions may be associated with PHACES syndrome (Posterior fossa anomalies, Hemangioma, Arterial lesions, Cardiac abnormalities and/or aortic Coarctation, Eye abnormalities, Sternal cleft or agenesis). The haemangiomas may be multifocal and be superficial or deep with variable external appearance. They are formed by proliferation of endothelial cells and pericytes with specific immunohistochemical (IHC) markers including glucose-transporter-1.

Congenital haemangiomas are present at birth and involute to varying degrees, with three subtypes: rapidly involuting (within 1 year), non-involuting and partially involuting (Fig. 17.3). They are less common than infantile haemangioma and histologically are formed by capillary lobules, with or without association to larger lymph vessels, veins and arteries. In contrast to infantile haemangioma, the congenital forms do not express the glucose-transporter-1 IHC marker.

Their radiological appearance is lobulated, often with foci of calcification, haemorrhage and necrosis. However, radiological images of congenital haemangiomas are characteristically less demarcated and more heterogenous than infantile lesions.

Usually, patients are advised to wait for involution of the haemangioma and no treatment is required; however, if the lesion is in the airway, large or ulcerating, or affecting important local structures (e.g. orbits, cranial nerves), treatment with beta-blockade (usually oral propranolol) is commenced.

Surgical excision is used only where there is no response to treatment in these critical situations.

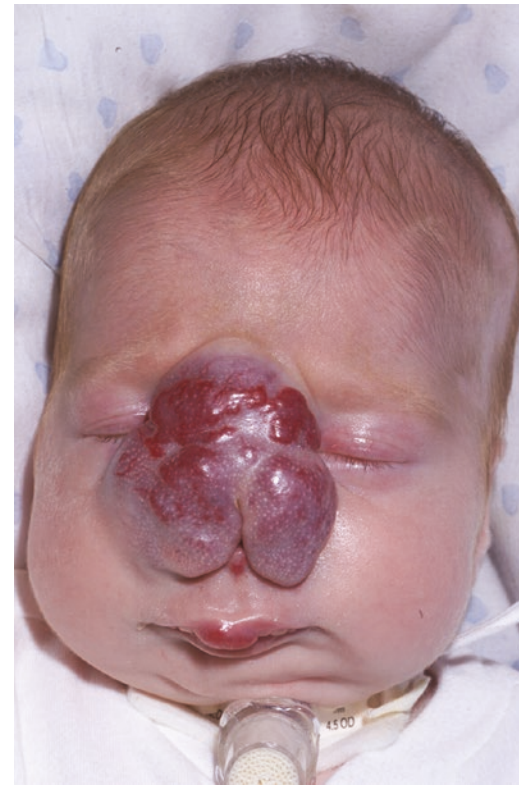

Fig. 17.3 Extensive congenital nasal haemangioma resulting in airway obstruction (tracheostomy tube in situ)

Tornwaldt Cysts

Tornwaldt cysts are found in the midline posterior nasopharyngeal wall at the site of the pharyngeal bursa (embryological pathway from anterior notochord to embryological pharyngeal roof). They develop following infection or trauma, usually in older children (or adults). They are lined with respiratory epithelium and are surrounded by adjacent adenoid tissue. Clinical presentation is of nasal obstruction, postnasal discharge, halitosis, or in large lesions, with eustachian tube obstruction and middle ear effusion.

On imaging, they are well-defined cystic lesions without local bone destruction and hyperintensity on MRI T2 weighted images.

If asymptomatic, no treatment is required; however, endoscopic or transoral marsupialisation is indicated for large, obstructive lesions.

Dentigerous Cysts

Dentigerous cysts arising around unerupted or impacted anterior secondary maxillary teeth may present as a painless mass in the floor of the anterior nose. More typically, the cysts are identified on orthopantomography (OPG) imaging performed for other dental reasons. They may be associated with mucopolysaccharidoses or basal cell nevus syndrome (Gorlin syndrome). A non-keratinising squamous epithelial-lined cyst arises at the cementoenamel junction of a permanent tooth and is seen as a well-defined cystic pericoronal radiolucency. Treatment requires marsupialisation of the cyst in an attempt to preserve the permanent dentition; however, if tooth development has been severely disrupted, enucleation and primary closure confers less chance of recurrence.

Benign Neoplastic Lesions

Juvenile Angiofibroma (Link to Juvenile Angiofibroma Chap. 33)

Juvenile angioma is a vascular tumour that arises in the nasopharynx around the sphenopalatine foreman in adolescent boys. It is covered in depth elsewhere in this text (refer to Chap. 33).

Teratoma

Teratomas are an embryological germ cell tumour, arising from the pluripotent cells of all three germ cell layers and characterised as tissue foreign to the site of origin (Fig. 17.4). They are unpredictable and may present with dramatic enlargement clinically over a short period of time. There is a strong association with concurrent congenital abnormalities. Histological features vary significantly, incorporating a wide range of tissue types that may be mature or immature. Malignant transformation is rare but may be either carcinomatous or sarcomatous. Whilst most are benign, they are locally aggressive. Complete surgical excision is required for both benign and malignant teratomas, with good associated prognosis.

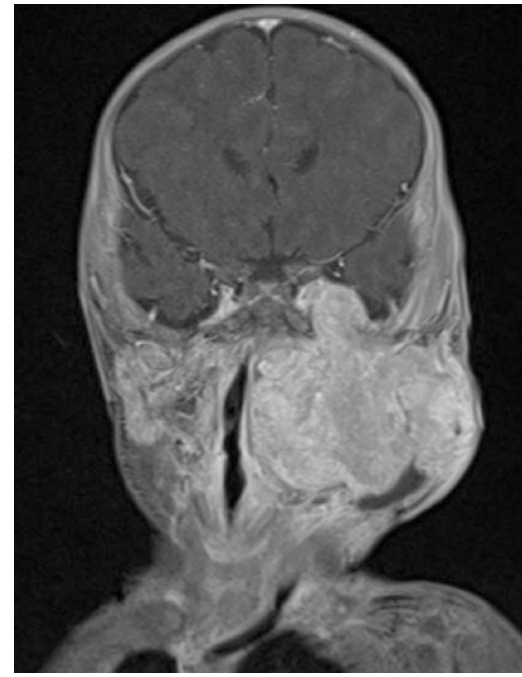

Fig. 17.4 Coronal MRI—Extensive left-sided teratoma with cranial extension through skull base, caudal extension into neck and parapharyngeal space, encroaching into postnasal space and pharynx

Fibrous Dysplasia

Fibrous dysplasia is a slow-growing fibro-osseous condition found throughout the skull base and is diagnosed in children in the first and second decade of life prior to puberty on the basis of classical radiological appearance (Fig. 17.5). It is a benign, idiopathic process that replaces normal medullary bone with structurally weaker fibro-osseous tissue and is associated with mutation of the GNAS1 gene.

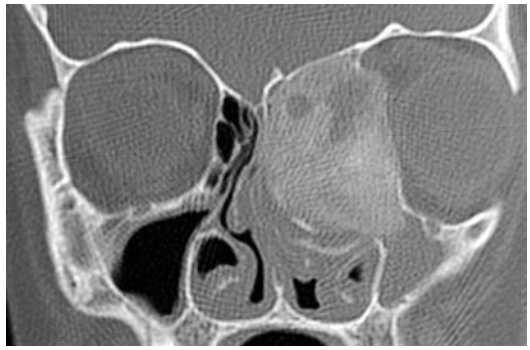

Fig. 17.5 Coronal CT—Ethmoidal focus of fibrous dysplasia with lateral displacement of the orbit and obstruction of the left osteomeatal unit

Well-circumscribed, intramedullary lesions expand and distort the bone. It is most commonly monostotic (>70% of cases); however, may present involving more than one bone in McCune-Albright syndrome associated with skin hyperpigmentation and endocrine abnormalities. Bony swelling lesions are typically painless as growth is slow, and discomfort may arise when there is a rapid growth spurt, mimicking osteomyelitis clinically and radiographically. Other symptoms, such as nasal obstruction or cranial neuropathies, arise when the lesion expands and narrows the nasal cavity or the proximity of skull base foramina. Malignant transformation to osteosarcoma is rare (<0.5%); however, it increases in McCune-Albright syndrome (4%).

In general, no treatment is required; however, the decision to proceed with decompression or curettage is based on location of the lesion and progression of symptoms.

Juvenile Ossifying Fibroma

Juvenile ossifying fibroma is a rare lesion, typically affecting children from 5 to 10 years of age and is more aggressive than when presenting in adulthood, and also more likely to recur. The lesions are expansile and, in contrast to fibrous dysplasia, well-demarcated. They are slow-growing, most frequently arise in the mandible, but affect the maxilla and ethmoid sinuses in approximately 20% of cases. The fibromas arise from the periodontal ligament and are composed of fibrocellular tissue mixed with variable osseous component and psammomatoid bodies.

Complete surgical resection is required (endoscopic where possible) and carries an excellent prognosis. There is no reported malignant transformation, and while recurrent tumours can be aggressive, recurrence is rare.

Malignant Neoplastic Lesions

Although covered elsewhere in this text (refer to Chap. 31), malignant lesions of the nose, nasopharynx and sinuses are important differential diagnoses not to miss in a child presenting with a nasal mass.

Rhabdomyosarcoma

As the most common paediatric solid tumour malignancy, 40% of all rhabdomyosarcomas (RMS) affect the head and neck. Nasopharyngeal RMS frequently presents late with advanced disease, and up to 25% of patients have metastatic disease at diagnosis. Paediatric RMS is associated with two subtypes: embryonal with an intermediate prognosis and alveolar with a poor prognosis (particularly when associated with the aggressive PAX3–FOXO1 fusion gene variant).

Staging and treatment is determined by tumour extent; para-meningeal involvement denotes advanced disease. Surgery is usually limited to biopsy for tissue diagnosis and may include debulking overall tumour volume; however, treatment centres on chemotherapy with adjunct radiotherapy, and increasingly proton beam radiation.

Olfactory Neuroblastoma

Olfactory neuroblastoma, or esthesioneuroblastoma, is a rare malignant tumour arising from neuroectoderm in the olfactory epithelium, high in the nasal vault. It presents with epistaxis and

nasal obstruction in a bimodal distribution: teenagers and patients in the sixth decade of life. Surgical resection and adjunct radiotherapy are the mainstays of treatment; however, induction chemotherapy plays an important role for younger patients prior to surgery. Prognosis is reasonable with a reported 5-year survival rate of 75%.

Nasopharyngeal Carcinoma

Nasopharyngeal carcinoma (NPC) in children is rare, usually affecting teenagers, and is associated with Epstein-Barr virus infection and exposure to nitrosamines. NPC classification by the World Health Organization involves three sub-types of squamous cell carcinoma: keratinising, non-keratinising differentiated and non-keratinising undifferentiated. Undifferentiated is the most common variant in children and is associated with a slightly better prognosis. Presentation may be prompted by nasal obstruction, otitis media with effusion, cranial neuropathies or fever of unknown origin. Cervical metastasis is also a common presentation for NPC. Primary disease is usually advanced, and distant metastases are frequently found at diagnosis.

The overall combined 5-year survival rate remains around 50%. Neoadjuvant chemotherapy improves response to radiotherapy and can assist treatment of metastatic disease. Surgical resection is reserved for salvage and is rarely performed.

Lymphoma

Paediatric extra-nodal lymphoma of the head and neck is very rare. Natural killer cell or T-cell lymphomas are most common, are related to immunosuppression or exposure to carcinogens (including Epstein-Barr virus) and are aggressive with a poor prognosis. A range of presentations are seen and correlate to the lymphoma's histological variant. More indolent disease presents with onset of nasal obstruction and sleep-disordered breathing, while aggressive forms with bleeding, ulcerated lesions or pain. The surgeon's role in lymphoma is typically limited to detection and biopsy of the lesion, with chemoradiotherapy as the mainstay of treatment.

Key Learning Points

- Nasal dermoid—imaging with MRI to stage and assess for intracranial extension key during preoperative planning.
- Haemangioma—distinct histological entities classified by International Society for Study of Vascular Anomalies affect infants:
  - 'Infantile' haemangiomas appear after birth, express glucose-transporter-1 and may be associated with PHACES syndrome.
  - 'Congenital' haemangiomas are present at birth, do not express GLUT-1 and a classified based on involution pattern.
- Fibrous dysplasia—benign monostotic condition in >70% cases. Rare multifocal disease associated with McCune Albright syndrome.
- Juvenile ossifying fibroma—more aggressive in childhood than the adult form and complete surgical excision is required.
- Malignant neoplasms in children are rare but must be included in the differential diagnosis of any nasal mass and require multidisciplinary team input for management.

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Paediatric Nasal Deformity

18

Claire Marie McLarnon

Introduction

In this chapter we will explore nasal development and congenital and acquired deformities including the impact of nasal trauma which in children can lead to significant long-term deformities. Surgical interventions and risks of surgery, including a discussion on the timing of septorhinoplasty surgery in children, will be discussed.

Nasal Embryology

The primitive mouth or stomodeum (stomatodeum) appears around the 4th week in the developing embryo. Around this time the first pair of pharyngeal arches surround the stomodeum, and five mesenchymal prominences appear. These are the paired maxillary and mandibular prominences and a single central frontonasal prominence. The nasal placodes develop from the surface ectoderm on the lateral sides of the frontonasal prominence. During the 5th week, each nasal placode then invaginates as the olfactory pit and tissue either side of the pit forms the medial and lateral nasal prominences or fold. The medial nasal folds become the septum, philtrum, medial crus of the lower lateral cartilage, columella and premaxilla of the nose, whereas the lateral processes form the sides of the nose. The apex and dorsum of the nose come from the frontonasal process (Fig. 18.1).

A nasobuccal membrane separates the oral cavity inferiorly from the nasal cavity superiorly. As the olfactory pits deepen, the choanae are formed. By 10 weeks there is differentiation into muscle, cartilage and bony structures. Any disruption to these phases in development can lead to various nasofacial anomalies that include choanal atresia, medial or lateral nasal clefts, nasal aplasia and polyrrhinia.

Nasal Development Through Childhood

Just as the rest of the human skeleton develops through childhood, the nose continues to form with leaps in growth correlating with generalised skeletal growth spurts, especially during puberty. The nasal septum is central to nasal growth and any surgical approach must be respectful to not disrupt the septal growth centre. Children who have had injuries to their noses in early childhood where there has been disruption to the growth centre of the nasal septum can be at significant risk of later developing nasal deformities [1]. These include septal and dorsal deviations, a small for age nose, altered/arrested midfacial development and supratip collapse.

C. M. McLarnon (✉)
Freeman & GNCH Hospitals,
Newcastle upon Tyne, UK
e-mail: claire.mclarnon@nhs.net

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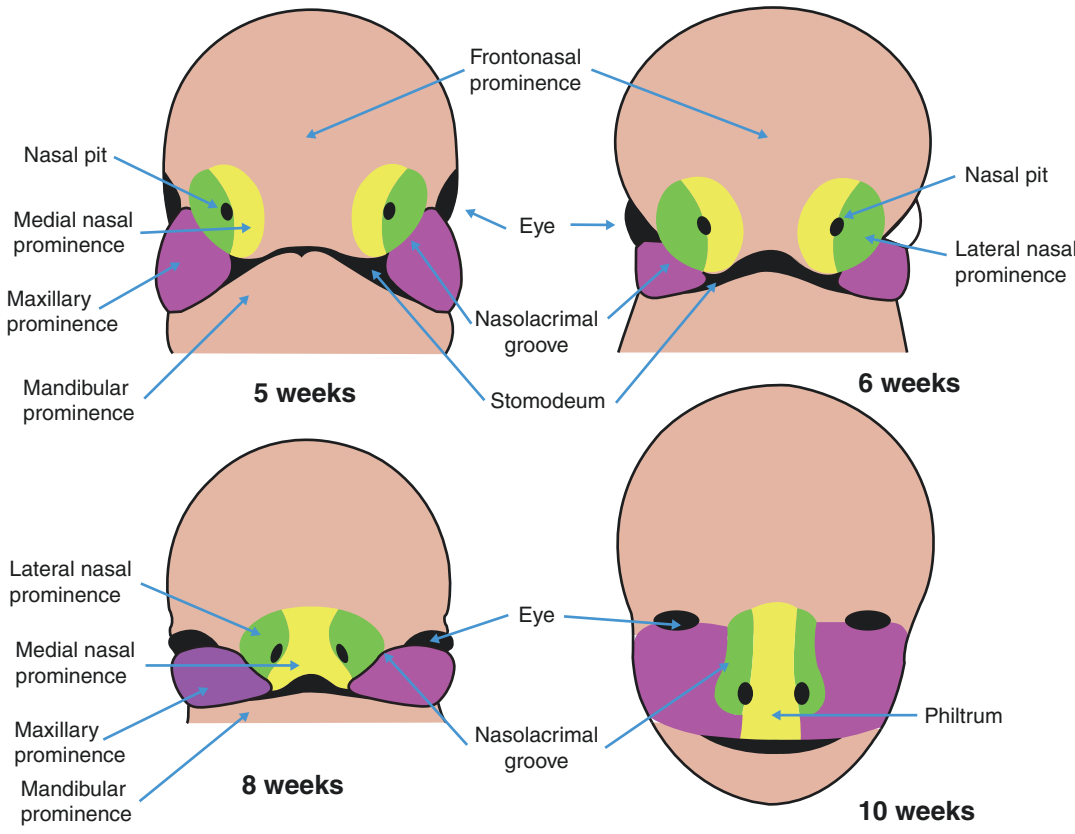

Fig. 18.1 Schematic demonstrating embryological development of the nose

Development of the Nasal Septum

In the adult, the nasal septum is composed of three parts: (1) the cartilaginous septum, (2) the perpendicular plate and (3) the vomer. The bony perpendicular plate develops via endochondral ossification of the cartilaginous septum during childhood. Ossification occurs in a cephalic to caudal direction from the skull base and reaches the vomer by puberty. The vomer is formed by intramembranous ossification and ossifies from the 12th week of foetal life. The vomer has two lamellae that form the V-shape in which the posterior septum resides. The perpendicular plate and vomer fuse around the ages 6–8 years. In the neonate, nearly all of the nasal septum is cartilaginous and extends from the columella anteriorly to the sphenoid posteriorly. A thin bony lamella between the basal rim of the cartilaginous septum and palate in the neonate becomes the vomer. A study, looking at septal growth, concluded that the growth rate of the nasal septum is highest in the newborn up until 2 years when it slows down continuously but does continue even after puberty (5). The cartilaginous part of the nasal septum increases rapidly in sagittal dimensions during the first year of life. After the age of 2 years, the growth of the septum is due to expansion of the perpendicular plate, i.e. the bony parts of the septum. The cartilaginous septum has a central role in driving the growth of the nasal pyramid, nasal cavity and midface. The caudal part of the septal cartilage influences outgrowth of the midface. The anterior part determines prominence and length of the nasal pyramid. Surgery or trauma involving the nasal septum in

children and adolescents therefore can interfere with different processes (growth, remodelling and ossification) depending on the site and timing of the injury.

Development of the Nasal Dorsum

In the neonate, the nasal bones have a fibrous connection with the frontal and maxillary bones and are supported by the upper lateral cartilages (ULCs) beneath them. At the caudal margin of the nasal bones, the periosteum is firmly connected with perichondrium of the underlying cartilage. The nasal bones ossify inwards from the nasal process of the lateral maxillary bones eventually fusing in the midline in adult life. Unlike the adult nose, the ULCs extend under the full length of the nasal bones to merge with the cartilaginous anlage of the anterior skull base, which later becomes the ossified cribriform plate. [15]. There are only limited reports on the rate of anterior regression; however, the ULCs can still be found to maintain their skull base connections up until at least age 4 years. The upper lateral cartilages and the nasal septum together constitute the 'T'-shaped septodorsal cartilage. As the ULCs gradually regress under the nasal bones caudally, all that is left is a small overlap with the ULCs sitting under the nasal bones—the so-called bony cap.

Development of the Nasal Tip

The nasal tip is formed by the two lower lateral cartilages (LLCs), each having three components, namely the medial, intermediate and lateral crus, and the caudal septum. The medial nasal process as described above in the development of the septum also gives rise to the medial crus of the lower lateral alar (LLC) cartilage. The lateral nasal process develops into the external wall of the nose including the alae, and lateral crus of the lower lateral cartilage. The nasal tip is thought of a tripod structure with the three 'legs' consisting of the paired medial crura and the other two 'legs' being each of the lateral crura of the LLCs. The soft tissues including skin, particularly in a younger child's nose, are thicker and more elastic compared to older adults; therefore, identifying abnormalities of the underlying alar cartilages is more difficult in children.

Nasal Growth Phase

Nasal growth rate continues post-partum at a high rate for the first few months after birth. It then slows down until puberty when another growth spurt occurs. Nasal growth rates tend to be in proportion to growth velocity of the skeleton. Growth spurts in girls continues to 16–17 years of age compared to boys' growth spurt that continues up to 16–18 years of age. However, when exactly the nose stops growing is debatable in the published literature [2, 3]. Some report that the nose stops growing around age 12, while other researchers report an older age, around 16 or 17, or even early adulthood. Gender and ethnicity may explain some of these differences. However, another important consideration is the different growth rates in the soft tissues versus the skeletal growth. An interesting study, looking at cephalometric radiographs, reported that anteroposterior growth and subsequent increased anterior projection of the nose continued in both males and females after skeletal growth had subsided [4]. They showed that overall growth of the nose was similar in both boys and girls between the ages of 7 and 12 years. However, after 12 years in females, a large proportion of their soft tissue development had also occurred, whilst in males they saw continued soft tissue growth until age 17 years. Once adulthood is reached, the nose stops growing, although many perceive that the nose continues to grow through adult life. Apparent lengthening occurs due to age-related changes of the key components of the nose: thinning of and loss of elasticity of the nasal skin, drooping of the nasal tip;

Table 18.1 Congenital nasal deformity classification, as described by Losee et al. [5]

Type 1	Hypoplasia/atrophy of skin, subcutaneous tissue, cartilage, muscle and/or bone
Type 2	Hyperplasia and duplications, ranging from part duplications to complete multiples
Type 3	Tessier craniofacial clefts classification is applied
Type 4	Congenital neoplasms (benign and malignant) and vascular anomalies

weakening and excessive softening of the nasal cartilage; separation and laxity of the intra-cartilage attachments.

Congenital Nasal Anomalies

Losee et al. in 2004 developed a scheme, following the study of a series of 261 patients over a 22-year period [5]. The following four types of congenital nasal anomalies were described in Table 18.1.

Type I Anomalies: Hypoplasia and Atrophy

Type I anomalies are the most common, accounting for over 60%. Failure or underdevelopment of all or some of the tissue components, such as skin, subcutaneous tissue, muscle, cartilage and bone, leads to range of issues from hypoplasia, partial absence and complete arhinia. Subcategories include the following:

Hemi-nose

Unilateral nostril agenesis is rare and usually found in combination with other anomalies affecting the ipsilateral face. The aetiology is unknown although thought to be due failure of nasal placode development.

Arhinia

Arhinia is exceedingly rare, with only a small handful of cases reported. Absence of the nose alone defines arhinia. Total arhinia is absence of the nose and olfactory system. Both are usually associated with major brain anomalies due to their shared embryological origins and unfortunately many infants do not survive long after birth. However, despite central nervous system anomalies, the potential for normal intelligence, well-developed speech and surgical rehabilitation have been reported in surviving infants.

Hypoplasia or Absence of Parts

Case reports describing hypoplasia or agenesis of portions of the nose are rare. Such cases have included absence of the columella only, isolated nasal bone agenesis, hypoplasia or aplastic nasal bones, resulting in a narrowed vault and cartilaginous hump.

Craniofacial Syndromes

Nasal hypoplasia is seen with many craniofacial syndromes, for example:

- Apert syndrome often presents with bilateral narrowing of the bony nasal cavity with choanal stenosis or atresia.
- Fraser syndrome is a rare autosomal recessive disorder, presenting with nasal anomalies such as a broad nose with midline groove and a depressed nasal bridge, hypoplastic nares with colobomas, choanal stenosis and a beak-like appearance.
- Binder syndrome, or naso-maxillary hypoplasia, is characterised by midface retrusion,

hypoplasia of the anterior nasal spine, a short columella and an obtuse nasofrontal angle.
- Craniofacial macrosomia and Goldenhar syndrome can both affect the nose with varying degrees of hypoplasia.

Nasal Cavity Atresia

Newborns are obligate nasal breathers, so any cause of nasal obstruction can present with significant airway obstruction leading to apnoea, cyanosis, failure to thrive and sometimes death.

- *Choanal atresia* is the commonest cause leading to posterior nasal cavity obstruction and can range from total bilateral bony choanal atresia to unilateral choanal stenosis. About half of the patients with choanal atresia have bilateral choanal atresia. In the general population, the incidence of choanal atresia is approximately 1 in 5000–7000 live births. It is thought to result from persistence of the buccona sal membrane and/or an insufficient deepening of the nasal pits [6]. Others believe it occurs from an alteration of mesenchymal migration; a view supported by the association with other common anomalies including brain anomalies in up to 25% of patients [7]. Choanal atresia may form part of a wider CHARGE diagnosis and a little more than 50% of children with CHARGE have some form of choanal atresia.
- *Pyriform aperture stenosis and mid-nasal stenosis* are more rare anomalies. Pyriform aperture stenosis is believed to be due to overgrowth of the maxillary nasal process and hypoplasia of the anterior hard palate and inferior pyriform aperture. Congenital pyriform aperture stenosis is associated with other anomalies, including a single central incisor and pituitary insufficiency, and may be a microform of holoprosencephaly.

The majority of outlet obstructions are believed to be both bony and membranous, consisting of a shortened and narrowed nasal cavity, lateral bony thickening, and obstruction by a thickened and deviated vomer. Diagnosis of these anomalies is made by the inability to pass a #6 to 8 French plastic catheter through the nares into the pharynx. A non-contrast high-resolution CT scan, and especially axial images, is now the single radiographic study of choice for confirmation of the diagnosis. Depending on the degree of nasal obstruction management, options include nasal decongestants, feeding supplementation, surgical widening of the stenosis +/− nasal stenting.

Case Presentation 1

A male infant referred by local paediatrician, age 3 months old, with upper airway obstruction and feeding difficulties. A 2.8 mm paediatric nasal endoscope could not be passed through either nostril at the level of the pyriform aperture. A CT scan confirmed congenital nasal pyriform aperture stenosis (Fig. 18.2). Surgical correction was performed via a sub-labial approach until a size

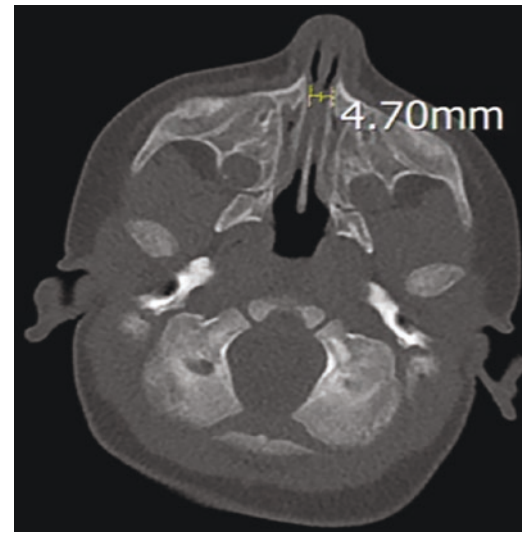

Fig. 18.2 Axial CT demonstrating reduced nasal aperture

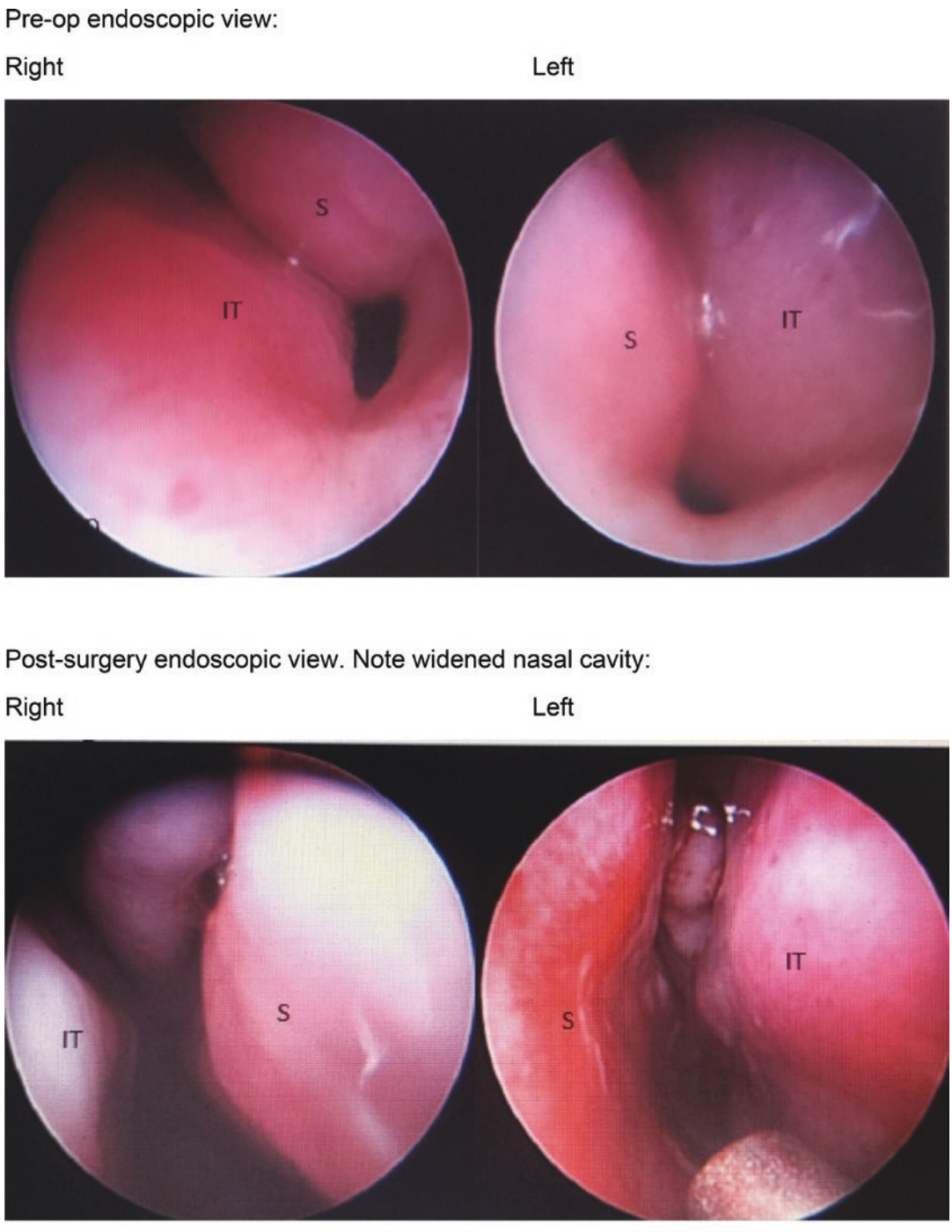

Fig. 18.3 Pre- and post-operative intra-nasal view in a case of pyriform aperture stenosis. Key: *S* Septum, *IT* Inferior turbinate

of 3.5 mm endotracheal tube could be passed into each nasal airway. The appearance of the nasal airway at the level of the pyriform aperture before and after surgical widening is shown in Fig. 18.3. Post-operative stents were secured and removed 1 month post-operatively.

Type 2 Anomalies: Hyperplasia and Duplications

Type 2 anomalies include excess tissue, ranging from part duplications to complete multiples and represent only 1% of patients with all nasal anomalies in Losee's study group [5]. Subclassifications include the following:

1. *Duplication of parts*. For example, a double columella and bifid caudal septum, resulting in two separate columella. Nostril duplication has been reported more frequently with the supernumerary nostril opening more often into a common cavity shared with the normal nostril. Polyrrhinia is true nasal duplication where two distinct noses are present, each having two nostrils and nasal cavities. It is postulated that two pairs of nasal placodes gave rise to four nasal pits and resulting in four nasal sacs undergoing usual development. Midline craniofacial clefts may result in anomalies presenting as apparent nasal duplications or a 'bifid nose'. Each nostril may be associated with its own blind ending cavity. Supernumerary nostrils have been associated with choanal atresia and pyriform aperture abnormalities. It is thought that a double nasal placode or accessory olfactory pit results in a supernumerary nostril.
2. *Proboscis lateralis* is a rare nasal anomaly, with a reported incidence of 1 in 100,000. It is most often described as a rectangular, tubular, fleshy appendage that is 1–3 cm long and 1 cm wide and connected to the inner canthus by a broad sessile attachment, although other positions and attachment points have been described. The orifice can drain secretions and experience coordinated flaring; however, the proximal canal is blind and so does not communicate with the nasal cavity. Boo-Chai sub-divided proboscis into four types: I, with a normal nose (the least common type); II, with ipsilateral nasal anomalies; III, with ipsilateral nose, eye and adnexal anomalies (the most common type); and IV, type III combined with cleft lip and palate. Many theories of its aetiology have been postulated including anomalies of the lateral nasal process, amniotic banding, healed encephaloceles, germinal anomalies, malformations or overgrowth of the lacrimal system and craniofacial clefting.

Congenital abnormalities are rare and require specialist knowledge in reconstruction techniques and surgery in children. Therefore, management of these types of nasal deformity should be referred to specialist centres with multidisciplinary experience that may include otorhinolaryngologist, plastic surgery, neurosurgery, ophthalmic and maxillofacial surgery. Discussion on Type 3 and 4 anomalies is out of the scope of this chapter and can be found in Losee's original article [5].

Assessment of Nasal Deformity

In the adult nose there are well-described angles and ratios when comparing male and female noses and the changes that occur with aging. The conception of what defines a beautiful nose and face is also broadly published with descriptions on facial proportions (mostly in Caucasian faces) based on facial width and height in one-third and one-fifth. However, in children the facial skeleton is proportionally very different to the adult. Children are born with a very large head compared to face size and small noses, which gradually over time develops into the adult proportions after the growth spurts. Therefore, assessment of nasal deformity relies more on comparison of the changes in shape pre-injury, which can be sought from photographs and descriptions from the child and caregivers and an experienced clinical assessment. Taking note of older siblings and parental nasal shape and size can also be helpful in determining if a deformity may just be a family trait rather than an acquired change. In planning a Rhinoplasty procedure, preoperative photography should be undertaken and recorded in the patient's clinical record. Photographs should follow standard pre-Rhinoplasty imaging protocols.

Functional assessments should be undertaken because restrictions in nasal airway caused by

septal deformities are a more accepted reason for considering surgical correction in childhood compared to cosmetic considerations. These should include:

- Symmetry of the nostrils and midline position of the columella and anterior septum.
- Shape and alignment of the nasal tip and dorsum—palpation is important to assess for tip and dorsal support.
- Consideration of the relation of the nose to the maxilla and overall facial symmetry.
- Check/look for alar collapse on inspiration—weak external nasal valve (very rare in children due to strong soft tissues)
- Septal deviations
- Inferior turbinate size and appearance
- Checking of nasopharynx for any persisting adenoidal hypertrophy
- Assessment for any other intra-nasal polyps/masses

According to the author's opinion, children aged 7 years old (and sometimes younger) will, in general, accept nasoendoscopy with pre-procedure topical anaesthesia spray and an honest and reassuring explanation of the process.

Rhinometry to assess nasal airway competency could be considered but clinically has little to add to the clinical assessment. Similarly, radiological investigation is rarely indicated unless to assess a more complex congenital deformity or complex nasofacial injury.

Nasal Trauma in Children

Trauma to the nose is common in children, and in many cases if the child is otherwise well, it is part and parcel of the minor knocks and bumps children incur in daily life; for example, trips and falls when running around, falling off bicycles and scooters, playing around with siblings, etc. As such, only a minority of cases will lead to the child being brought to the Emergency Department for review. Therefore, it is easy to understand why many injuries of the nasal skeleton are not diagnosed or treated at the time. However, aesthetic and/or functional problems do manifest later, resulting to the child being referred to a specialist, often several years after the injury. The decision whether a surgical intervention is indicated, at what age and which surgical technique will then require careful consideration. In many cases a 'wait and see' policy might be preferable and surgery even postponed until after the adolescent growth spurt. As many surgeons do opt to wait, there is still a paucity of evidence to support clinical decisions. Many of the experiments following nasal growth after injuries and/or surgical interventions are in animals (usually rabbit) or case reports, thus making it difficult to extrapolate to current-day decision-making. Sarnat and his co-workers published many experimental studies on rabbit midfacial growth patterns noting the impact that resection, particularly of the anterior septum, had on snout growth [8–10].

The decision-making process when counselling children and their caregivers can be complex and should include a discussion on:

1. the end goal—cosmetic vs functional outcome,
2. avoidance of doing harm by disrupting normal nasofacial growth,
3. context of child's current environment—love of sports, risk of further injury, and
4. psychological aspects—teenagers can be very concerned with their appearance and issues with body confidence and peer pressure are not uncommon.

The age of the 'selfie' photograph has led to many children and adolescents overanalysing and becoming very concerned about the size, symmetry and shape of their nose, when in fact there is often no significant or concerning deformity. During the adolescent growth spurt, the nose, in keeping with the rest of the body, does undergo significant physical changes into the 'adult' body. It is during this time that the nose takes on its adult appearance, which may include inherited and normal ethnic morphology, which can cause distress and lead to requests for surgery in some children and/or their caregivers. Purely cosmetic Rhinoplasty surgery in otherwise

healthy children is a contentious issue with many interplaying factors including psychosocial impact and private cosmetic surgical practice. Ultimately, as surgeons we have a duty to do no harm and as such extreme caution should be given to consideration of such surgery in pre-adolescent children.

Septoplasty

Many of the injuries more typically incurred by children usually involve damage to the nasal septum. Injuries include septal fractures and dislocations. Septal haematomas can also result, posing the risk of septal perforation and abscess development if left untreated. The underlying cartilage takes its blood supply from the overlying mucoperichondrium, so when this is disrupted, such as in a septal haematoma or abscess, then the underlying cartilage may undergo necrosis, leaving a septal perforation. Septal perforations can have disastrous effects both functionally and cosmetically.

Poor outcomes of septum surgery (septoplasty) in children were described over 100 years ago by Hayton using submucous resection [11]. Other similar reports up to the 1940s led to extreme caution in dealing with nasal anomalies in young children. During the mid-twentieth century, however, a resurgence of surgical approaches to the septum resumed with some preliminary successful reports of septoplasty published. However, the reports varied considerably, and most were too short a follow up in relation to the adolescent growth spurt. In the 1970s, Huizing followed 150 children up after septoplasty and described for the first time a boy who had surgery at the age of 4 years and developed characteristic midfacial disturbances following puberty, more than 12 years after his surgery [12].

Therefore, in younger pre-pubertal children, the decision to operate on the nasal septum must be carefully balanced with the deformities and functional problems that result in nasal airway obstruction. A significant traumatic septal deviation and/or dislocation in a young child can go on to form a complex situation as the child grows, leaving not just the resultant septal deformity but also its adverse effects on nasal growth. These can include asymmetric nasal growth and midfacial stunted growth. Learnings from previous case series reports and animal studies include the following:

- Preservation of the septodorsal cartilage in the growing nose and avoidance of resection wherever possible is vital.
- Autologous cartilage grafts are best, but these heal by forming fibrous unions and sometimes lamellar bone remodelling can occur.
- Proper end-to-end anastomosis of cartilaginous septum/autologous graft is critical to preventing surgery-induced growth anomalies in the long run.
- Submucosal implants of cartilage including crushed cartilage do not restore normal septal growth or midfacial development.
- Nasal septal cartilage scoring is unreliable (scoring techniques are used to encourage cartilage to deviate away from scored side) and can lead to weakening of the cartilage. Long-term outcomes of this technique are not known.

Septal Perforation

The most common aetiologies of nasal septal perforation in children are trauma, nasal cautery and, more recently, button battery insertion. A summary of potential causes is given below:

Most likely causes:

- *Trauma*: direct nasal injury.
- *Iatrogenic*: cauterisation for epistaxis, septoplasty, nasotracheal intubation.
- *Small batteries insertion*: button batteries pose a serious risk as they start to corrode on contact with the moist epithelium inside the nose and can lead to alkaline burns with rapid tissue necrosis. This can progress on to septal perforation, so any child presenting with the possibility of a battery in the nose should be treated as a medical emergency.

Uncommon causes to be considered in the differential diagnosis:

- Cocaine use should be considered in adolescents, especially in their late teenage years (but legally still referred to as children).
- Nasal packing: very unusual now that firm packing is rarely used in children.
- Chronic use of vasoconstrictor nasal sprays and, in rare cases, steroid nasal sprays.
- Granulomatous lesions: rare reports can be found in cases of childhood onset granulomatosis with polyangiitis (previously known as Wegner's granulomatosis) [13].
- Neoplastic lesions are quite rare.

Nose picking is common in children and as a consequence, digital trauma is often cited as being a common cause of septal perforation, but in reality, the pathogenesis is unlikely to be as simple as this. Nose picking is a natural response to clear irritating crusts. Local mucosal trauma may well induce chronic perichondritis that eventually leads to septal perforation. The simple explanation of scratching through the sensitive mucosa and exposed cartilage would be very painful, induce bleeding and be highly unlikely. However, there is a rare psychiatric disorder, called rhinotillexomania, in which the patient repeatedly picks at the nasal septum, but most publications are single case reports in adults.

The site of the perforation in children usually involves the anterior nasal septum. Anterior perforations are typically more symptomatic and can present with nasal crusting, bleeding and nasal obstruction. Perforations in early childhood have been reported to adversely affect nasal and midfacial growth both in clinical case reports and in animal studies [14]. Larger perforations can also lead to supratip depression.

Management options for septal perforations in children include medical management, septal button and surgical closure. The choice of treatment is complex and involves consideration of the symptoms and age of the child in discussion with the child and his/her caregivers. It is also important to consider the aetiology of the perforation, co-morbidities, ability to comply with post-operative care/restrictions, availability of adjacent tissue/grafts and potential effects on nasal growth. Generally, septal perforations that are asymptomatic and stable in size can be managed expectantly until the child reaches the end of their pubertal growth spurt and with the child's informed consent. Larger, symptomatic perforations that have failed medical management (avoidance of picking nose, nasal saline douches and topical antibiotic cream) may be considered for surgical correction. There is a paucity of long-term outcome data to recommend the best modality in children and adolescents. Endonasal and open approach techniques have been used in children with the use of pedicled flaps and interposition cartilage to repair the defect.

Nasal Fracture

Assessing the child following nasal trauma can be difficult due to the small nose and the immediate resultant soft tissue swelling. However, in any case of trauma, the child should also be assessed for a potential head injury, additional facial and orbital rim fractures and in rare cases consideration of non-accidental injury (NAI). NAI should be considered where the described cause of injury does not correspond with the clinical findings, delayed presentation, other signs of bruising or neglect and a previous history of NAI. Any concerns should be referred to the local child protection officer or paediatrician to further investigate. The risk of nasal fracture tends to increase with age and is also more common in boys.

Symptoms and signs of nasal fracture are as follows:

- Nosebleed
- Swelling
- Bruising around nose and under eye
- Tenderness
- Crepitus on palpation
- Blocked nose
- Nasal deformity

Ideally, the child should be reviewed 5–7 days following injury to better assess for any persisting deformity. In younger children (pre-puberty),

nasal bone injuries are less likely than cartilaginous ones but should be assessed for—particularly dehiscence of the nasal bone sutures. Plain X-rays are not useful in helping evaluate or diagnose a nasal bone fracture; however, CT scan may be considered in cases of more severe injury where other facial/orbital/head injuries may be suspected. Closed reduction of the nasal fracture under general anaesthesia should be offered and, in general, the same techniques are used to manipulate/reduce the nasal fracture as in adults. This involves both elevation of a depressed nasal dorsum along with external digital compression of the nasal bones until a satisfactory position is achieved. Post-operative external nasal splinting may be considered depending on the stability of the reduction.

Rhinoplasty

A detailed discussion on Rhinoplasty techniques is out of the scope of this chapter and is a topic that is still very much debated when managing childhood deformities. Severe breathing difficulties due to a deviated septum with significant external deviation, however, do present a clinical dilemma. A significant injury left untreated risks the longer term nasal and midfacial growth problems already discussed, which needs to be balanced against the risk of operating in a child under 16 years. Less severe deformities and breathing problems would be better monitored and surgery postponed (especially where the injuries do not progress to more severe problems) until the child has passed their adolescent growth spurt and is mature enough to better engage in the decision-making process. After reviewing the available literature, there are some key factors to consider when a decision to perform a Rhinoplasty has been made.

- Avoid resection or incisions of the septal cartilage, and most importantly, do not disrupt the septal bony–cartilaginous junction. This is often separated in adult Rhinoplasty practice but could lead to significant growth disruption in childhood.
- Deviated or dislocated cartilaginous fragments should be carefully re-aligned end to end.
- Avoid disruption of the anterior nasal spinal–cartilaginous ligament as it anchors the septum midline and may cause disruption of normal forward growth of the maxilla.
- Higher risk of injury to the skull base due to variable ossification of the septum to skull base, with risk of CSF leak and olfactory dysfunction.
- Currently, there is no strong evidence to support open versus closed septorhinoplasty surgery in children. The least disruption to normal anatomical support structures, however, would support a closed approach. However, open approaches have been used successfully in even very young children to remove congenital lesions such as nasal dermoid cysts, although division of the intra-cartilaginous ligaments is rarely needed in this situation.

Other factors also important to consider when exploring the risks and benefits of performing septorhinoplasty in pre-adolescent children include the following:

- *Aftercare—keeping the splint clean and in place*. Attending post-operative visits is important.
- *Social—risk of further injury after surgery*. Particular note should be taken of the child's sporting interests and general likelihood of further accidents.
- *Psychological*: Body dysmorphic syndrome and social peer pressures both in person and via social media are increasing and sadly occurring in younger children. Input from a child psychologist prior to surgery may be valuable when there is significant anxiety around the external nasal deformity.
- *Conflict between the child's wishes and their caregivers*: In many cases the caregivers may be pushing for early intervention despite the child not expressing any significant concerns and vice versa.
- *Experience of the surgeon*: Rhinoplasty is challenging and especially in pre-adolescent children a referral to an experienced Rhinoplasty surgeon should be made.

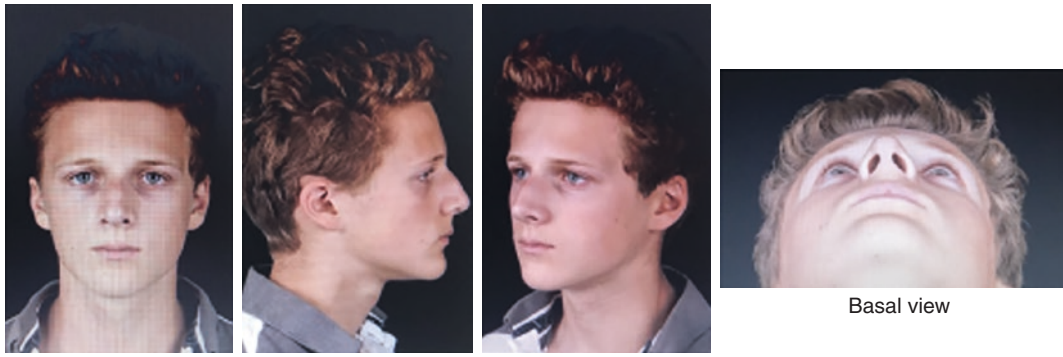

Fig. 18.4 Preoperative 'Rhinoplasty' views

Case Presentation 2

A 15-year-old boy was referred complaining of worsening nasal obstruction and a bump on the nasal dorsum following a nasal fracture during a rugby game 2 years prior. Examination findings included a prominent nasal dorsum, significant subluxation of nasal septum into left nasal airway causing obstruction and reduced nasal tip support. His preoperative appearance is shown in Fig. 18.4.

After a detailed discussion of risks and benefits, a closed septorhinoplasty was performed. Surgical correction included reduction of a maxillary crest spur, re-alignment of the nasal septum and reduction of the nasal hump followed by medial and lateral osteotomies.

Conclusion

Nasal congenital deformities are rare, but an understanding of how they may present and the underlying embryology is important, especially when planning any surgical interventions. Such cases should be referred to specialists and/or multidisciplinary teams where available because of the complexity of these deformities. Conversely, paediatric nasal trauma is relatively common although the majority will not present to medical services at the time of injury. Timing corrective surgery to both the nasal septum and nasal bones is still an area of controversy in children and adolescents, and ideally it is best performed by surgeons with significant expertise in septorhinoplasty surgery.

Key Learning Points

- Early closed reduction of a traumatic nasal deformity should be offered.
- Septorhinoplasty surgery in pre-adolescent children should be very carefully balanced with the severity of the deformity and functional impact. A high level of surgical expertise and opinion should be sought.
- Congenital nasal deformities, especially when associated with other craniofacial abnormalities, should be managed by a specialist multidisciplinary craniofacial team.
- The risk of future underdevelopment of the midface and nose following nasal trauma needs to be carefully weighed against the same risk that surgical intervention may lead to.
- To date, the evidence on the impact of both trauma and surgery to the nose in childhood is mostly based on animal studies and case/series reports.
- A holistic approach to the child and his/her nasal deformity is required in the decision-making process, including consideration of the social, psychological and educational

impact of the deformity and any surgical intervention.
- Non-accidental injury in cases of trauma should be considered.
- A button battery in the nose is a surgical emergency.

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Section IV

Inflammatory Sinus Disorders

Non-allergic Rhinitis

19

Wout Backaert and Laura Van Gerven

Introduction

Strictly speaking, rhinitis is defined as inflammation of the nasal mucosa. In clinical practice, however, inflammatory parameters are seldomly assessed. Consequently, the term 'rhinitis' is used for the presence of nasal complaints that have no anatomical cause. Various rhinitis phenotypes can be distinguished. Allergic rhinitis (AR) is present when rhinological symptoms are caused by a type 1 hypersensitivity reaction to one or more airborne allergens. The term 'infectious rhinitis' is used in case of presence of microbial or viral infection, such as seen in the common cold. A final group, non-allergic rhinitis (NAR)—previously known as non-allergic, non-infectious rhinitis (NANIR); non-allergic, non-infectious perennial rhinitis (NANIPER); or vasomotor rhinitis—is defined when no sensitisation or sign of nasal infection can be determined.

For all rhinitis phenotypes, clinical presentation is similar with patients reporting mainly nasal obstruction, rhinorrhoea/post-nasal drip, nasal itch or sneezing. By definition, symptoms should be present for two or more consecutive days and for more than 1 h on most days. These symptoms can be acute when lasting less than 12 weeks or persistent when lasting longer. In addition, sinusitis symptoms like facial pain and reduced sense of smell may be reported. Making a correct diagnosis based on the individual patient's history alone is not easy. A thorough clinical investigation with nasal endoscopy and additional technical investigations such as a skin prick test may assist in reaching the correct diagnosis. NAR remains a diagnosis *per exclusionem*, i.e. when symptoms cannot be explained by allergic inflammation, infection or anatomical factors (Fig. 19.1). Once the diagnosis of NAR has been made, the patient's history is the most important tool for further subcategorisation.

In practice, the clinical diagnosis can be complicated by the presence of two or more phenotypes. For example, when a patient with hay fever has symptoms during the pollen season, but also throughout the year, there is the possibility of

W. Backaert
Department of Otorhinolaryngology, University Hospitals Leuven, Leuven, Belgium

Department of Microbiology, Immunology and Transplantation, Allergy and Clinical Immunology Research Unit, KU Leuven, Leuven, Belgium
e-mail: wout.backaert@kuleuven.be

L. Van Gerven (✉)
Department of Otorhinolaryngology, University Hospitals Leuven, Leuven, Belgium

Department of Microbiology, Immunology and Transplantation, Allergy and Clinical Immunology Research Unit, KU Leuven, Leuven, Belgium

Department of Neurosciences, Experimental Otorhinolaryngology, KU Leuven, Leuven, Belgium
e-mail: laura.vangerven@uzleuven.be

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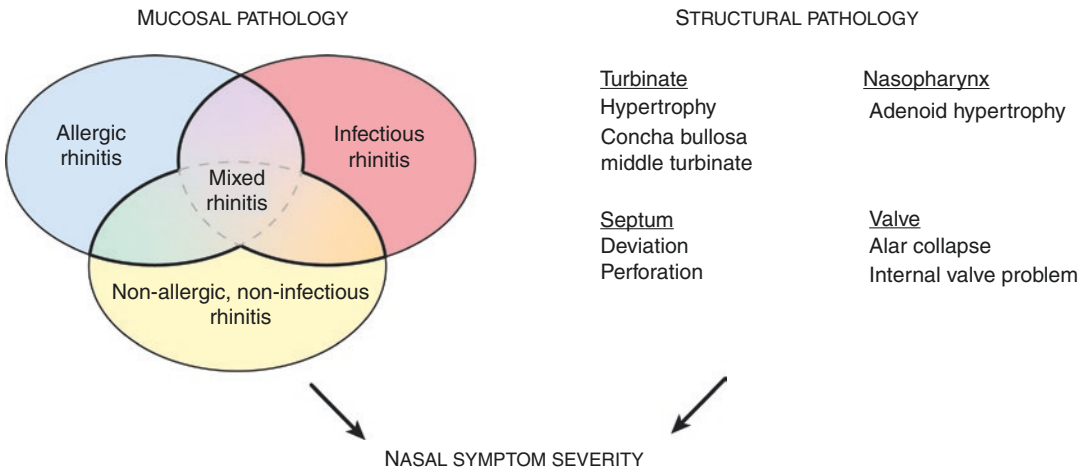

Fig. 19.1 Both mucosal and structural factors contribute to nasal symptom severity. © 2017 EAACI and John Wiley and Sons A/S. Adapted with permission from Hellings PW, Klimek L, Cingi C, Agache I, Akdis C, Bachert C, et al. Non-allergic rhinitis: Position paper of the European Academy of Allergy and Clinical Immunology. Allergy. 2017;72(11):1657–65

concomitant AR and NAR. This phenotype is referred to as 'mixed rhinitis'. Lastly, overlap is possible between mucosal and structural pathology, both contributing to the patients' symptoms (Fig. 19.1).

Assessment

Patients with NAR often have nasal symptoms with neither clinical signs of infection such as purulent secretions, nor signs of allergic inflammation such as allergen-specific IgE in serum or a positive skin prick test. NAR is a heterogeneous group of inflammatory phenotypes, covering all non-allergic, non-infectious rhinitis phenotypes (Fig. 19.2). In NAR, one can distinguish various subgroups including occupational/irritant-induced rhinitis, drug-induced rhinitis, hormonal rhinitis, rhinitis of the elderly/senile rhinitis, gustatory rhinitis, smoking rhinitis and—by exclusion—idiopathic rhinitis. Since there is no clear consensus on the diagnostic criteria, epidemiological data is scarce. However, it is estimated that more than 200 million people worldwide suffer from NAR [1].

Patient History

In cases of NAR, symptoms are usually bilateral and similar to other rhinitis phenotypes. The subcategorisation of NAR is mainly based on the patient history because of current limitations in diagnostic testing. In reality, there is often overlap between physiological and pathophysiological processes. In other words, multiple NAR subtypes can be present at the same time.

In cases of *occupational or irritant-induced rhinitis*, symptoms are triggered by specific irritants or molecules present in the workplace. In order to make a diagnosis, a thorough occupational patient's history is mandatory. What is the patient's job title? Where does the patient work? What is the patient's specific role in the workplace? Do co-workers experience nasal symptoms as well? Are the nasal symptoms linked to recent changes in work processes or materials? Does the patient work in an environment or with products that are known to frequently lead to occupational rhinitis such as laboratory animals, cleaning agents, chemicals, dyes, pharmaceutical products, etc.? It is often easier to ask the patient what he/she is actually *doing* in the workplace

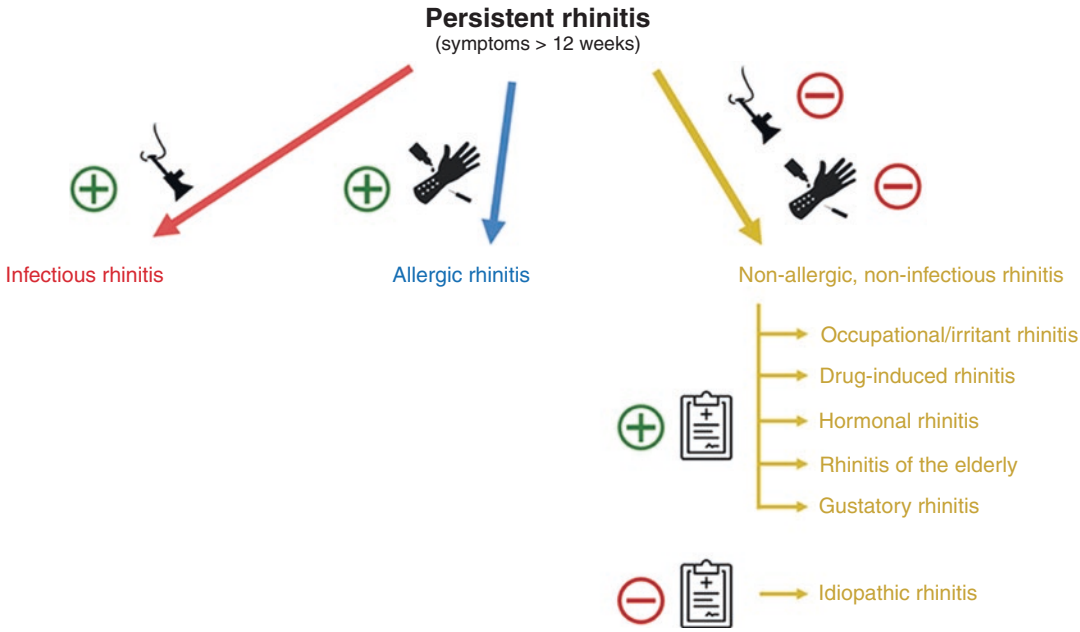

Fig. 19.2 Approach to the persistent rhinitis patient. Non-allergic, non-infectious rhinitis is diagnosed after exclusion of infectious and allergic rhinitis by absence of purulent secretions on nasal endoscopy and a negative skin prick test/specific IgE in the serum. Patient history remains the most important tool for further categorisation in subgroups. © 2017 EAACI and John Wiley and Sons A/S. Adapted with permission from Hellings PW, Klimek L, Cingi C, Agache I, Akdis C, Bachert C, et al. Non-allergic rhinitis: Position paper of the European Academy of Allergy and Clinical Immunology. Allergy. 2017;72(11):1657–65

rather than asking what he/she is *exposed to*. For example, a patient will know he/she is working with paint products but could be unaware that the paint contains isocyanates, which are potent low molecular weight sensitisers. At onset of the disease, there is a clear relationship with exposure, i.e. patients may have nasal symptoms during work but less or none during weekends or holidays. However, this relationship can diminish with time and symptoms may persist outside the work environment. A diary where nasal symptoms can be scored on a daily basis over a longer period of time covering both working days and holidays can be a useful tool. If available, a peak nasal inspiratory flow (PNIF) device can be used at home and work to easily and objectively monitor nasal patency. Since occupational rhinitis often precedes occupational asthma, one should also address lower airway symptoms such as dyspnoea, wheezing and cough during history taking.

Industrialisation has led to a substantial increase in the amount of *air pollutants* in the environment. Many of these pollutants have detrimental effects on respiratory health and can lead to chronic rhinitis. Indeed, pollutants promote the formation of reactive oxygen species, leading to oxidative damage. In patients with chronic rhinosinusitis undergoing functional endoscopic sinus surgery, it has been shown that exposure to environmental low molecular weight agents correlates with the need for revision surgery [2]. Additionally, diesel exhaust particles can aggravate asthma and anthropogenic nanoparticles can enhance allergic inflammation. Indeed, pollutant-exposure increases allergen-specific IgE levels, severity of asthma and airway hyper-responsiveness. Therefore, one should address questions on pollutant-exposure during history taking. Where does the patient live: in a rural, urban or industrial environment? Did the nasal complaints start after a domestic reloca-

tion? Are nasal complaints better during holidays to more rural areas?

Similarly, patients with rhinitis who are exposed to cigarette smoke have a higher chance of developing asthma. Smoking itself can induce a type 2-like inflammation with increased eosinophils and interleukin-4, leading to *smoking rhinitis*, with the classical symptoms of nasal obstruction and rhinorrhoea.

Drug-induced rhinitis encompasses two different groups of patients who experience nasal symptoms that can be associated with the use of certain medications.

The best known is the so-called *rhinitis medicamentosa*, where there is an overuse of topical nasal decongestants. They are typically used in the relief of nasal congestion due to allergic rhinitis, acute or chronic rhinosinusitis or upper respiratory tract infection. However, after a prolonged use of >7–10 days, a rebound effect occurs, characterised by rebound congestion and tachyphylaxis. Consequently, increasingly higher doses are needed to reach the same clinical effect. Patients typically complain of recurrent nasal obstruction, without rhinorrhoea.

Other drugs, such as antihypertensives or psychotropic agents, can induce nasal symptoms as 'side effects'. Therefore, it is important to review a patient's medication list carefully and to verify a possible correlation between symptom onset and the start of new medication or the temporal relationship between taking the drug and symptom onset (Table 19.1).

Table 19.1 Overview of systemic drug categories often leading to nasal symptoms

Angiotensin-converting enzyme inhibitors	**Phosphodiesterase-5 inhibitors**
Captopril	Sildenafil
Lisinopril	Tadalafil
Perindopril	Vardenafil
Enalapril	
Ramipril	**Psychotropic drugs**
	Chlorpromazine
Antihypertensive drugs	Thioridazine
α-Methyl dopa	Amitriptyline
Guanethidine	Alprazolam
Reserpine	
	Immunosuppressants
α-Adrenoreceptor antagonists	Cyclosporin
Prazosin	Mycophenolic acid
Tamsulosin	
Terazosin	**Hormonal**
	Oral contraceptives
β-Adrenoreceptor antagonists	Antithyroid medication
Carvedilol	Human growth hormone supplement
Propranolol	Bromocriptine
Sotalol	
Timolol	**Cocaine**
Atenolol	
Metoprolol	

The group of *hormonal rhinitis* consists of various subtypes. In gestational rhinitis, patients complain of nasal obstruction in the third trimester of pregnancy. Complaints typically resolve spontaneously within weeks after delivery. Hormonal rhinitis can also be present in non-pregnant women, where the severity varies with the menstrual cycle. Lastly, hormonal rhinitis is also linked to some endocrine disorders, such as hypothyroidism or acromegaly, although the literature remains scarce.

Rhinitis of the elderly, or senile rhinitis, typically manifests in the seventh decade or later and is characterised by profound watery rhinorrhoea. This problem is probably underreported in literature since older adults are often excluded from epidemiological studies. However, it has been described that the prevalence of self-reported rhinitis remains similar through the course of life, but allergic sensitisation decreases with age. Hence, NAR is more frequent in older patients compared to AR. Rhinitis of the elderly should be distinguished from physiological changes when growing older, such as anatomical (loss of tip support, weakening of cartilaginous structures, etc.) or mucosal changes (reduced blood mucosal blood flow, impairing the humidifying properties of the nasal mucosa).

In *gustatory rhinitis*, symptoms are present during mealtimes, especially when eating hot or spicy foods. Within minutes after ingestion, watery rhinorrhoea occurs, without other nasal symptoms including nasal obstruction.

Lastly, nasal hyper-reactivity is defined as the aggravation of nasal symptoms caused by expo-

sure to environmental stimuli that would produce little or no effect in healthy subjects, such as temperature or humidity changes, air conditioning, strong odours or cigarette smoke. It is a hallmark feature of *idiopathic rhinitis* but is probably also present in other inflammatory disorders of the upper airways. Once nasal endoscopy and skin prick testing are negative and patient history does not give any clue to one of the mentioned NAR subtypes, the diagnosis of idiopathic rhinitis can be made.

Clinical Examination

There are no specific clinical signs upon anterior rhinoscopy or nasal endoscopy specific to a diagnosis of NAR. In parallel with other inflammatory disorders, nasal congestion and serous secretions may be present. One particular feature of mainly rhinitis medicamentosa is hypertrophy of the inferior turbinates. However, as in other rhinitis phenotypes, thorough clinical examination remains mandatory to exclude other factors contributing to nasal symptoms such as anatomical abnormalities (e.g. septal deviation, septal perforation, alar collapse), inflammatory changes (e.g. purulent secretions indicating infectious rhinitis, nasal polyps or chronic sinus disease) or neoplastic processes.

Special Investigations

In parallel with the clinical assessment, there are few additional specific diagnostic investigations in patients with NAR. Since NAR is diagnosed by exclusion of other possible causes of rhinitis symptoms, allergen skin prick test should be negative or allergen-specific IgE absent in the serum, and computed tomography of the maxillofacial region—if performed—should show no opacification of the paranasal sinuses.

Subjective nasal obstruction can be objectified using nasal patency tests, such as anterior/posterior rhinomanometry, acoustic rhinometry or measurement of the PNIF. However, this has limited added value since a decreased nasal patency can be present in all phenotypes of upper airway inflammation.

Some rhinitis phenotypes can be diagnosed with nasal provocation tests. Specific molecules or solutions are administered directly endonasally to mimic a relevant exposure. For example, a nasal allergen provocation test (NAPT) can aid in diagnosing local allergic rhinitis (or occupational rhinitis). In local allergic rhinitis (entopy), there is allergic inflammation and presence of allergen-specific IgE in the nasal mucosa, but not in the peripheral blood and skin prick tests remain negative. Hence, nasal symptoms are triggered by administration of allergens directly to the nasal mucosa. Allergens can be administered via nasal sprays or by placement of paper disks impregnated with allergens on the anterior end of the inferior turbinate. With the use of a nasal spray or a micropipette, allergens can be applied in increasing concentrations to determine the threshold for evoking nasal symptoms. Generally, the starting concentration is a 1:1000 dilution of the concentration used in skin prick tests. In poly-sensitised patients, a NAPT can be useful to determine the most important allergen before starting allergen immunotherapy. The same principle can be applied for diagnosing occupational or irritant-induced rhinitis where small doses of suspected triggers are administered endonasally.

Several provocation tests have been developed to diagnose patients with NAR. A cold, dry air provocation test has a high sensitivity and specificity in diagnosing nasal hyper-reactivity, a common feature in idiopathic rhinitis patients. Patients are exposed to air of <-10 °C and a relative humidity of <10% for 15 min, delivered via a common anaesthesia mask at a flow of 25 L/min. Before and after the provocation, PNIF is measured (the median of three measurements varying less than 10% is taken as final value). A reduction of 20% or more is taken as a threshold for diagnosis [3]. Historically, other provocation tests using chemical compounds have been used, such as mannitol, capsaicin, metacholine and histamine. They were not implemented in daily practice because of several limitations such as lower sensitivity/specificity, less patient/investigator-friendly, etc.

Pathophysiology

Due to the lack of diagnostic criteria, the group of NAR consists of several poorly characterised subgroups, impeding pathophysiological studies. Physiologically, afferent nerve activation results in signal transduction to the central nervous system. Consequently, a sympathetic or parasympathetic response is triggered. The former is characterised by norepinephrine and neuropeptide Y as main neurotransmitters, and induces vasoconstriction and decreases mucous secretion. The latter uses acetylcholine and vasoactive intestinal peptide, which results in vasodilation and increased mucous secretion. This pathway from afferent nerves to the central nervous system and next to efferent nerves is the orthodromic pathway of neuronal signalling. In general, the pathophysiology of NAR is suspected to be caused by dysregulation of the neurogenic pathway and can originate from either afferent or efferent neuronal abnormalities (Fig. 19.3).

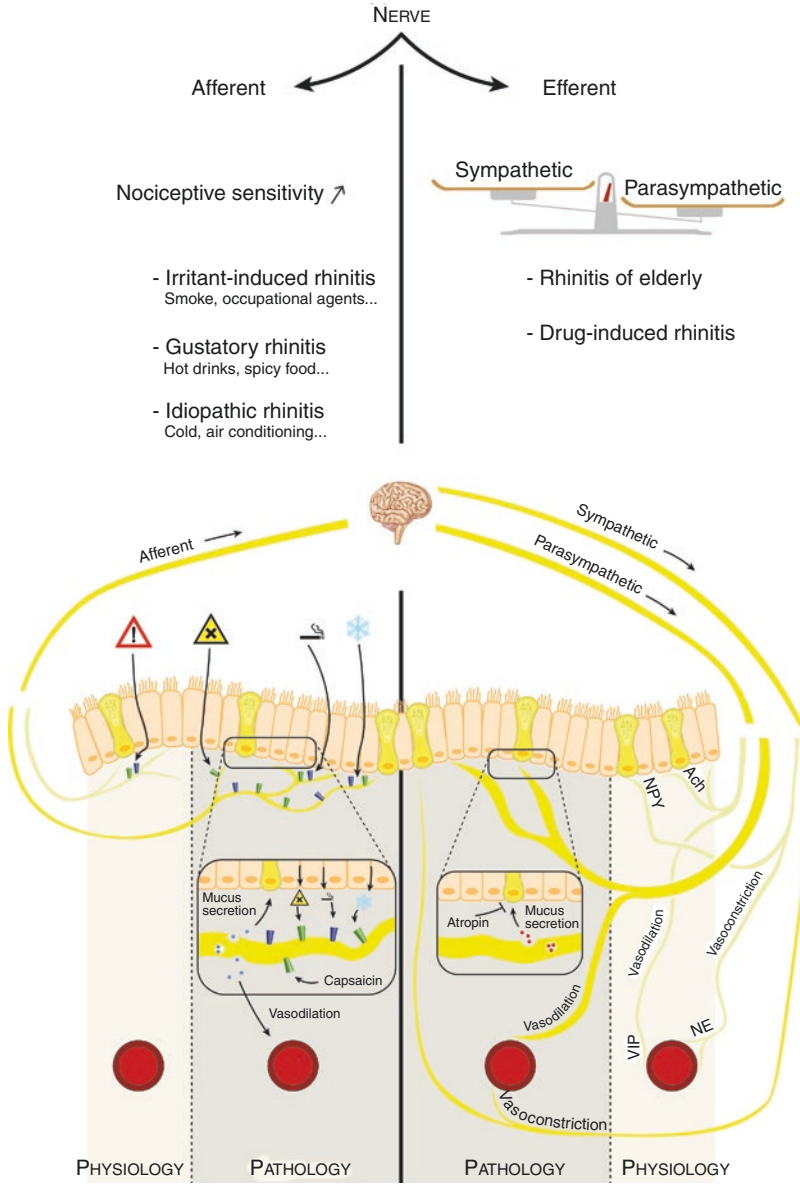

Fig. 19.3 Presumed pathophysiological mechanisms in non-allergic rhinitis. Pathology can be situated on the afferent nerves, where an increased nociceptive sensitivity to irritants, herbs or environmental triggers induces release of neuropeptides, leading to vasodilation and increased mucus secretion. On the other hand, neurogenic imbalance with a relative overweight of a parasympathetic efferent response can lead to similar end-organ effects. NPY: neuropeptide Y, ACh: acetylcholine, NE: norepinephrine, VIP: vasoactive intestinal peptide

Occupational/Irritant/Smoking-Induced Rhinitis

In occupational rhinitis, (sino)nasal symptoms are evoked in response to airborne agents present in the professional environment. Both high molecular weight (e.g. mites, flour, dander from lab animals) and low molecular weight agents (e.g. isocyanates, anhydrides, reactive dyes) can induce allergic inflammation. The latter can act as a hapten for immunologic interactions. Also, inhaled irritants can directly damage the nasal epithelium, which subsequently releases pro-inflammatory cytokines. However, symptoms are often induced by environmental irritants via a non-immunological way but rather by direct irritation. It is most likely that irritants interact with nociceptors such as **transient receptor potential (TRP) channels** present on trigeminal afferent nerves. Upon activation, afferent nerves release neuropeptides leading to vasodilation and increased mucous production via an antidromic pathway, hence mediating nasal symptoms. This hypersensitive state can be the result of a single event with a high level of exposure, such as a spill of chemical products or of periodic exposure to moderate levels of irritants. Symptoms are dependent on the exposure and can be perennially or seasonally present when work varies through the course of the year. As a diagnostic tool, daily PNIF measurements can be used to seek a temporal pattern related to working periods and holidays/weekends. Additionally, a provocation test to mimic the workplace environment can be performed. Lastly, in patients suffering from smoke-induced rhinitis, a type 2-like inflammation with increased eosinophils and increased interleukin-4 in the nasal mucosa is seen.

Drug-Induced Rhinitis

Drug-induced rhinitis can be divided into two pathophysiological groups.

The most common form, rhinitis medicamentosa, develops in case of prolonged use or overuse of topical vasoconstrictive agents. The vascular network of the nasal mucosa consists of both resistance vessels (arterioles), which contain α_2-adrenoreceptors, and capacitance vessels of the venous plexus, containing both α_1- and α_2-adrenoreceptors. Topical decongestants typically contain α_1-adrenergic β-phenylethylamine derivates, such as ephedrine or phenylephrine, or α_2-adrenergic imidazoline derivates, such as naphazoline, oxymetazoline or xylometazoline. Long-term use of these vasoconstrictors can lead to tachyphylaxis due to downregulation of α-receptors with rebound congestion as result. Chronic hypoxia of the nasal mucosa leads to histologic changes and mucosal hypertrophy.

Systemically administered drugs can also influence the nasal function as side effect. One should be aware of antihypertensive drugs (angiotensin-converting enzyme inhibitors, β-blockers), drugs used in treatment of prostate hypertrophy (α-antagonists), oestrogens or psychotropic agents (Table 19.1).

Hormonal Rhinitis

Nasal symptoms can have an endocrine cause, for example when they develop near the end of pregnancy or varying with the menstrual cycle with most complaints around the time of ovulation. Symptoms usually disappear after normalisation of oestrogen levels. Oestrogens induce nasal vasodilation, hence leading to nasal obstruction. In addition, oestrogens enhance eosinophil migration and, together with progesterone, they induce eosinophil degranulation. In contrast, testosterone reduces eosinophil migration and viability. Finally, rhinitis also has been linked with hypothyroidism and acromegaly. Hypothyroidism is suspected to induce oedema and decrease mucociliary transport, though complete understanding of the underlying pathophysiology is lacking.

Rhinitis of the Elderly

Rhinitis of the elderly is so called because it predominantly affects patients from the age of 65 years. These patients typically complain of

persistent clear rhinorrhoea as the main symptom. An imbalance of the sympathetic/parasympathetic efferent nervous system, with a loss of the physiological sympathetic predominance, is suspected to cause these symptoms. As such, relative overactivity of the parasympathetic nervous system activates submucosal glands to secrete clear mucous.

Furthermore, with increasing age, additional physiological changes occur in the nose. The mucosal epithelium becomes drier and there is a decreased blood flow in the nasal mucosa, leading to impaired humidification and warming of inhaled air. Furthermore, mucociliary clearance becomes less efficient and mucous is usually thicker in older patients, which can lead to rhinorrhoea, or postnasal drip with subsequent cough.

Gustatory Rhinitis

Eating certain foods, and particularly ingestion of hot or spicy foods may lead to nasal obstruction or watery rhinorrhoea. There is a clear temporal pattern with mealtime. The pathophysiology remains incompletely understood, but is probably linked to neurogenic reflex mechanisms via oral fibres of the trigeminal nerve or vagal nerve, inducing activation of the parasympathetic nervous system. This is suspected to be a physiological response, although it might be more pronounced in some patients.

Idiopathic Rhinitis

When a diagnosis of NAR is made as a result of negative findings on examination and special investigations and the history does not clearly point to one of the previously mentioned NAR subgroups, a diagnosis of idiopathic rhinitis is made. Here, no apparent cause can be found for the patient's nasal symptoms, neither mucosal nor anatomical related. Despite being a diagnosis *per exclusionem*, up to 50% of the NAR patients fall into this subgroup. Idiopathic rhinitis is suspected to be an afferent nerve disorder. Trigeminal sensory afferent nerves contain neuropeptides such as substance P and calcitonin gene-related peptide, which are released antidromically after activation of transient receptor potential (TRP) channels present on the afferent nerves by environmental triggers. Indeed, nasal hyper-reactivity—where patients react to environmental triggers such as temperature or humidity changes, or air conditioning—is a key feature in these patients. In idiopathic rhinitis, the TRP vanilloid 1 (TRPV1)–substance P pathway is upregulated.

Therapeutic Options

Depending on the presumed underlying mechanism, various treatment options are available. However, due to the heterogeneity of the group of NAR patients, achieving definitive disease control can be difficult. In addition, for many subtypes of NAR, the pathophysiology remains unclear. Hence, in practice, treatment of a patient with NAR is rather trial-and-error.

Nasal Douching

Nasal douching is the first treatment option for all upper airway inflammatory diseases. The principle is to flush away abundant secretions possibly containing inflammatory mediators, irritants, pathogens and allergens. In practice, a volume of 200–300 mL water at 37 °C containing 0.9% sodium chloride is lavaged through the nose 2–3 times daily.

Avoidance of the Causative Triggers

In such cases of afferent nerve pathology (irritant/smoke-induced rhinitis, gustatory rhinitis, idiopathic rhinitis), the triggers exacerbating nasal symptoms should be avoided. If avoidance is difficult, efforts should be made to minimise exposure. For example, by wearing protective equipment (mouth mask, goggles) and by reducing the exposure time. In drug-induced rhinitis, drug avoidance is important. In rhinitis medicamentosa, immedi-

ately halting short-term intranasal vasoconstrictors is mandatory. Supportive therapy with a short course of oral corticosteroids and nasal douching can help counter rebound symptoms. Where nasal symptoms are considered to be a side effect of, for example, antihypertensive drugs, one should discuss the possibility of substituting alternative types of drugs/therapy with the treating general practitioner or cardiologist.

Corticosteroids

The beneficial effect of locally or systemically administered corticosteroids in mainly type 2-mediated inflammatory disorders is well described. In NAR, they are far less effective [4]. Due to limited therapeutic options, however, a 2-month period of intranasal corticosteroids is often recommended in daily practice.

Ipratropium Bromide

Ipratropium bromide, a short-acting anticholinergic drug, can be used in a nasal spray for rhinitis of the elderly, where it counteracts the parasympathetic overweight. It restores the neurogenic balance with a relative predominance of the sympathetic nervous system. As a consequence, there is less secretion of mucous from goblet cells. Similarly, application of an ipratropium bromide nasal spray 5–10 min before food ingestion can inhibit the typically watery rhinorrhoea present in gustatory rhinitis.

Antihistamines

Antihistamines blocking the histamine 1 receptor (Hrh1-receptor) are mainly used in the treatment of allergic rhinitis. However, there is some evidence that azelastine, an old Hrh1-receptor blocker, can also block TRPV1, tempering nociceptive function of the sensory nervous system [5, 6]. Indeed, patients with pronounced nasal hyper-reactivity may benefit from azelastine nasal spray thrice daily.

Capsaicin

Capsaicin, the pungent agent of chili peppers, is a strong and selective TRPV1 agonist. Strong activation of TRPV1 induces a massive calcium influx, leading to a toxic intracellular calcium overload in afferent neurons. This defunctionalises the afferent nerve endings with a therapeutic effect lasting 6–9 months. Capsaicin therapy has mostly been studied in idiopathic rhinitis patients, with a success rate of 70–80%. In practice, 0.3 mL of a capsaicin nasal spray in a concentration of 0.1 mM is applied 5 times at hourly intervals on a single day [7]. To minimise a burning discomfort, the first two applications are administered after topical anaesthesia.

Surgery

When all pharmacological interventions fail to provide adequate benefit, surgery can be indicated in specific cases.

In cases of turbinate hypertrophy, often caused by rhinitis medicamentosa, a partial inferior turbinectomy can be considered. However, ceasing the use of nasal decongestive sprays or drops remains mandatory as symptom recurrence is otherwise inevitable. Multiple surgical techniques have been described (with scalpel/scissors, electrocautery, radiofrequency ablation, diode laser, submucosal turbinate reduction). One should avoid an excessive resection, since this could induce the Empty Nose Syndrome where a lack of the cool-sensing TRP melastatin 8 causes a subjective sensation of blocked nose but in the absence of objective findings.

When persistent rhinorrhoea is the main complaint, a Vidian neurectomy can improve symptoms [8]. The aim is to interrupt the parasympathetic innervation of serous and seromucinous glands. This leads to a significant reduction in rhinorrhoea and in some studies a better nasal patency was reported as well. With the development of nasal endoscopes came excellent visualisation of the surgical field, leading to better surgical outcomes and reducing operative complications such as cranial nerve injury. After

widening the natural orifice to the sphenoid sinus, the Vidian canal can be visualised in the floor of the sphenoid sinus. The canal should be drilled out and the Vidian nerve together with the Vidian artery should be cauterised. However, because the lacrimal gland is additionally innervated by parasympathetic fibres in the Vidian canal, xerophthalmia is a potential side effect. This effect has only a mild to moderate impact on patients' quality of life and is temporary in most cases. However, surgical interruption of the Vidian nerve should only be considered as final option and the procedure should always be performed unilaterally. If this is tolerated well and has good effect, the contralateral Vidian nerve can be interrupted as well.

Areas of Uncertainty

A definitive diagnosis of NAR remains challenging. Even more, due to the lack of specific diagnostic tests, it is not easy to subcategorise a particular patient with NAR. This also complicates performing studies on specific subgroups. Consequently, the pathophysiology of most subcategories remains only vaguely discovered and hence, few specific therapies exist. Taking everything into account, the diagnostic approach and clinical management of patients with NAR is challenging and often a matter of trial-and-error.

Key Learning Points

- Non-allergic rhinitis is diagnosed in case of nasal symptoms that have no anatomical cause and after exclusion of infectious and allergic rhinitis.
- Non-allergic rhinitis is a heterogeneous group and further subcategorisation is mainly based on patient history.
- Pathophysiologically, the various subcategories can be divided in pathology of the afferent or efferent nervous system.
- Avoidance of the causative triggers and nasal douching are the first treatment options. There is room for ipratropium bromide in case of profound rhinorrhoea and some evidence suggests therapeutic potential for antihistamines. In selected cases, intranasal capsaicin therapy or surgery (turbinectomy, Vidian neurectomy) can be indicated.

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Allergic Rhinitis

20

Quentin Gardiner

Pathophysiology

Allergic rhinitis (AR) is manifested in patients with a genetic propensity to being atopic. Following primary exposure to a possible allergen, IgE is produced, which then primes the immune system to trigger an allergic reaction on subsequent exposure. Along with nasal symptoms, patients may also develop eczema, asthma, allergic conjunctivitis and food allergies. This IgE-driven response is an abnormal manifestation of an otherwise useful immune response aimed at defending the body against infection, mainly with parasites. The inflammatory reaction caused is termed a type 1 hypersensitivity reaction in the Gell and Coombs classification.

In the sensitisation phase, an allergen is processed by an antigen-presenting cell (APC) and presented to a Th2 lymphocyte, which becomes activated. These activated Th2 cells trigger plasma cells to produce specific IgE antibodies that bind to a mast cell, therefore sensitising it to degranulate when the same allergen crosslinks the bound IgE on subsequent exposure.

This causes the release of histamine, tryptase and other newly synthesised inflammatory mediators such as leukotrienes and prostaglandins (Fig. 20.1).

The early phase reaction is mainly driven by histamine causing nerve irritation (sneezing and itching), stimulation of submucosal glands and hyperpermeability of blood vessels (running) and vasodilatation (block). Other mediators involved in the late phase reaction cause continued block and other systemic effects such as wheeze. These mediators and the clinical effects of nasal block may have an effect on other organ systems both directly and indirectly (Fig. 20.2).

Q. Gardiner (✉)
Department of Otolaryngology, Ninewells Hospital and Medical School, Dundee, UK
e-mail: quentin.gardiner@nhs.scot

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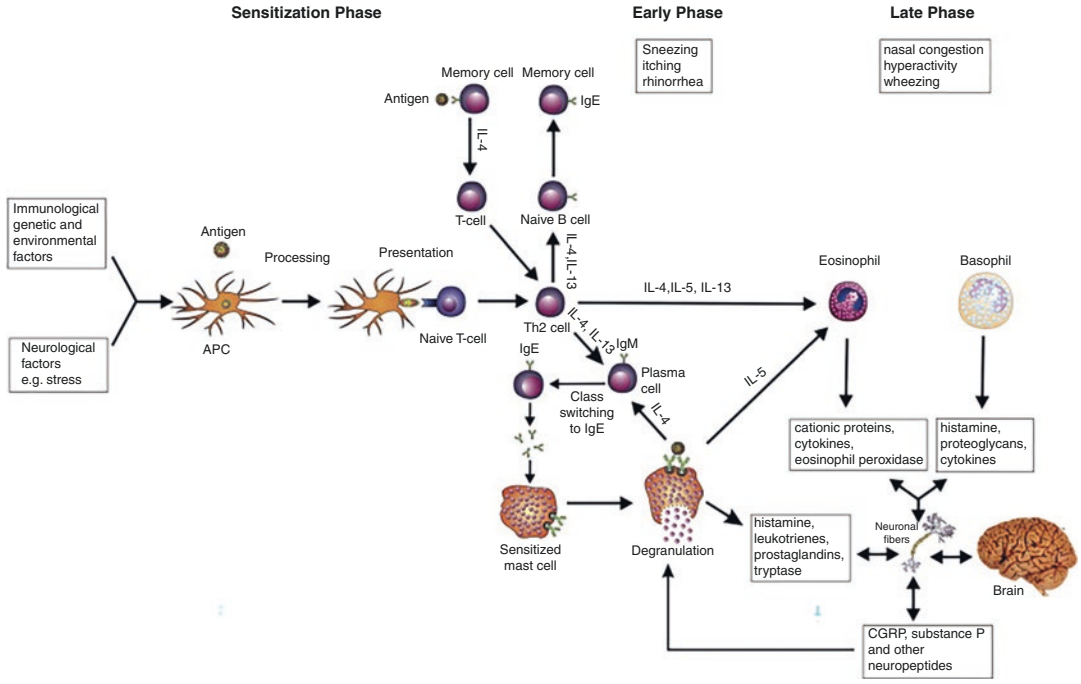

Fig. 20.1 Sensitisation, early and late phases of the allergic reaction (reproduced with permission from Elsevier)

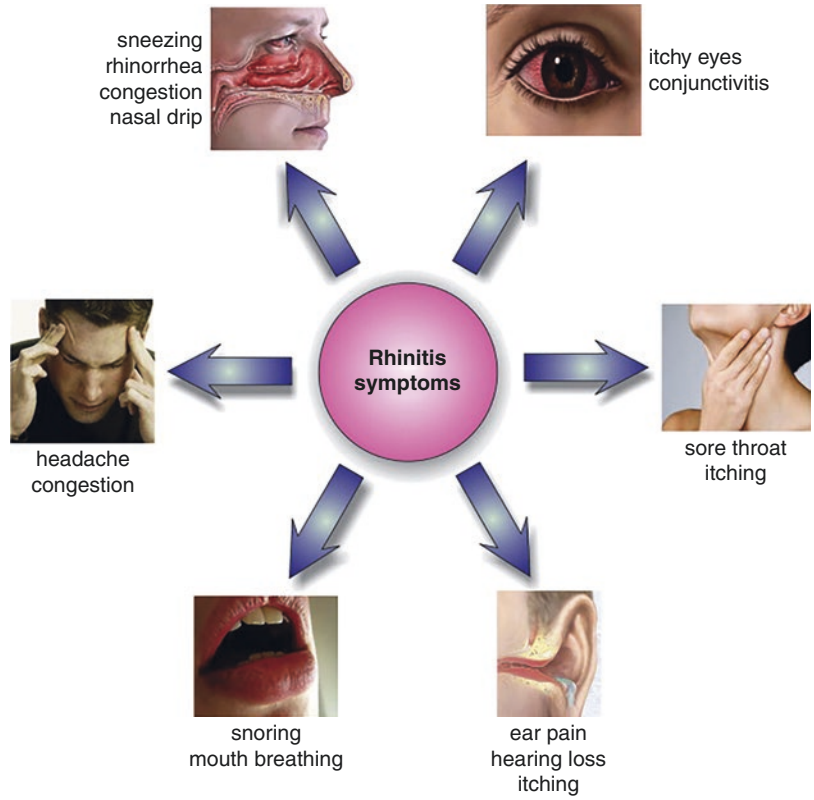

Fig. 20.2 The direct and indirect effects of allergic rhinitis on other systems (reproduced with permission from Elsevier)

Epidemiology of AR

The prevalence of AR varies widely around the world [1] (Fig. 20.3).

Rates vary between 2 and 40% of the population around the world, with prevalence in Europe varying between 20 and 40% [2]. The WHO estimates that 500 million people in the world suffer from AR, making it the third most prevalent chronic disease in adults and the most prevalent chronic disease in children.

The prevalence of allergic disease in general has increased significantly over the last century, particularly in the industrialised world, but the reasons for this are not entirely clear. The hygiene hypothesis suggests that reduced exposure to microbes in early life, and a genetic predisposition to atopy, has caused the immune system to become dysregulated with a consequent excess production of IgE and therefore expression of allergic symptoms. Protection against parasitic infection (which is the underlying reason for mammals to express IgE) may also be involved. Infestation with worms has a strong protective effect against developing allergy, probably by the production of blocking IgG antibodies and the release of helminth-produced anti-inflammatory chemicals that block cytokines such as IL33, which drive the inflammatory process. Worm infestation remains very prevalent in developing countries where there is generally a low burden of allergic disease.

Clearly, sensitisation also depends on exposure to a potential allergen. This varies around the world with countries near the equator having less seasonal variation in allergens, and cooler, damper countries having higher levels of exposure to indoor allergens. The physical size of the allergen also plays a role, with larger particles tending to be deposited in the nose and smaller ones penetrating into the lower respiratory tract.

AR has been subdivided into two main groups—intermittent AR (IAR) and persistent

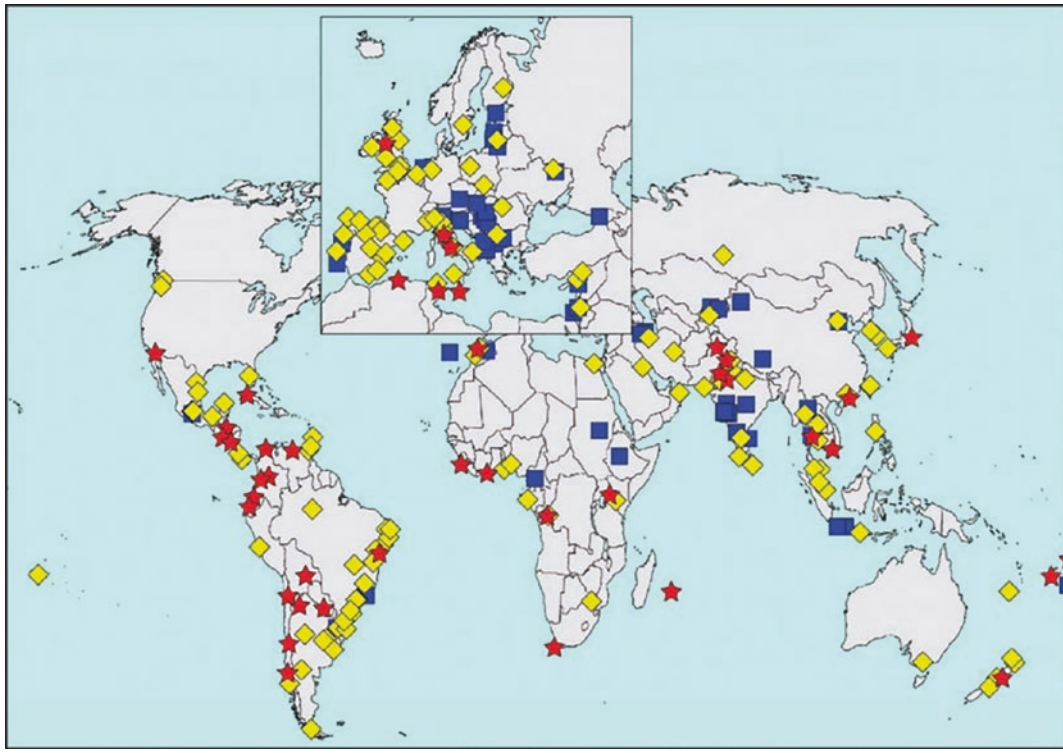

Fig. 20.3 Map of prevalence of current symptoms of rhinoconjunctivitis, 13- to 14-year age group. Symbols indicate prevalence categories of ≥20% (red stars), ≥10 to <20% (yellow diamonds) and <10% (blue squares) (reproduced with permission from John Wiley and Sons)

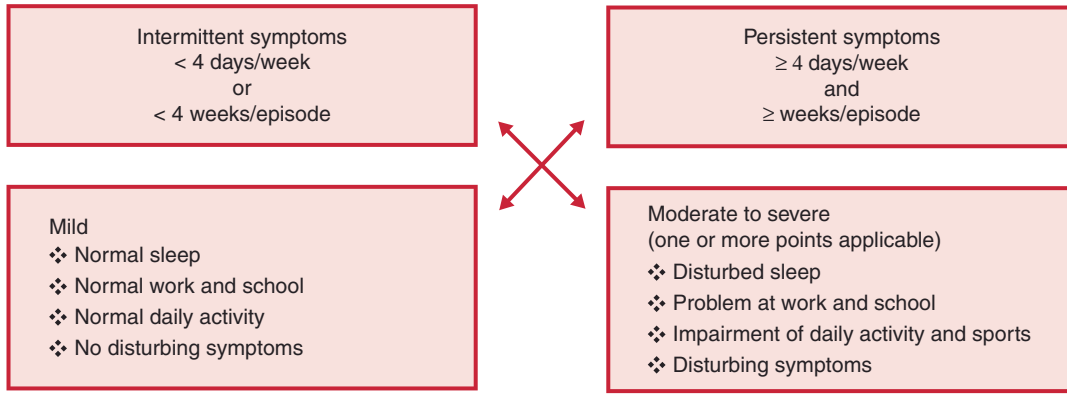

Fig. 20.4 ARIA classification of AR (reproduced with permission from Springer Nature)

AR (PER), and into mild or moderate/severe (Fig. 20.4) [3]. Approximately 75% of patients have a PER.

In Europe, the principal allergens causing IAR are tree pollen in the spring, grass pollen in summer, and moulds and spores in the autumn. PER is caused by house dust mite (HDM) allergen and HDM faeces, cockroach and pet allergens (such as dog and cat), which are mainly enzymes in the dried saliva or urine in their fur. People may also be exposed to a variety of allergens because of their occupation. Food allergies have also become more common, but while they may have an effect on the nose, their principal symptoms will be in the gastrointestinal system.

AR and Asthma

The term 'unified allergic airway' refers to the underlying similarity of the mucosa of the upper and lower respiratory tracts and the reactions that occur when exposed to allergens. In patients with allergic asthma, 65% will have a symptomatic AR. In patients with AR, approximately 25% will have asthma. The inflammatory mediators released in the nose have systemic as well as local effects.

The effect is also more marked because of reduced nasal function. Apart from filtering the air and reducing the quantity of allergen reaching the lungs, the nose also warms and humidifies the air. If the nose is blocked and the patient breathes by mouth, these functions are lost; bronchial hyperreactivity is increased, leading to an increase in asthma symptoms. Patients with AR and asthma have twice the rate of requiring oral corticosteroids or urgent care for an exacerbation of their symptoms than do asthmatic patients without AR [4].

There are also links with the effects of treatment. It seems that adequate treatment of nasal disease can reduce exacerbations of asthma requiring oral steroids or hospital admission, and in some cases of mild AR and asthma that treatment of the nose alone may allow good symptom control of asthma without inhaled steroids being required at all.

Clinical Presentation: Symptoms and Quality of Life

The diagnosis of AR rests on the history, nasal examination and diagnostic tests, but of these the history is usually the most useful.

The classic symptoms of AR are of cycling nasal blockage, clear nasal discharge, itching and sneezing. The vast majority of patients will complain of two or more of these symptoms. Although smell may be affected, this is not usually mentioned unless specifically asked about, and most patients with AR retain at least some sense of smell. Secondary symptoms may also be noted such as itchy eyes, throat and ears and dry mouth and halitosis (due to mouth breathing). Sometimes patients may have a wheeze (particularly in peak allergen season) and this should be asked about specifically.

The nasal block is often variable, cycling from side to side. A fixed block is more likely to be due to an anatomical abnormality such as septal deviation or nasal polyps. The discharge is usually clear and bilateral. Coloured discharge is more likely with an infective cause. When and where symptoms appear is crucial to making a diagnosis. A patient may know that when they are near a cat, they become symptomatic, or that they have problems only in the summer suggesting a grass pollen allergy. Symptoms all year round with a blocked nose worse in the morning may suggest HDM as the underlying cause.

As shown in Fig. 20.4, the Allergic Rhinitis and its Impact on Asthma (ARIA) classification groups patients by their symptom duration and severity. If a patient has one or more of the symptoms that affect quality of life (disturbed sleep, impairment of daily life and so on), then they are categorised as having moderate to severe disease and will be treated as such.

A more formal assessment of quality of life can be made with a variety of tools such as the 36-Item Short Form Health Survey (SF-36) (36-Item Short Form Survey Instrument (SF-36) | RAND) or more specific questionnaires for patients with nasal disease such as the Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) (Qoltech - Measurement of Health-Related Quality of Life & Asthma Control) or the 22-item Sinonasal Outcome Test (SNOT-22) (SNOT22.pdf (canvasc.ca)). These tests can be useful in clinical practice to understand the wider problems patients may have and to document their response to treatment.

Endoscopic nasal examination should also be undertaken, but is often most useful in excluding pathologies other than AR. The classic visual description of AR is of congested inferior turbinates, which have a pink or bluish tinge, and a clear or slightly sticky mucus. Depending on disease activity at the time of examination, these features may or may not be seen and their absence is not useful in the diagnosis. Endoscopy should exclude other causes such as nasal polyps, chronic infective rhinosinusitis or enlarged adenoids. Signs of concern such as septal perforation and bleeding or crusting may suggest a vasculitis, and a unilateral mass that could be a tumour.

Examination of the mouth and eyes may show the secondary effects of nasal block (with mouth breathing or a dry mouth) and a history of asthma or wheeze should prompt respiratory investigation as required.

Diagnostic Tests

The diagnosis of AR is made when the symptom complex fits the diagnosis and is confirmed by the presence (directly or indirectly) of specific IgE causing allergy. In practice, most patients in the community will be treated on the basis of a classic history and perhaps an anterior nasal examination without any diagnostic testing. Patients referred for ENT or allergy advice, however, may have more severe or difficult to treat symptoms and for them diagnostic tests may be useful to allow more specific advice and treatment.

Skin prick tests (SPTs) are the mainstay of diagnosis. They are quick to perform and allow a rapid diagnosis but do need trained staff to perform them. It is also possible then to advise the patient on avoidance measures and to check that they are using medications correctly. As a rapid screen the patient should be tested, at a minimum, against the most common allergens of grass pollen, dog, cat and HDM, as well as other possible allergens that are suggested by the history (and a positive and negative prick test). This will pick up the vast majority of the allergens commonly found (**Note**: these may not be appropriate as a screen outside Europe). Remember, the positive SPT must be correlated with the patient's symptoms to be useful and if several are positive it may be that only one or two are clinically relevant.

The other commonly used test is to measure serum IgE levels. Commonly called a RAST (radioallergosorbent test), this is now more commonly performed as a fluoroenzymatic immunoassay (FEIA). Elevated total IgE levels may indicate an underlying allergic process, but specific IgE is needed to specify the allergen(s) involved. It is more expensive than an SPT but only requires a blood sample to be taken. This

test may be useful if there are reasons why an SPT cannot be performed, such as a lack of trained staff, skin disease, patient anxiety or severe allergic reactions in the past.

Other tests that can be performed are usually not required but include CT scanning of the nose and paranasal sinuses if there is doubt about the findings of the nasal examination or other concerns. Nasal airflow can be roughly assessed by looking at the vapour pattern produced on a cold metal surface or tested more accurately by rhinomanometry, rhinospirometry or peak nasal inspiratory flow, and nasal anatomy with acoustic rhinometry. Nasal provocation tests measure symptoms following controlled allergen exposure, such as a reduction in nasal airflow and an increase in sneezing and running. Nasal cytology may be used to assess inflammatory cells in the nasal mucus, looking specifically for eosinophils, which may suggest a non-allergic cause such as non-allergic rhinitis with eosinophilia syndrome (NARES). While these tests are all available, their use is limited in the diagnosis of most patients.

Differential Diagnoses

Having taken a history, performed an examination and had confirmation of positive tests for allergy, the diagnosis may be made with some confidence. Occasionally, however, there may be some uncertainty and other diagnoses should be considered and excluded.

Non-allergic rhinitis may have a number of underlying causes. The commoner forms may be summarised as:

- Idiopathic rhinitis (vasomotor rhinitis)
- Non-allergic occupational rhinitis
- Hormonal rhinitis
- Drug-induced rhinitis
- Non-allergic rhinitis with eosinophilia syndrome (NARES)
- Chemical rhinitis
- Atrophic rhinitis

The history, symptoms and likelihood of exposure will often point toward a diagnosis but there is no specific test for non-allergic rhinitis, except the presence of rhinitis and a negative test for allergy. Patients should have nasal endoscopy performed to exclude physical abnormalities, chronic infection, tumour or nasal polyps as would happen for AR. Some tests, such as measurement of eosinophils in nasal mucus, may help but non-allergic rhinitis is often a diagnosis of exclusion.

Treatment of AR (Including Immunotherapy)

The sites of action of the various drugs for managing AR are summarised in Fig. 20.5.

The treatment of AR can be divided into a hierarchy:

- Avoidance (or reduction of exposure)
- Symptomatic treatment
- Modification of the disease process

Avoidance

Avoidance sounds like the ideal method of controlling symptoms but can be difficult to achieve in practice. If a specific allergen has been determined, then it may be worth making an attempt to reduce exposure.

Tree and grass pollen, which is spread by the wind, is widespread in the appropriate season and can be difficult to avoid. Remaining indoors, or in a car with good air filtration, can help but may not always be possible. Changing clothes on returning home to reduce pollen exposure (or other allergens such as horse if the patient is a rider) can help, as can the use of a saline nasal spray or rinse to physically remove the allergen.

Pet allergens are persistent and will be widespread within a house. Obviously not having a pet reduces exposure but washing hands after contact and keeping dogs and cats out of the bedroom may be useful.

House dust mites are found in high levels in pillows and mattresses and an anti-allergen cover may be purchased to reduce levels. Switching curtains to blinds and carpets to hard flooring may also reduce numbers. Unfortunately,

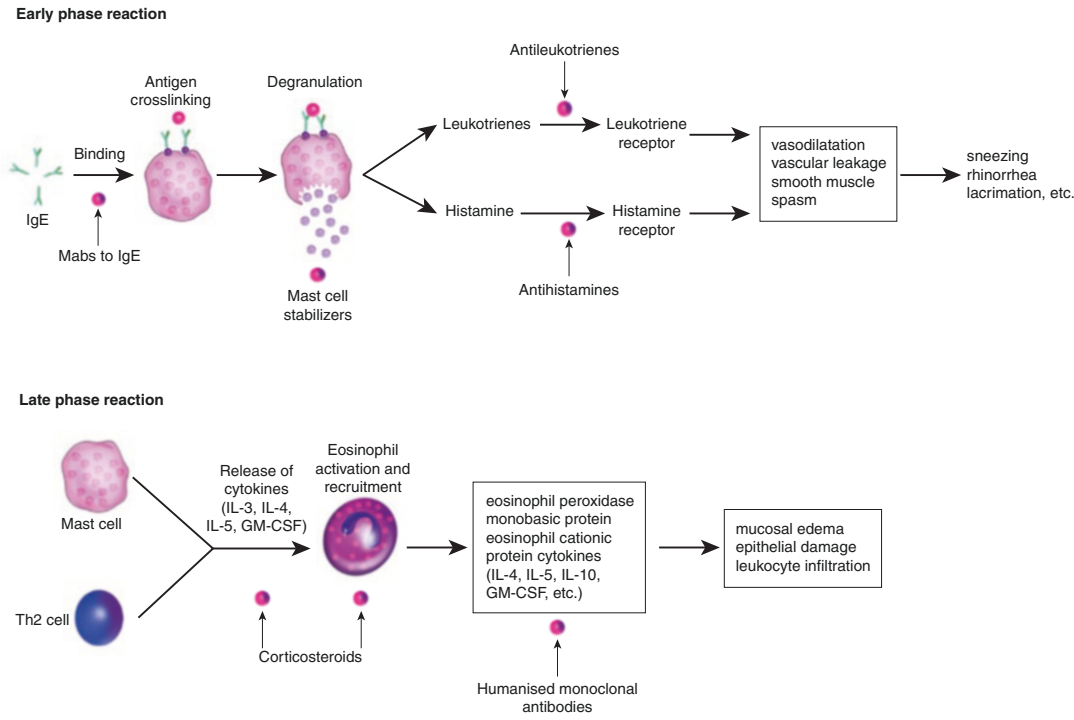

Fig. 20.5 The sites of action of medications for managing AR (reproduced with permission from Elsevier, with minor addition)

although levels may be reduced using these methods, the evidence that they have a significant clinical effect is weak.

Cockroach and mould levels can be controlled by appropriate pesticides and attention to damp within the home.

Symptomatic Treatment

The vast majority of patients with AR will be treated symptomatically, mostly with a combination of topical corticosteroids and topical or oral antihistamines. The ARIA guideline for suggested treatment from 2008 [5] is summarised in Fig. 20.6, and a possible update using visual analogue scores (VAS) to assess symptom control in Fig. 20.7 [6].

Antihistamines

Second-generation, non-sedating oral antihistamines such as cetirizine and loratadine may be effective in controlling symptoms such as sneezing and itching. They have a rapid onset of action and are safe for long-term use. They have no significant effect on the symptom of block. More benefit is usually found if they are taken before symptoms appear (i.e. for hay fever sufferers to start treatment before the appropriate pollen season begins and the patient becomes symptomatic).

Topical antihistamines such as azelastine (often combined in a spray with fluticasone) have a rapid onset of action and the combined treatment is more effective than a nasal steroid alone.

Azelastine eyedrops may also help with itching of the eyes.

Leukotriene Receptor Antagonists (LTRA)

Montelukast is the main LTRA used in AR.

It blocks the effect of some leukotrienes that are synthesised after mast cell degranulation. Leukotrienes promote inflammation and increase vascular permeability contributing to the symptoms of blockage and running. Montelukast seems to have a clinical effect similar to loratadine but is less effective on block than a topical

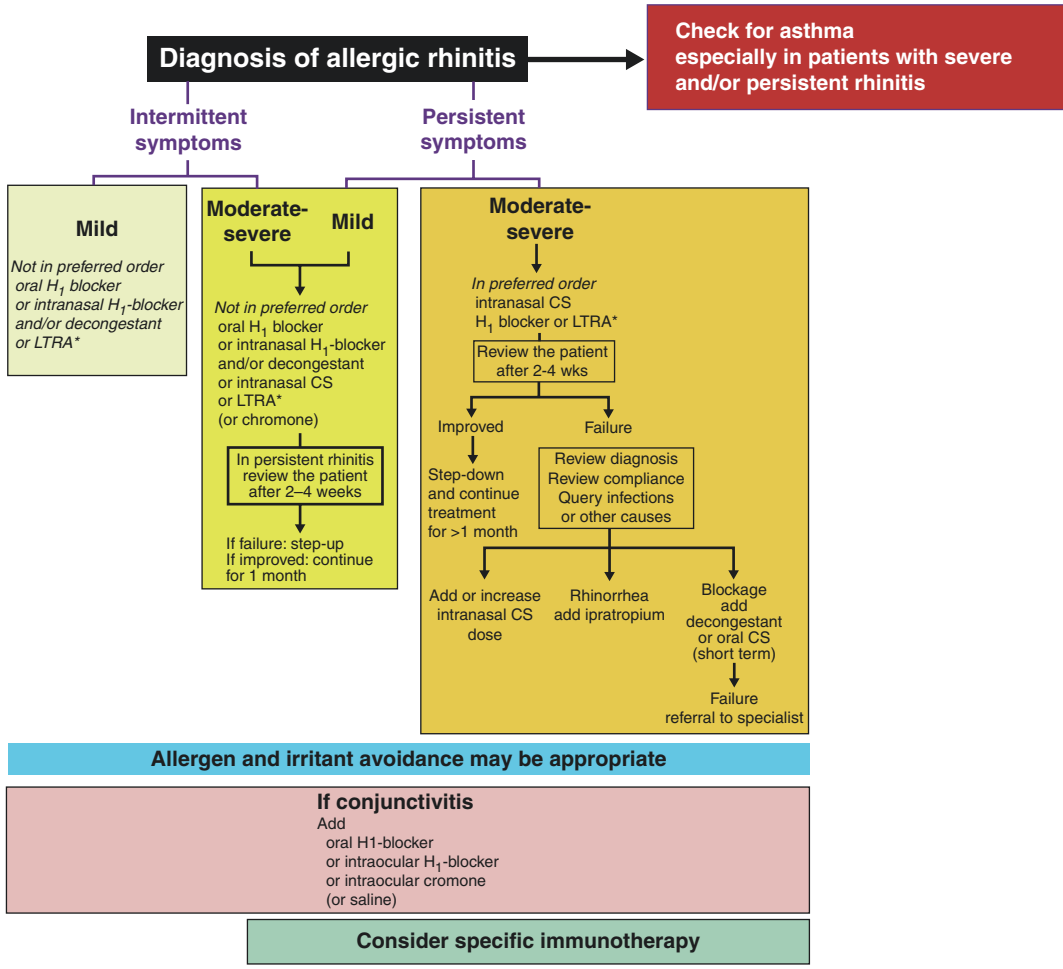

Fig. 20.6 Recommendations of the ARIA update 2008 (*CS* corticosteroid, *LTRA* leukotriene receptor antagonist) (reproduced with permission from Elsevier)

steroid. Not all patients get a significant response to LTRAs, but a trial of treatment can be worthwhile for some.

Sodium Cromoglicate

Mast cell stabilisers such as chromones are now hardly used in the nose as the have a very limited clinical effect, but cromoglicate eyedrops may relieve allergic conjunctivitis.

Intranasal Glucocorticosteroids

Beclometasone, fluticasone, triamcinolone and mometasone are some of the more commonly used intranasal corticosteroids.

They are used topically at the lowest necessary dose to limit the side effect profile. They reduce all the symptoms of AR, including blockage.

They work by inhibiting inflammatory gene transcription in the cell nucleus (among other actions) and therefore take some time to have an effect.

Patients should be advised that the effect will not be immediate and that they may have to stay on treatment for significant lengths of time as the drugs do not ‘cure’ the allergy but suppress it during allergen exposure. A side effect of epistaxis is usually due to incorrect use of the spray

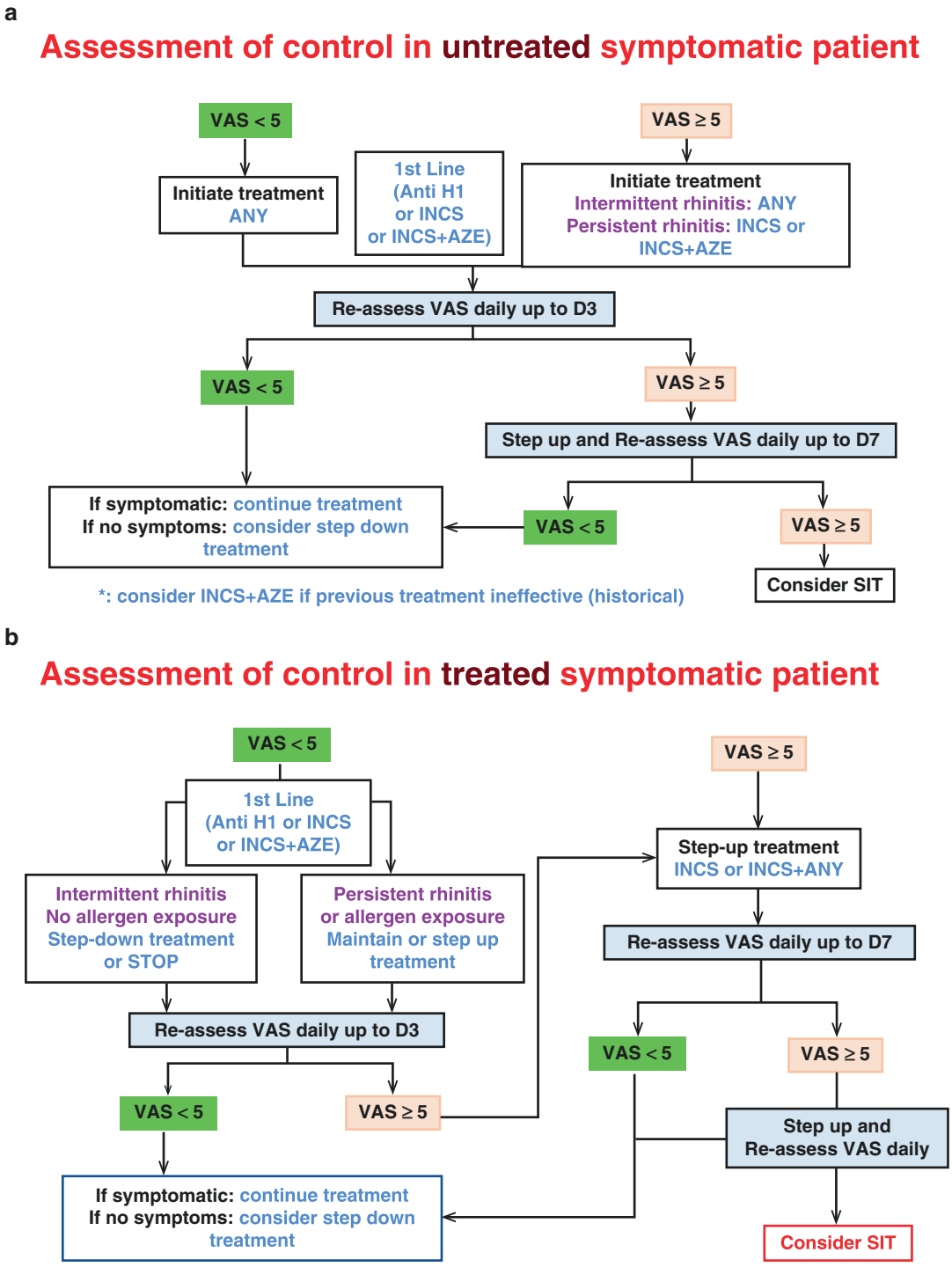

Fig. 20.7 Proposed update to the ARIA guideline, 2020. Step-up algorithm in untreated (**a**) and treated (**b**) patients using VAS to assess symptoms. 'ANY' means any one treatment selected from the adjacent box in the algorithm marked first line of the treating practitioner's choice. *Anti H1* Oral antihistamine, *INCS* Intranasal corticosteroid, *AZE* Azelastine, *SIT* Specific immunotherapy (reproduced with permission from Elsevier)

and patient education will usually allow resolution of the problem.

Ipratropium

Topical ipratropium spray, an anticholinergic, can be added to treatment with a topical steroid if the patient complains of continuing rhinorrhoea. The dose can be titrated to the patient's symptoms.

Monoclonal Antibodies

A variety of humanised monoclonal antibodies are now becoming available for the treatment of allergic disease and work in a variety of ways.

Omalizumab binds to circulating IgE, thus inhibiting it from binding to mast cells. This both prevents mast cell degranulation and also reduces cellular expression of IgE binding sites, therefore giving a longer mode of action. It is generally only used for patients with severe AR and asthma.

Mepolizumab, reslizumab and benralizumab block IL5 (or the IL5 receptor), thus preventing the function of this pro-inflammatory cytokine.

Dupilumab targets the receptor for IL4 and IL13, again stopping the actions of these cytokines. These drugs are not widely used yet for the treatment of AR but it seems likely that targeted treatments for individual patients will become more commonly used in the future.

Surgery

There is a limited role for surgical intervention in AR. Occasionally, there are patients who have developed a fixed hypertrophy of the nasal mucosa with a block that does not improve even with decongestion. Reduction of the bulk of the inferior turbinates may allow an improvement in nasal airflow and a consequent increase in the ability of topical steroids to penetrate into the nasal cavities to control inflammation.

Modification of the Disease Process

Immunotherapy

Immunotherapy (sometimes termed desensitisation) refers to a process whereby a patient develops tolerance to an allergen and therefore no longer exhibits an allergic reaction when exposed to it. It is the only treatment known currently that can rebalance the disordered immune system in AR and modify the progression of allergic disease. The regular administration of an allergen, either subcutaneously (SCIT) or sublingually (SLIT), causes the production of regulatory T cells (Treg) that switch the immune response from the excess production of Th2 cells to a Th1 profile. There is also a production of IgG4 that acts as a blocking antibody-preventing IgE binding. Both these mechanisms result in a reduction of the allergic reaction following subsequent allergen exposure. After a 3-year course of treatment, patients should experience a long-lasting reduction in symptoms and a halt in disease progression. Efficacy rates vary between different trials, but most patients would expect to have a reduction in symptoms and medication use of approximately 30% [7].

Immunotherapy is generally only used for patients with more severe disease, which cannot be controlled by standard medication [8]. It does have a small risk of causing anaphylaxis and therefore should only be prescribed by a practitioner experienced in its use and with the necessary resuscitation facilities available.

SCIT is usually given in two phases: induction, with a gradually increasing dose often given weekly, followed by a maintenance phase with injections every few weeks over a period not less than 3 years.

SLIT may be made up as drops or soluble tablets and may not need an induction phase. The allergen given is taken up by antigen-presenting cells in the oral mucosa and then works in much the same way as SCIT, with a similar efficacy. Treatment should also be given over a 3-year period to give long-lasting tolerance and symptom control.

Children with AR

The term the atopic (or allergic) march refers to the progressive development of allergic symptoms in childhood onwards. This starts with atopic dermatitis (allergic eczema) and may progress first to short-lasting food allergy and then to allergic asthma and AR (Fig. 20.8).

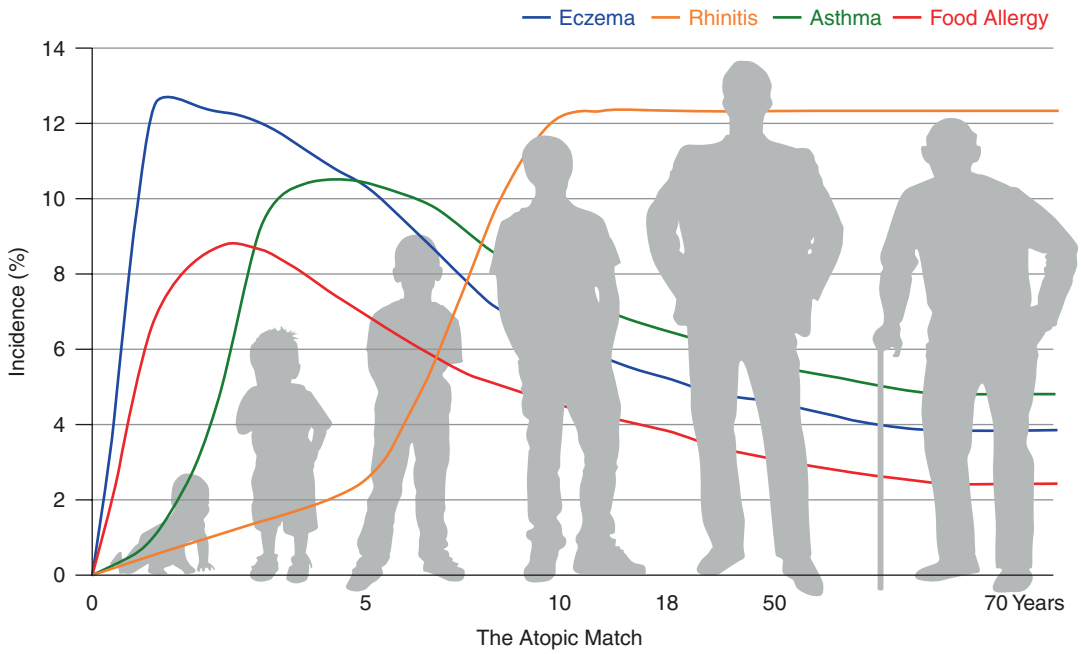

Fig. 20.8 The atopic march—progressive development of allergy (reproduced with permission from Elsevier)

The presence of eczema in a young child may predict further allergies developing in later life, but only in 30–50% of affected children, so the link between atopic dermatitis and other allergies is complex. Whether the epithelial breakdown in eczema allows sensitisation to allergens in individuals predisposed to allergy, or whether the atopic march is a systemic dysfunction that manifests differently at different ages, is unclear.

Children will usually have several episodes of viral acute infective rhinitis in a year, and as one may immediately follow another, it can be difficult to differentiate from an ongoing AR. If there is itching and sneezing, or a seasonal or environmental difference, then allergy is more likely. A coloured nasal discharge means infection is more likely, either an infective rhinitis or adenoiditis. Chronic infective rhinosinusitis is unusual in children. SPTs may help to give a diagnosis.

The treatment guidelines for children are similar to those for adults. Fluticasone can be used from 4 years; mometasone and triamcinolone from 6 years. It is preferred not to use beclometasone in younger children as it has a greater systemic bioavailability and may cause growth retardation in higher doses.

Treatment with immunotherapy is useful in children to reduce symptoms and to prevent the atopic march but its availability at present is unfortunately limited in many countries.

Areas of Controversy or Uncertainty

- What are the underlying causes of the increase in allergic disease seen in the industrialised world?
- Can we effectively change our environment to reduce allergic disease?
- What is the role of parasitic infection in modifying allergic disease?
- What combinations of treatment are best for managing patients with AR and asthma?
- What will be the role for monoclonal antibodies in AR?
- Should immunotherapy be more widely available, especially for children?

Key Learning Points

- AR is a common disease that may have a significant impact on quality of life and is frequently poorly managed.
- AR is part of a systemic disease termed the unified allergic airway and is often associated with asthma.
- Diagnosis is based on correlating typical symptoms with tests for specific IgE (either SPTs or serum IgE).
- Contemporary management is with avoidance and antihistamines and topical steroids, but immunotherapy and humanised monoclonal antibodies may have increasing roles.

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Current Scientific Understanding of Rhinosinusitis

21

Sietze Reitsma and Wytske J. Fokkens

Introduction

The scientific work on rhinosinusitis is very broad. It covers topics such as epidemiology, the burden of disease, medical or surgical treatment of rhinosinusitis and more basic scientific work, such as animal models of rhinosinusitis, laboratory studies, immunological studies, etc. It would be impossible to cover all these research items in one book chapter; rather, this chapter is focused on conveying a few important scientific principles that every ENT surgeon needs to be familiar with to have a good understanding of the disease itself, and of the scientific work that is performed on rhinosinusitis.

Principle I: Acute and Chronic Rhinosinusitis are Distinct Disease Entities

Rhinosinusitis is a diagnosis based on symptoms (nasal obstruction and/or rhinorrhoea combined with facial pressure and/or loss of smell) and observable abnormalities (purulence, polyps and/or oedema in the middle meatus) [1]. By definition, the duration of symptoms dictates whether a patient has acute rhinosinusitis (ARS; <12 weeks) or chronic rhinosinusitis (CRS; 12 weeks or more). This might suggest that CRS is simply a long-lasting ARS, but this is not true. They are entirely different disease entities.

Acute Rhinosinusitis

ARS is an upper respiratory tract infection. Most often, it is viral in origin and self-limiting, with complaints lasting less than 10 days. In a small percentage of cases, other forms of ARS are seen, such as post-viral ARS and acute bacterial rhinosinusitis. Research on ARS is hampered by its short-lived nature and the overlap with other upper respiratory tract infections [1]. For the clinical assessment and management of ARS, we refer to Chap. 23. In many countries, ARS seems to be of little importance to most ENT surgeons given its self-limiting nature. This changes once complications arise that require (surgical) intervention. For the management of these, refer to Chap. 28.

There is one controversial subject in the field of ARS: recurrent ARS (RARS), which is defined as having four or more episodes of ARS per year. Some authors deem it is best to classify as a special form of CRS. Regardless of its classification, RARS is a rare disease with a point prevalence estimated at 0.035% in the United States [2]. With this low prevalence, and a usually normal

S. Reitsma (✉) · W. J. Fokkens
Department of Otorhinolaryngology and Head and Neck Surgery, Amsterdam University Medical Centres, AMC, Amsterdam, The Netherlands
e-mail: s.reitsma@amsterdamumc.nl; w.j.fokkens@amsterdamumc.nl

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appearance upon nasal endoscopy and/or imaging in between episodes, it is difficult to gather data on the disease. In some cases, an underlying immunodeficiency can be found, which warrants investigation [1]. Furthermore, it is important to realize that by definition, patients suffering from RARS are free of symptoms between their episodes. This is an important clue, as it distinguishes patients with RARS from patients suffering from acute exacerbations of CRS.

Chronic Rhinosinusitis

In contrast to the self-limiting episodes of ARS, patients with CRS struggle with their condition for months to years (or even decades). Studies show that these patients experience a reduced quality of life, are hampered in their daily activities/work and that CRS thus poses an important burden to the individual patient as well as to society as a whole. Despite medical and surgical interventions, many patients remain uncontrolled [1]. As such, CRS is of great importance to ENT surgeons. Therefore, the rest of this chapter will deal with CRS only.

Principle II: CRS Is a Multifactorial Disease

To explain how and why CRS is expressed as a chronic disease, several factors have been investigated. These can best be summarized in the paradigm of the host, the environment and their interactions.

The central player in this theme is the nasal mucosa, as it is the interface between host and environment. In healthy conditions, it has distinct inflammatory reactions to the various (pathogenic) stimuli it encounters, each of which have a limited time-span. This way, the nasal mucosa functions as an epithelial barrier and a significant line of defence (see also Chaps. 3, 4 and 5). In CRS, however, the barrier function is impaired and inflammatory processes endure. This is a result of an interplay between the host (qualities/properties of the nasal mucosa and host immune system) and the environment (stimuli attacking/affecting the nasal epithelium), in combination with a specific (inflammatory) endotype that is activated in a CRS patient (see Fig. 21.1). In the following sections, the main factors are listed and briefly discussed.

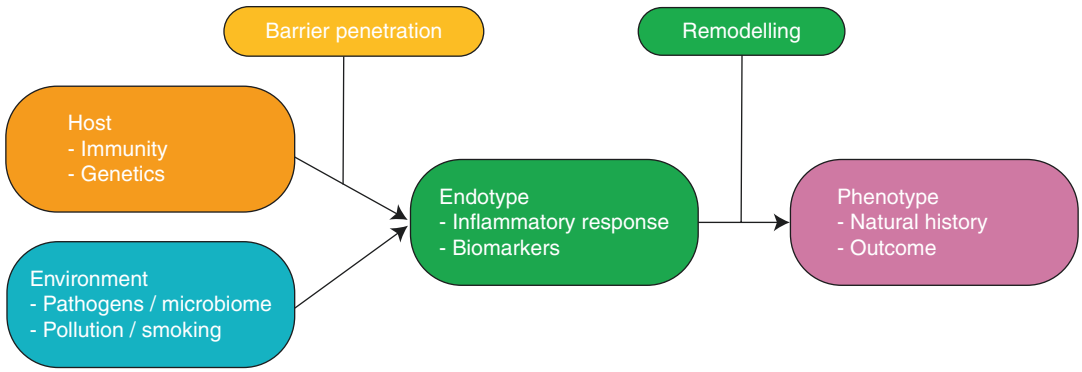


Fig. 21.1 Chronic rhinosinusitis is a multifactorial disease
By interaction between host and environment at the level of the nasal mucosa, an inflammatory endotype is elicited once there is disruption of the epithelial barrier. The ensuing tissue remodelling will eventually determine the patient phenotype.
Adapted with permission from the European Position Paper on Rhinosinusitis and Nasal Polyps 2020

Host Factors

Genetics

CRS is a multifactorial disease and each factor might be influenced by the genetic background of the patient. As such, a straightforward genetic explanation is unlikely. Nevertheless, a certain hereditary component is present as various studies show increased risk of developing CRS within families. On the other hand, studies in monozygotic twins show that the development of CRS might occur in one and not the other sibling. As such, other (environmental) factors are likely to be at least equally important. For more information, we refer to an excellent review [3].

Diffuse CRS secondary to cystic fibrosis or primary ciliary dyskinesia clearly have a genetic background. However, for both underlying diseases, multiple causative genes/mutations may be involved (see also Chap. 7).

Immunity

For a normal nasal epithelial barrier to function, a well-functioning immune system is paramount (Chap. 5). Studies show that especially in difficult-to-treat CRS patients, immunodeficiencies are relatively common. The reported prevalence varies between 10% and even 50%, depending on patient cohorts and definitions used [4]. Examples are immunoglobulin deficiencies such as selective IgA deficiency, specific antibody deficiencies or a common variable immunodeficiency. It is at this point unknown to what extent these immunodeficiencies are clinically relevant in CRS.

Environmental Factors

Apart from the host factors as described above, environmental factors need to be considered as well, since they have the ability to disrupt the epithelial barrier function of the nasal mucosa, which might start or maintain the inflammatory response in the nose.

Bacteria

Bacteria have been considered a causative or disease-modifying agent in CRS for many decades. Much attention has been aimed at specific pathogens, such as *Staphylococcus aureus*, with conflicting conclusions. Other specific bacteria have been proposed to play a major role in CRS as well, especially those capable of forming a biofilm and thus evading immune responses or medical therapy (see also Chap. 8). A more general disruption of the local microbiome, termed dysbiosis, has also been hypothesized, stating that a lack of normal commensal flora would create a damaging microbiome, continually evoking an inflammatory response in the nasal epithelium. However, therapies aimed at specific bacteria or the microbiome as a whole have had very limited success in the treatment of CRS. Possibly, certain subgroups/phenotypes of CRS might have a stronger correlation with specific bacteria or dysbiosis, but clear data are currently lacking.

Viruses

Many viruses have the capability to acutely disrupt the nasal epithelium, impair ciliary function and increase the production of mucus. Various papers describe an increase in viral presence in nasal tissue/polyps of patients with CRS, suggesting a role for viruses in the pathogenesis of CRS as well. Furthermore, viral infections have been shown to be able to induce exacerbations of CRS. On the other hand, the same studies show that viruses are not found in all patients with (an exacerbation of) CRS [5]. Therefore, the exact role of viruses in the initiation and/or continuation of the inflammatory processes in CRS remains unclear.

Fungi

Similar to bacteria and viruses, fungi have been studied as initiators or modifiers of CRS pathogenesis as well, but with disappointing results. The few exceptions, where fungi are clearly involved, are mainly dominated by host immunity. In allergic fungal rhinosinusitis, there is a

hypersensitivity of the immune system to fungi. On the other hand, invasive fungal rhinosinusitis is almost uniquely seen in an immunocompromised state (such as an haematologic malignancy) (see also Chap. 26).

For more (general) information on the role of bacteria, viruses and fungi in health and disease, see Chap. 9.

Pollution/Occupational Exposure

There are several studies describing correlations between pollution or occupational exposure and the risk of developing CRS, the severity of CRS and the need for (multiple) surgeries. A very strong example is the work done by New York fire fighters responding to the attack on the World Trade Centre, showing a dramatic increase in CRS prevalence after this event, related to the amount of exposure [6].

Smoking

There is now clear evidence that tobacco smoking associates significantly with the risk of developing CRS [7]. Pollutants and toxins from cigarette smoke induce oxidative stress of the nasal mucosa and act as pro-inflammatory agents. Children exposed to second-hand smoke are at increased risk as well.

Tissue Remodelling

Once the epithelial barrier is chronically compromised, the specific combination of host and environmental factors in a patient will result in remodelling of the sinonasal tissue such as polyp formation and/or goblet cell hyperplasia. Remodelling of the barrier itself might also contribute to the perpetuation of the inflammation in CRS. The amount of remodelling will vary between patients; depending on host and environmental factors, as well as the patient endotype, remodelling will result in different patient phenotypes and, thus, outcomes of CRS. Studies with biologicals that intervene at the endotype level show nasal polyps to disappear rapidly, meaning that tissue remodelling can be (in part) reversible.

Clinical Application

An ENT surgeon treating CRS should realize that management of CRS should encompass—if possible—strategies directed at all the various factors that lead to the patient phenotype. Especially in those patients where disease control cannot be attained through appropriate medical therapy (and if needed surgery), the multifactorial paradigm of host–environment remodelling might help to formulate a full approach. This includes paying attention to and treating specific traits (e.g., smoking, occupational exposure, patient immunity). With the advent of biologicals, treatment at the endotype level will be more and more common, possibly revolutionizing CRS care (see the next chapter).

Principle III: CRS Is an Umbrella Term Requiring Classification

The diagnostic construct of CRS is based on symptoms and observable abnormalities. As such, it will encompass many conditions; patients with an odontogenic maxillary sinusitis, a bilaterally obstructed nose filled with polyps or an isolated unilateral sphenoiditis all classify as having CRS. It is obvious that the underlying aetiologies may vary greatly. This means that the pathophysiology, epidemiology, treatment and outcomes for each entity will be different. There is no ‘one size fits all’ in CRS.

The Presence or Absence of Nasal Polyps in CRS

For decades, the main differentiation for patients with CRS was based on the endoscopic appearance of nasal polyps, giving either CRS with nasal polyps (CRSwNP) or without nasal polyps (CRSsNP). Much (clinical) research has been performed based on this distinction. However, the presence or absence of nasal polyps is only poorly related to the underlying pathophysiological processes. For example, in most Western

countries, nasal polyps are usually associated with an eosinophilic (Type 2) inflammation of the tissue, whereas it is more often neutrophilic in Asian countries. For CRSsNP, the same point can be made; a patient with an odontogenic sinusitis and a patient with rhinosinusitis due to an immunodeficiency would both qualify as CRSsNP, whereas the underlying pathology and choice of therapy are obviously quite different. As such, a more sophisticated classification helps to structure research in the area of rhinosinusitis and enables a better understanding of pathophysiological processes in various patient groups/diseases.

The New Classification of Chronic Rhinosinusitis

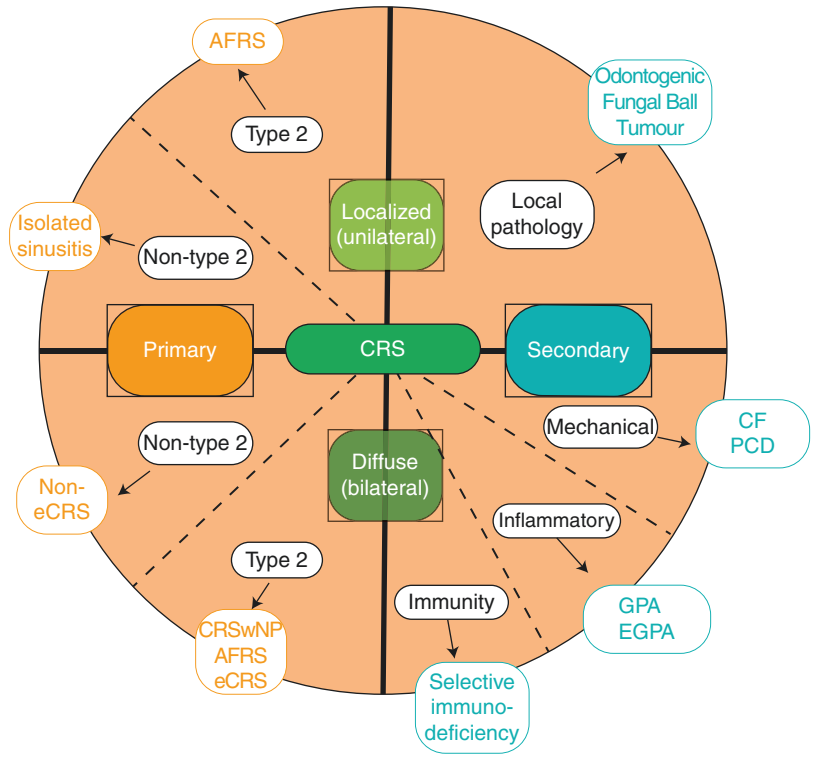
Using a few clinical properties, the current classification for CRS determines whether it has a primary or secondary aetiology, and what the anatomical distribution is (localized/unilateral versus diffuse/bilateral). Thus, the given set of clinical phenotypes can then be further differentiated based on the predominant endotype (see Fig. 21.2). This classification system has obvious clinical merits, but helps the scientific understanding of CRS as well [1, 8] (see Table 21.1).

Primary Versus Secondary, Localized Versus Diffuse CRS

Once a patient meets the criteria for CRS, the first step should be to determine whether it is a primary CRS or that the disease is secondary to an underlying disease process. Depending on the localization of the disease (localized/unilateral versus diffuse/bilateral), discerning primary from secondary CRS may be more or less apparent.

In localized disease, clinical features of a secondary CRS include signs and symptoms of an odontogenic (maxillary) sinusitis, an isolated sinusitis based on a fungal ball or an underlying tumour (either benign or malignant). If none of these are present, an isolated sinusitis per se is diagnosed as a primary localized CRS. For most of these conditions, the underlying immunological responses have only been poorly investigated. However, despite this lack in knowledge, the treatment for both primary and secondary localized CRS usually consists of a surgical approach to the affected sinus(es) to remove the pathology, restore ventilation and drainage, and often this suffices to overcome the disease. In secondary localized CRS, other measures to address the underlying pathology need to be considered as well (such as referral to the maxillofacial department).

In diffuse CRS, the differentiation between primary and secondary can be more challenging and might take time. Overall, the majority of patients with diffuse/bilateral disease will have a primary CRS. Signs and symptoms pointing to CRS secondary to inflammatory processes include excessive bleeding and crusting, mucosal abnormalities outside the middle meatus, loss of tissue, severe pain and importantly, the involvement of other organ systems and systemic manifestations such as fatigue and weight loss. If the CRS has a childhood onset, underlying diseases such as primary ciliary dyskinesia or cystic fibrosis should be considered.



		Primary CRS		Secondary CRS		
Localized / unilateral	*Endotype*	Type 2	Non-type 2	Local pathology		
	Example	AFRS	Isolated sinusitis	Odontogenic Fungal ball Tumour		
Diffuse / bilateral	*Endotype*	Type 2	Non-type 2	Mechanical	Inflammatory	Immunity
	Example	CRSwNP AFRS eCRS	Non-eCRS	CF PCD	GPA EGPA	Selective immunodeficiency

Fig. 21.2 Classification of CRS
Once the diagnostic criteria for chronic rhinosinusitis have been met, a distinction is to be made based on the absence (primary) or presence (secondary) of an underlying condition. Next, the localization (localized or diffuse) and the dominant endotype will determine the type of chronic rhinosinusitis. The boxes at the perimeter of the circle contain several examples of clinical disease entities.

CRS Chronic rhinosinusitis, *AFRS* Allergic fungal rhinosinusitis, *CF* Cystic fibrosis, *PCD* Primary ciliary dyskinesia, *GPA* Granulomatosis with polyangiitis, *EGPA* Eosinophilic granulomatosis with polyangiitis, *CRSwNP* Chronic rhinosinusitis with nasal polyps, *(non-)eCRS* (non-)eosinophilic chronic rhinosinusitis.
Adapted with permission from the European Position Paper on Rhinosinusitis and Nasal Polyps 2020

Table 21.1 Classification of CRS (accompanies Fig. 21.2)

		Primary CRS		Secondary CRS		
Localized/ unilateral	*Endotype*	Type 2	Non-Type 2	Local pathology		
	Example	AFRS	Isolated sinusitis	Odontogenic Fungal ball Tumour		
Diffuse/ bilateral	*Endotype*	Type 2	Non-Type 2	Mechanical	Inflammatory	Immunity
	Example	CRSwNP AFRS eCRS	Non-eCRS	CF PCD	GPA EGPA	Selective immunodeficiency

Principle IV: The Inflammatory Endotype in Primary Diffuse CRS Determines Treatment and Outcomes

A large portion of CRS patients is represented by those with primary diffuse CRS. In this group, more and more attention is turned towards the inflammatory processes involved (i.e., the inflammatory endotypes). Classically, three types of immune responses are recognized: **Type 1** responses are invoked by viruses, and associated canonical cytokines include interferon gamma and interleukin (IL)-12; **Type 2** responses are targeting parasites and involved in tissue repair processes, and associated canonical cytokines include IL-4, -5 and -13; **Type 3** responses deal with extracellular bacteria and fungi, and associated cytokines are IL-17A and IL-22. In CRS, often a mixture of these response types is present, and in contrast to 'classical' response arcs, the activation of the inflammatory pathways is extended and chronic. In a cornerstone publication, Tomassen et al. showed that in CRS patients, various clusters of cytokine profiles are present in their sinonasal mucosa/polyps revealing mixed inflammatory endotypes. In these clusters, IL-5 positivity (i.e., Type 2 dominance) had a clear association with CRSwNP and asthma [9].

Clinical Determination of Endotypes in Primary Diffuse CRS

Although scientific papers often examine a myriad of cytokines, mediators and/or inflammatory cells, the applicability of these tests to common clinical practice is limited [10, 11]. Furthermore, most treatments for primary diffuse CRS are only loosely based on the underlying endotype (with some exceptions, such as biologicals which will be discussed in the next chapter). Also, in a significant number of patients (~25%), mixed endotypes can be present [12].

Therefore, EPOS2020 recognizes the major clinical difference to be made: Type 2 versus non-Type 2 CRS, at least in patients not responding to appropriate medical therapy such as intranasal corticosteroids, saline rinses and the treatment of other treatable traits (such as comorbid allergic rhinitis) [1]. One needs only simple and available tools to make this distinction, the most important one of which is taking a detailed and targeted history.

The clinical pattern of Type 2 patients is those complaining of loss of smell and nasal obstruction, suffering from asthma or even NSAID-exacerbated respiratory disease (N-ERD). Often nasal polyps can be found, and laboratory tests show eosinophilia and elevated serum IgE. Typically, these patients respond well to oral corticosteroids, with smell recovery within days. Also typically, these effects are short-lived. Surgery often has a limited effect with recurrence of complaints and regrowth of polyps at an unsatisfying rate [8, 13].

A typical subtype of primary diffuse Type 2 CRS is the patient with N-ERD. Sensitivity to NSAIDs can often be established rather easily during history taking and will point to a (severe) Type 2 profile. Indeed, both canonical cytokines IL-5 and -13 are increased in nasal secretions from N-ERD patients compared to those with non-N-ERD nasal polyps [14].

In contrast, non-Type 2 primary diffuse CRS often presents with facial pain and (purulent) discharge in patients without asthma. Nasal endoscopy reveals purulence in the middle meatus, but typically no polyps. Laboratory tests show normal levels of eosinophils and serum IgE (except in patients with comorbid allergic rhinitis). Here, oral corticosteroids seem less effective, and patients tend to respond better to (prolonged) courses of antibiotics. Surgery is often helpful for longer periods of time [8, 15].

Once the clinical pattern of Type 2 or non-Type 2 is recognized, treatment can be directed to meet the patient's endotype. For detailed information on new therapies for CRS stratified by its classification, refer to the next chapter.

Conclusion

Rhinosinusitis encompasses a broad spectrum of diseases. In chronic rhinosinusitis, much is still unclear regarding the pathogenesis of the underlying inflammatory processes. Both host factors and environmental factors are involved. The advised classification system of CRS will help guide therapy and facilitate research.

Short Summary of Areas of Controversy or Uncertainty

- It is unclear whether recurrent ARS should be considered as a form of ARS or CRS.
- It is unclear whether the recommended classification of CRS will correlate closely with inflammatory endotypes; the number of underlying endotypes/clusters and the best way to characterize them are still subject of ongoing research.

Key Learning Points

- Principle I: Acute and chronic rhinosinusitis are distinct disease entities.
- Principle II: CRS is a multifactorial disease.
  - The aetiology and pathophysiology are only partly understood; they involve both host and environmental factors.
- Principle III: CRS is an umbrella term requiring classification.
  - Currently, a classification based on the presence or absence of an underlying condition, the localization of the disease and the predominant endotype is advised.
- Principle IV: The inflammatory endotype in primary diffuse CRS determines treatment and outcomes.
  - The main distinction to guide research and therapy is Type 2 versus non-Type 2.

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New Innovations and Treatments for Chronic Rhinosinusitis

22

Wytske J. Fokkens and Sietze Reitsma

Primary Chronic Rhinosinusitis

Recently, in EPOS2020, a new classification of CRS has been proposed [1]. This classification divides CRS into primary and secondary CRS (for more details see Chap. 21) and further divides into local versus diffuse disease and categorizes based on endotype.

Primary Localized Non-type 2 Chronic Rhinosinusitis

Typical examples of primary localized non-type 2 chronic rhinosinusitis (CRS) are (iatrogenic) sinusitis of a single sinus without underlying disease such as odontogenic problems. The treatment for this kind of disease is mostly surgical, and opening of the sinus often results in the sinus inflammation subsiding.

The most prominent innovation in the treatment of primary localized non-type 2 CRS is the balloon dilatation technology (BDT).

Two systematic reviews (including 1–2 RCTs) were done in 2016 and 2017 [2, 3]. Both systematic reviews concluded that in patients with medically refractory CRS with limited CT evidence of sinus disease, treated with ESS or in-office balloon dilation, outcomes were comparable for FESS and BDT, with significant reductions in symptom scores, SNOT-22, paranasal sinus opacification, absenteeism, health care visits, and antibiotic usage in both groups. Recovery was faster in the balloon dilation group. Recently a third meta-analysis had comparable conclusions: analysis did not reveal a clinically meaningful difference in outcomes between FESS and BSD alone nor FESS and hybrid procedures [4]. For now, current evidence supporting the role of BDT in CRS remains incomplete, but one might consider patients with primary localized non-type 2 CRS with limited disease the most likely candidates.

Primary Localized Type 2 Chronic Rhinosinusitis

A typical example of primary localized type 2 CRS is a localized form of allergic fungal rhinosinusitis (AFRS). Unlike the management of classical CRS, the foundation of AFRS treatment is surgery.

Although evidence is limited [5], treatment of AFRS, both localized and diffuse, almost always requires surgical debridement of the involved sinuses, thus removing the antigenic stimulation for AFRS patients, but also providing wider access

W. J. Fokkens (✉) · S. Reitsma
Department of Otorhinolaryngology, Amsterdam University Medical Centres, AMC, Amsterdam, The Netherlands
e-mail: w.j.fokkens@amsterdamumc.nl

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for surveillance, clinical debridement, and application of topical medication. Surgery can be combined with systemic and local corticosteroid treatment. There is limited evidence for efficacy of allergen immunotherapy, to both fungal and non-fungal antigens in atopic individuals with AFRS to improve symptoms and reduce revision surgery. Oral and topical antifungals do not improve symptoms in AFRS but may reduce recurrences, although data are very incomplete. The use of biologicals for the treatment of AFRS is in its infancy [6], and larger studies are underway.

Primary Diffuse Chronic Rhinosinusitis

After appropriate medical treatment, check of treatable traits and compliance (see Fig. 22.1), the care pathways for management of diffuse (i.e. bilateral), CRS depends on endotyping (see Fig. 22.2).

Primary Diffuse Non-type 2 Chronic Rhinosinusitis

Primary diffuse non-type 2 CRS is what we would formerly call non-eosinophilic CRS. The phenotype is usually without nasal polyps although in Asia non-eosinophilic CRS with nasal polyps occurs, but with decreasing frequency.

When one considers the diagnosis of primary diffuse non-type 2 CRS, EPOS2020 advises to do an additional work-up including evaluation of blood eosinophils and total serum IgE to exclude type 2 inflammation. After appropriate medical treatment, consisting of nasal saline rinsing and local corticosteroids, one can chose between (F) ESS and long-term antibiotics. The evidence for long-term antibiotics is still very limited [5].

Xylitol

A relatively new evidence-based treatment option is rinsing with a xylitol solution. Xylitol is a five-

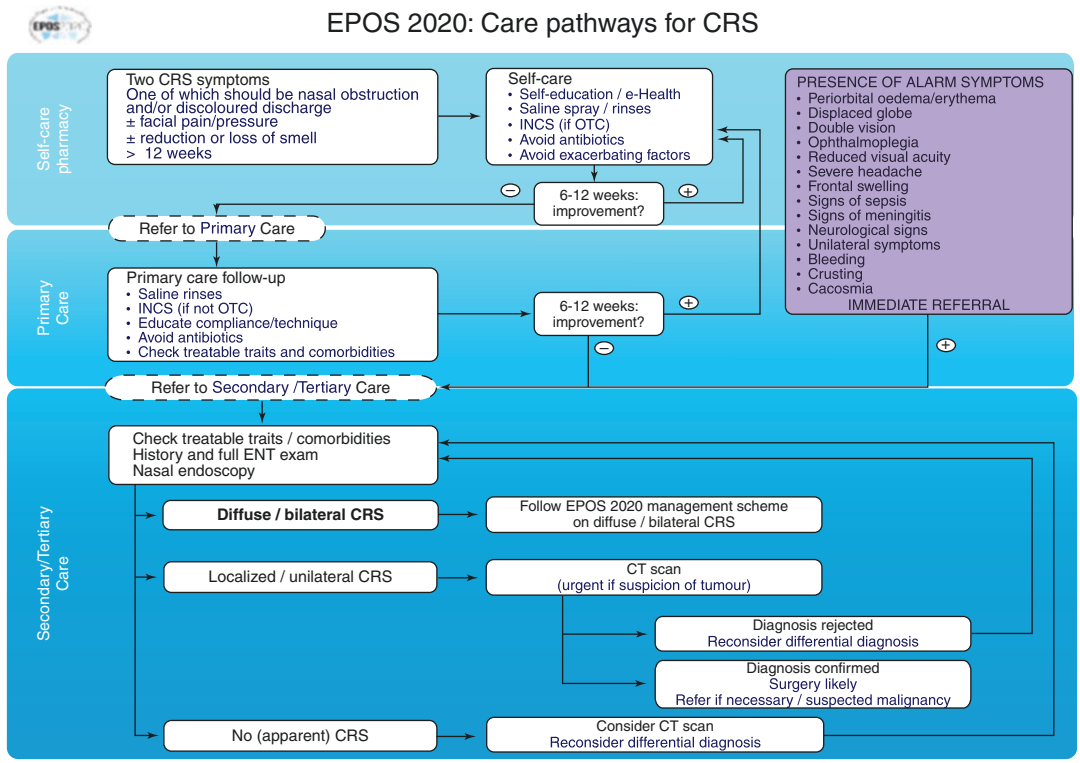

Fig. 22.1 Care pathways for management of CRS, intranasal corticosteroid (INCS), over-the-counter (OTC) [5]

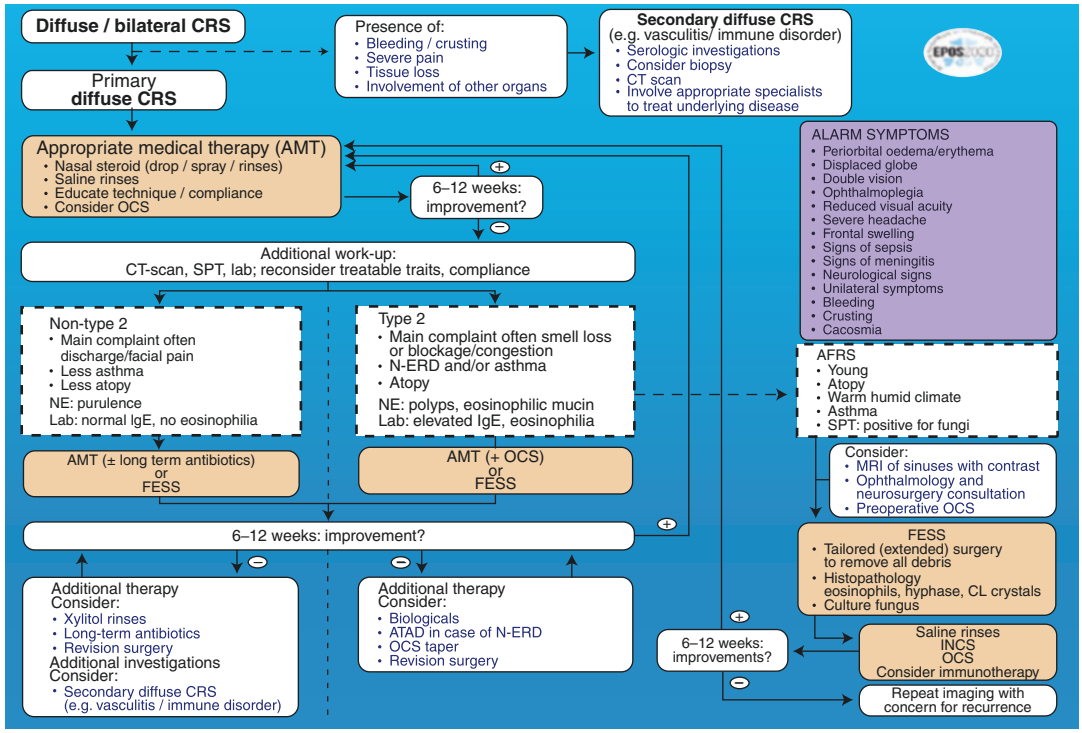

Fig. 22.2 Care pathways for management of diffuse bilateral CRS, oral corticosteroids (OCS), aspirin treatment after desensitization (ATAD) [5]

carbon sugar alcohol that occurs naturally in many fruits and vegetables and is used widely in the food industry as a sweetener. It has gained interest as a natural antibacterial agent. Xylitol significantly reduces biofilm biomass, inhibits biofilm formation, and reduces growth of planktonic bacteria. The use of xylitol in saline lavages has been evaluated in four studies.

Weismann et al. evaluated in a prospective, randomized, double-blinded, controlled crossover pilot study the efficacy of a xylitol 5% in saline irrigation once-daily compared to saline irrigation during 10 days with a 3-day washout irrigation rest period in 20 subjects with CRS [7]. There was a significant reduction in SNOT-20 score during the xylitol phase of irrigation as compared to the saline phase (difference 6.3 points). There was no difference in VAS scores.

Lin et al. evaluated in a prospective, randomized, double-blind, controlled study the efficacy of xylitol 5% nasal irrigation compared to saline nasal irrigation in 25 of 30 patients with CRS who completed the 30-day study [8]. Standard subjective assessment scores were reduced significantly only in the xylitol group (SNOT-22 reduction of 12 points; VAS reduction of 1.1). The concentrations of nasal nitric oxide (NO) and inducible nitric oxide synthase (iNOS) mRNA in the right maxillary sinus increased significantly, but only in the xylitol group.

Rabago et al. evaluated [9] in a prospective, randomized, three-arm controlled study for 26 weeks the efficacy of xylitol 5% nasal irrigation compared to saline irrigation and standard care in 40 patients with chronic rhinosinusitis with Gulf War illness. Patients using xylitol rinsing reported improved SNOT-20 scores over the full period, significantly better than standard care but not significantly better than saline irrigation (subgroups too small for statistical analysis).

Kim et al. [10] examined the effect of xylitol nasal irrigation in a double-blinded randomized controlled crossover study in 34 CRS patients. A significant improvement of SNOT-20 and VAS

symptom scores for sneezing ($p = 0.003$), headache ($p = 0.02$), and facial pain ($p = 0.037$) was found compared to saline rinsing.

In conclusion, addition of xylitol to saline rinses resulted in a significant reduction of SNOT (all studies) and VAS (reported in two) scores in four small studies in primary diffuse non-type 2 CRS patients. Larger studies are needed to evaluate the magnitude of the improvement.

Other biofilm reducing agents like colloidal silver and (Manuka) honey showed no effect in in vivo studies, and addition of sodium hyaluronate or xyloglucan to nasal saline irrigation may have some positive effect [5].

Primary Diffuse Type 2 Chronic Rhinosinusitis

Typical examples of primary diffuse type 2 CRS are CRS with nasal polyps (CRSwNP) or eosinophilic CRS (eCRS). The diffuse disease of the sinuses in these patients is characterized by type 2 inflammation symbolized by hyper-eosinophilia in blood and/or tissue or increased IgE.

For years, the treatment of diffuse type 2 CRS consisted of a combination of appropriate local medical treatment (nasal saline rinsing and local corticosteroids), combined with surgery and short courses of systemic corticosteroids. The potential side effects of more than a few weeks of systemic corticosteroids per year significantly limited treatment possibilities. Hence, a large part of the patients with primary diffuse type 2 CRS remained uncontrolled most of the time with repetitive ESS and courses of systemic corticosteroids as only options to reduce the burden of disease. Some authors have suggested using a tapering dose of systemic corticosteroids to find the lowest dose to attain disease control (especially anosmia). Often tapering to a dose of less than 5 mg of prednisolone every other day is possible (personal experience of the authors). However, the potential side effects of systemic corticosteroids remain a significant limitation [11].

Aspirin Treatment After Desensitization (ATAD)

A subgroup of patients with diffuse type 2 CRS suffer from non-steroidal anti-inflammatory drug (NSAID)-exacerbated respiratory disease (N-ERD). In general, these patients have more severe disease, and many have co-morbid asthma [12]. N-ERD is a chronic eosinophilic, inflammatory disorder of the respiratory tract occurring in patients with asthma and/or CRSwNP, symptoms of which are exacerbated by NSAIDs, including aspirin.

The management options in patients with N-ERD are essentially based on strict avoidance of the culprit drug and cross-reactive drugs. Patient education is important, since NSAIDs respiratory symptoms are not limited to a specific drug, but may appear after the intake of other cyclooxygenase (COX)-1 inhibitors.

In N-ERD patients, aspirin may induce a period lasting 24 to 72 h, in which patients are refractory to repeated aspirin challenges and experience less symptoms. Based on this principle, N-ERD can be treated with aspirin. Aspirin treatment after desensitization (ATAD) with oral aspirin is effective in improving QOL and total nasal symptom score in patients with N-ERD. However, the effects seem to be less than treatment with biologicals [13]. Some retrospective studies also reported clinical benefit from nasal lysine-aspirin treatment. However, in a randomized, double-blind placebo-controlled cross over trial, these positive findings could not be confirmed.

Drug-Eluting Stents and Exhalation Delivery Systems

Nasal corticosteroids are the mainstay of treatment of diffuse type 2 CRS. First used mainly as nasal sprays, later forms of delivery such as nasal drops and rinses have become popular.

Exhalation Delivery Systems (EDS)

The newest possibility is the use of an exhalation delivery system that claims to deliver the medication higher and deeper into the nose [14].

The exhalation delivery system features a mouthpiece that the patient blows into and a nosepiece that seals to one side of the nose. When the patient blows into it, it elevates and seals the soft palate, which isolates the nasal cavity from the oral cavity. The dosage of fluticasone dipropionate delivered by the device is higher than standard nasal sprays. There are no comparative studies with fluticasone nasal spray but in a meta-analysis the effect seems larger [5].

Drug-Eluting Stents

A major issue for all treatment with nasal corticosteroids is compliance. There are a number of studies showing the compliance to nasal corticosteroids is often poor. Drug-eluting stents, particularly in the ethmoid sinuses, offer a potential solution to both the compliance and delivery issues of nasal corticosteroids. Drug-eluting biodegradable nasal implants/stents provide a sustained release of nasal corticosteroids for several months. They can be placed directly postoperatively to prevent recurrence of disease or alternatively, can be placed in the ethmoid cavities during an in-office procedure. Steroid-impregnated nasal spacers have been shown to reduce the rates of postoperative intervention, recurrent polyposis, and mucosal inflammation in CRS patients undergoing ESS during the early months after surgery [15]. Although potentially of greater benefit than steroid nasal sprays or non-steroid eluting packs, recent studies did not demonstrate a significant difference compared to steroid nasal sprays. However, a significant difference in short-term polyp formation was found compared to non-steroid eluting packs [16–18].

In conclusion, drug-eluting stents and exhalation delivery systems create potential benefits in the treatment of diffuse type 2 chronic rhinosinusitis but direct comparisons to nasal sprays are missing (or small with a potential type II error). Large studies comparing these new options to nasal sprays are needed.

Biologicals

The understanding of different endotypes in CRS has also led to tailored approaches to manage the underlying inflammation. Biologicals are monoclonal antibodies that directly target inflammatory mediators involved in pathogenesis. In CRSwNP biologicals, target one or more of the important biomarkers of CRSwNP that drive the inflammation in the sinonasal mucosa (i.e. interleukin-4, IL-13, IL-5, and IgE). Biologicals are used in various type 2 inflammatory diseases, such as eosinophilic asthma, urticaria, and atopic dermatitis. In general, biologicals seem to have few side effects, none of which are serious. At the time of writing (2023), three biologicals have been approved for CRSwNP in the European Union: dupilumab (anti-interleukin-4Rα), omalizumab (anti-IgE), and mepolizumab (anti-IL5). Trials with other biologicals like benralizumab (anti-IL5, tezepelumab (anti-thymic stromal lymphopoietin: anti-TSLP) and depemokimab, a long-acting anti-IL5, are ongoing.

Dupilumab is a human monoclonal antibody directed against IL-4Rα. By inhibiting IL-4R signalling of both IL-4 and IL-13, it effectively downregulates the molecular pathways that drive type 2 inflammation (e.g. pro-inflammatory cytokines, chemokines, IgE, and nitric oxide). In 2019, dupilumab was the first biologic to be approved for severe, uncontrolled CRSwNP in the European Union and the US. Treatment with dupilumab results in a significant improvement of QoL (measured as SNOT-22), rhinosinusitis disease severity, symptoms of rhinosinusitis and especially sense of smell, nasal polyp score, Lund-Mackay CT score and asthma outcomes (ACQ5 and FEV1) compared to placebo [19].

Omalizumab (anti-IgE) followed suit in 2020. Treatment with omalizumab demonstrated significant improvement of QoL (measured as SNOT-22), rhinosinusitis disease severity, symptoms of rhinosinusitis including sense of smell, nasal polyp score, Lund-Mackay CT score, and asthma outcomes (AQLQ), compared to placebo as well [20].

Treatment with mepolizumab demonstrated significant improvement of QoL (measured as SNOT-22), rhinosinusitis disease severity, symptoms of rhinosinusitis including sense of smell, nasal polyp score (NPS), Lund-Mackay CT score, and asthma outcomes (AQLQ), compared to placebo as well.

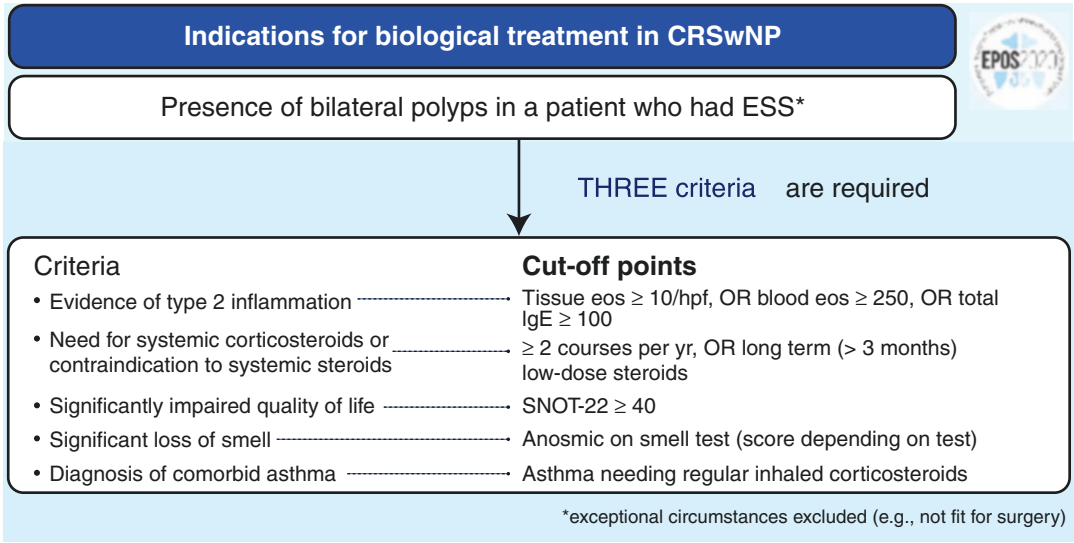

Fig. 22.3 Indications for biologic treatment in primary diffuse type 2 chronic rhinosinusitis [5]

Benralizumab reduced the NPS, decreased nasal blockage, and reduced difficulty with sense of smell compared to placebo in patients with CRSwNP [21].

Phase 3 trials with tezepelumab (anti-TSLP) and depemokimab (long-acting anti-IL-5Rα monoclonal antibody) are underway.

Indication for a Biologic

At the moment, the annual costs of biologicals in Europe are 10,000–20,000 Euros per patient per year. The cost of biologicals compared to regular treatment is high and in most health care systems, one cannot ignore the consideration of cost.

In line with these new developments, several bodies have issued guidelines for the positioning of biologicals in the treatment of CRSwNP [22, 23]. Most guidelines position biologicals in the treatment of CRSwNP after at least one endoscopic sinus surgical intervention unless the patient is not fit for surgery. Further criteria proposed by researchers include the existence of type 2 inflammation, the regular need for systemic corticosteroids, (severe) impairment of quality of life, loss of smell, and the presence of various comorbidities. The latest EPOS2020/EUFOREA guidelines propose a set of three out of five criteria in patients with CRSwNP and at least one (F)ESS (see Fig. 22.3). Cut-off criteria for the criteria are given (see Fig. 22.3).

Choosing the Correct Biologic

In the light of these new developments, a crucial question is the choice of biologic. There are no direct published comparisons performed between biologicals for CRSwNP although some are ongoing. However, a number of network meta-analyses have been performed all pointing to a superiority of dupilumab over the other biologicals and ATAD [13]. Until direct comparisons are available, it is difficult to draw strong conclusions. Future important discussions around the use of biologicals and their evaluation in daily practice will include the choice of biologic for individual patients; the expansion of indications for specific patient subgroups with CRSwNP; the indications for surgery and extent of individual endoscopic sinus operations.

At the moment, the current biomarkers that are readily accessible to clinicians have limited use in identifying response to biologicals and are unhelpful in predicting which biologic to use in specific cases.

In conclusion, the development of biologicals as treatment for diffuse type 2 chronic rhinosinusitis is a breakthrough. For now, the availability in some countries and the high cost of the treatment are limitations for the use.

Real-Life Experience with Biologicals

In recent years, a number of registries have been started to evaluate real-life experience with biologicals in CRSwNP [24, 25]. The registries are mainly performed using dupilumab therapy. Interestingly, one of the registries shows the potential to significantly reduce the dose interval between dupilumab treatments to once every 6–8 weeks (or even longer) without losing disease control [26]. Further evaluations are needed to determine whether this is also true for other biologicals.

Secondary Chronic Rhinosinusitis

Secondary CRS can also be divided into localized and systemic disease.

Localized Secondary Chronic Rhinosinusitis

Localized secondary CRS is induced by a local problem like a tumour. The treatment is outside the scope of this chapter.

Diffuse Bilateral Secondary Chronic Rhinosinusitis

Diffuse bilateral secondary CRS can have mechanical, inflammatory, or immunological reasons.

Diffuse Bilateral Secondary Chronic Rhinosinusitis Due to Mechanical Reasons

Typical examples of diffuse bilateral secondary CRS due to mechanical reasons are cystic fibrosis (CF) and primary ciliary dyskinesia (PCD). Developments in the treatment options for CF in the past decade have been evolutionary. For patients with the Phe508del homozygosity, cystic fibrosis transmembrane conductance regulator (CFTR) modulators such as elexacaftor, tezacaftor, ivacaftor, and combinations of these medications can give significant benefit [27, 28]. At this moment, several new treatments are being evaluated through clinical trials, which aim to improve lung function by directly interacting with CFTR or by altering its downstream effects. Gene manipulating techniques and new molecular targets are also being explored [29].

Diffuse Bilateral Secondary Chronic Rhinosinusitis Due to Inflammatory Reasons

Diffuse bilateral secondary CRS due to inflammatory reasons is a large group of diseases often caused by an underlying vasculitis or granulomatous disease. Patients often show ANCA positivity. A growing body of research is available on novel treatment options for remission induction, clarifying some uncertainties concerning the optimal use of the available drugs. Efforts are being made to reduce the toxicity associated with high-dose, prolonged glucocorticoids regimens. Intensified immunosuppressive strategies for patients with life-threatening manifestations, including the combination of rituximab (RTX) with cyclophosphamide (CYC) have revealed promising data [30, 31]. The management of refractory or relapsing eosinophilic granulomatosis with polyangiitis (EGPA) has been improved by the recent demonstration of efficacy and safety of interleukin-5 inhibitors, such as mepolizumab [32]. The treatment of diffuse bilateral secondary CRS due to inflammatory reasons is usually led by immunology or rheumatology colleagues. Close collaboration with the otorhinolaryngologist is relevant for early detection of relapse and local treatment. Surgery, in general, is best avoided.

Diffuse Bilateral Secondary Chronic Rhinosinusitis Due to Immunological Reasons

In difficult to treat CRS, an immunological disorder has to be considered. Immunodeficiency can be primary or secondary to other diagnoses or to immunosuppressive medication. There is some evidence for treatment with long-term antibiotics. The decision to treat with intravenous immunoglobulin replacement and the supervision of that treatment should ideally be made by a clinical immunologist.

Summary of Areas of Controversy or Uncertainty

A vast subject such as new innovations and treatment in CRS has many points of discussion. Regional discrepancies in management, such as the use of balloon technology and the place and choice of biologicals, raise points of debate, as previously addressed in this chapter. In these rapidly developing domains of disease management, many issues remain unclear, and real-life experience, in combination with new trials, will help to define the optimal personalized therapy for each individual patient.

Key Learning Points

- There is a new classification of CRS with significant impact on treatment choices
- The management of CRS has significantly changed in the past decade
- The major development in the treatment of primary diffuse type 2 chronic rhinosinusitis is the development of biologicals (monoclonal antibody therapy)
- The exact indication for biologicals in precision medicine has to be defined

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23

Clinical Assessment and Management of Acute Rhinosinusitis

Stephen R. Ell and Richard Wei Chern Gan

Introduction

Acute rhinosinusitis (ARS) may be regarded as a spectrum of disease, which may be mild with minimal patient impact and requiring only supportive treatment, or, at the other extreme, it may be associated with life-threatening complications requiring specialist medical and surgical treatment. The challenge is to identify where, between these extremes, the patient presents so that the most appropriate treatment may be given. Correct diagnosis is important since other conditions may present with similar symptoms.

Definitions

ARS is symptomatic acute inflammation of the nose and one or more of the paranasal sinuses. The use of the term 'rhinosinusitis' is more accurate than 'sinusitis' since inflammation of the nasal cavity and paranasal sinuses almost always occur together.

The clinical definition of ARS in adults, according to the European Position Paper on Rhinosinusitis and Nasal Polyps (EPOS) 2020 [1], is an acute onset of two or more symptoms, at least one of which should be either nasal blockage, obstruction or congestion; anterior nasal discharge or post-nasal drip; with or without facial pain or pressure, or a reduced sense of smell. Since children are less likely to describe a loss of sense of smell accurately, EPOS 2020 defines ARS in children as being an acute onset of two or more symptoms of nasal blockage, obstruction, or congestion, or discoloured nasal discharge or cough. A single episode lasting less than 12 weeks is defined as acute. Recurrent ARS is defined as four or more episodes of ARS per year with symptom-free intervals.

The American Academy of Otolaryngology—Head and Neck Surgery Foundation (AAO-HNS) Clinical Practice Guideline: Adult Sinusitis (2015) [2] defines ARS as up to 4 weeks of purulent nasal discharge accompanied by nasal obstruction or facial pain, pressure or fullness, or both: stressing that purulent discharge is a cardinal symptom.

Both EPOS 2020 and AAO-HNS Clinical Practice Guidelines subdivide and distinguish the range of ARS conditions from the milder viral form to the more severe bacterial forms of disease. This emphasises the spectrum of severity requiring tailored management.

EPOS 2020 describes three subgroups:

1. Viral ARS, also known as the 'common cold', is a mild, self-limiting episode of ARS lasting

S. R. Ell (✉) · R. W. C. Gan
Hull University Teaching Hospitals NHS Trust, Castle Hill Hospital, Cottingham, East Yorkshire, UK
e-mail: srell@doctors.org.uk; stephen.ell@nhs.net

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less than 10 days. A viral cause is either presumed or confirmed by microbiology.
2. Post-viral ARS is an episode of acute rhinosinusitis with an increase in symptoms after 5 days or persistence of symptoms for more than 10 days, but without the symptoms and signs of ABRS. This encompasses the group of patients with persistent symptoms, the majority of which will not have acute bacterial infection, since acute bacterial infection makes up only 0.5–2.5% of cases [3].
3. ABRS is an episode of ARS with at least three additional symptoms or signs of discoloured mucus, severe local facial pain (often unilateral), fever more than 38 °C, raised serum C-reactive protein (CRP) or erythrocyte sedimentation rate (ESR) or 'double sickening' or 'double worsening', which is a deterioration of symptoms after an initial milder phase of acute rhinosinusitis.

The AAO-HNS Clinical Practice Guideline: Adult Sinusitis [2] defines ABRS as symptoms worsening within 10 days or lasting more than 10 days, which is akin to the EPOS 2020 Post-viral ARS, but given their emphasis on the cardinal symptom of purulent discharge, their definition of ABRS may be appreciated.

It should be noted that although there are minor variations in how other consensus groups or clinical guidelines around the world define the disease, there are also many similarities especially in terms of defining cardinal signs and symptoms [3]. In this chapter, the terms used will be based on the definitions described in EPOS 2020.

Epidemiology and Economic Impact

There are fewer published studies on the epidemiology of ARS than there are on allergic rhinitis and chronic rhinosinusitis. In the pre-Covid era, the incidence of acute viral rhinosinusitis was very high, with most adults having around two to five episodes of viral ARS per year [1]; however, the pandemic precautions of physical distancing, wearing of facemasks and restrictions on large gatherings are likely to be associated with a significant reduction in the incidence of ARS. The following paragraphs describe the pre-pandemic incidence of ARS; all are likely to be reduced by the precautions necessitated by the Covid pandemic.

In Europe, the incidence of ARS is estimated between 21 and 28 episodes per 1000 people per year [4, 5], which makes up about 2% of visits to general practice [4] and more commonly occurs in the winter months [6]. In Norway, it is a significant financial burden, mostly due to sick leave [4].

In the United Kingdom, the prevalence and incidence of ARS is unknown; however, the prevalence of all types of rhinosinusitis in the United Kingdom is estimated at 24.9% [7]. Risk factors include a history of smoking, chronic rhinosinusitis, allergic rhinitis and eczema [8]. ARS is more common in Caucasian women [4, 8, 9].

In the United States, the prevalence of rhinosinusitis as a whole is 11.6% [10]. Recurrent ARS is estimated to have a prevalence of 1 in 3000 patients per year in the United States, costing $1000/patient/year [9].

In Asia, the prevalence of chronic rhinosinusitis has been published for various countries, but less is known on the prevalence of ARS.

Aetiology and Pathogenesis

Episodes of ARS are due to viruses in 80–90% of cases. In a poorly ventilated room full of people, it only takes one unrestrained sneeze from an infected person to generate an aerosol of about 40,000 droplets, each droplet carrying up to 2 million virions. Trillions of viruses are suspended in the air waiting for someone to breathe in, waiting to coat their respiratory mucosa with hordes of viral invaders; invaders that drill into healthy ciliated columnar cells and use the cell machinery for their own replication. Of these infections, up to 50% are incited by rhinoviruses or coronaviruses. The other 50% are due to influenza, parainfluenza, adeno- and enteroviruses and respiratory syncytial viruses. All these viruses survive longer in damp conditions and are highly contagious.

After the infecting virus has been taken into the nasal epithelial cells by receptor-mediated endocytosis, viral replication is underway within hours. Upon invasion, however, the natural defences of each epithelial cell respond immediately. Innate sensors within the cytoplasm, such as toll-like receptors (TLRs), detect viral components and mobilise the cells' acute defence machinery, raising the alarm by sending signal proteins to alert the nucleus. These signal proteins, STAT 1 and STAT 2 (signal transducer and activator of transcription), activate quiescent genes and defensive DNA is transcribed. Once activated, these genes are also stimulated by interferon and are known as ISGs (interferon stimulated genes) and produce pro-inflammatory signalling molecules that ignite inflammation. These molecules are cytokines: messengers that induce changes in other cells. Cytokines that specialise in attracting cells are called chemokines (*chemo*tactic cyto*kines*). Chemokines, e.g. interleukin 8 (IL-8), recruit macrophages and T-cells to the battlefield and these cells are activated by cytokines, e.g. interferon gamma (IFN-γ), to produce yet more cytokines in an 'amplification cascade' that spread the fire of inflammation across the mucosa. Pyrogens fuel this process and a potent example is tumour necrosis factor-alpha (TNF-α). This is produced mainly by macrophages and is a killer of infected cells.

Once a cell's innate defences have been overwhelmed by invading viruses, the cell must be destroyed: sacrificed to prevent further viral replication and spread to healthy epithelial cells. IFN-γ is a major cytokine in the process of destroying virus manufacturing cells. It is made by T-helper 1 cells (Th1 cells) and it indirectly stimulates the conversion of naïve T-cells (T0 cells) to Th1 cells, in a positive feedback action, thereby ensuring its own reproduction. IFN-γ acts as a bridge between our innate and adaptive immune responses, stimulating the natural killer (NK) cells of our innate defences and, as part of our adaptive cellular immune response, it polarises macrophages to the (destructive) M1 type that phagocytose virions. IFN-γ also recruits CD8+ (cluster of differentiation 8) cytotoxic T lymphocytes to the battlefield.

Cytotoxic T cells (CD8+) begin apoptosis (cell death) of virus-manufacturing epithelial cells, and spent infiltrating white cells, by tearing them apart, or by using perforin to punch holes in the cell membrane through which they pour granzymes: protein-dissolving enzymes, which cause the cell to explode by osmosis. They are serial killers, killing an infected cell and moving on to the next. They also manufacture IFN-γ and TNF-α, accelerating inflammation.

While the might of the inflammatory response targets the destruction of the viral attack and all its consequences, it is the damage to, and the associated inflammatory changes in, the respiratory mucosa that are responsible for the symptoms of viral ARS. Usually, these are temporary and reversible, with recovery taking place within 10 days. Unusually, if the response is too florid, the epithelium may be damaged permanently and recovery lasts longer than 10 days giving rise to the symptoms of post-viral ARS. The attack of millions of virions devastates the sinonasal mucociliary clearance and the mucosal oedema of inflammation obstructs sinus drainage, trapping opportunistic bacteria within. The numerous cellular corpses from apoptosis provide a feast for bacterial colonisation and secondary infection. The most common bacteria associated with acute bacterial rhinosinusitis: *Streptococcus pneumonia*, *Haemophilus influenza* and *Moraxella catarrhalis*, rampage across the wounded surface. And yet, only 0.5–2.5% of acute viral rhinosinusitis cases progress to acute bacterial rhinosinusitis. This is surprisingly low when thinking about the pathogenesis, and progression of disease, and is testimony to the efficiency of our immune defences. Our immune defences may overshoot the mark creating Cytokine Storm Syndromes.

Cytokine Storm Syndromes

When the innate immune system rages uncontrollably, large numbers of white blood cells are activated and release inflammatory cytokines systemically in an amplification cascade, damaging other vital organs in the maelstrom of hyper-

cytokinaemia. This is also known as a Cytokine Release Syndrome (CRS), and is a form of Systemic Inflammatory Response Syndrome (SIRS). These are the 'Cytokine Storm Syndromes'. Cytokine storms may be associated with a number of viral respiratory infections such as H5N1 influenza, SARS-CoV-1 and with SARS-CoV-2, so prevalent in the Covid pandemic and require intensive care.

Clinical Presentation and Assessment

Background

If ARS is suspected, an assessment is essential to confirm the diagnosis, the subtype and the presence of any complications. An accurate initial diagnosis is critical to exclude sinister mimics and to prevent false diagnostic labelling, inadequate or inaccurate treatment and a false prognosis. So, we follow the traditional paths of eliciting the clinical history and examining the patient.

History

The history of a patient with ARS will include nasal blockage/obstruction, or discharge, or both. The sensation of nasal blockage (poor airflow) is bilateral, affecting alternate nostrils in an increased awareness of the nasal biorhythm/cycle, and may be complete nasal obstruction (no airflow). Nasal discharge may be anterior, or posterior, or both. The patient may also have facial discomfort ascending to pain, or pressure, or a loss of sense of smell. For ARS to give rise to facial pain, trapped mucus or mucopus within a sinus associated with a build-up of pressure, likened to a 'pressure cooker', evokes increasing facial discomfort culminating in pain. Such sensations around the glabella, or between the eyes, may be due to pressure in the frontal sinus or ethmoids. If behind the eyes, or on the cranial vault at the vertex, the sphenoid sinuses may be affected; if below the eyes, the maxillary sinuses may be at fault. Exact correlation between site and sensation, however, is poor. If the loss of the sense of smell is accompanied with a loss of taste, then this is a good indicator of significant nasal blockage.

Patients with ARS will commonly have the symptoms of an upper respiratory tract infection (URTI) such as sore throat, cough, hoarse voice, drowsiness and malaise.

Predisposing Conditions

The patient's past medical history, social circumstances and habits provide potential predisposing factors that may indicate a diagnosis of ARS. Common predisposing factors may be divided into trauma, inflammation and neoplasia. Less commonly, comorbid chronic disease, immunodeficiency and environmental factors, such as poor air quality, also favour infection.

Facial trauma, both brutal and surgical, disrupts tissue and implants infecting organisms, more so in the blunt and penetrating trauma of street violence than (we hope) in surgery. However, in sinonasal and dental surgery, foreign bodies such as nasal packs, nasogastric tubes and nasopharyngeal airways may all be associated with infection, especially when a biofilm forms on the surface of a foreign body and predisposes the patient to ABRS.

Inflammation, both infective (e.g. odontogenic abscesses) and non-infective (e.g. the inhaled fumes of active and passive smoking, nicotine vapour and products of combustion), occupies those resources reserved to defend us against invading organisms and so invite infection.

Neoplastic lesions obstructing the nose and sinuses, e.g. polyps, favour episodes of ABRS by stasis of trapped organisms.

On the defence side, immunodeficiency and ciliary impairment reduce the patient's ability to resist infection [1, 11]. Patients with chronic diseases, such as asthma, chronic obstructive pulmonary disease (COPD), diabetes, cardiovascular disease or cancer, are predisposed to ARS associated with influenza [12] and are more susceptible to ABRS.

Environmental factors such as dampness in the home may confer an increased risk of rhinosinusitis [13]. If ABRS were to occur, it usually follows a period of viral ARS; however, ABRS can occur at any stage of ARS [2].

Examination

Inspection of the face, external nose and nares yields information about facial swelling, discolouration and epiphora. Anterior rhinoscopy, and the assessment of nasal patency, reveals mucosal inflammation, nasal blockage, discharge and the presence of large polyps. Nasal endoscopy may show discharge from the middle meatus, or spheno-ethmoidal recess, or both, indicating which sinuses are affected, and allows examination for small nasal polyps, tumours or distorted anatomy; a targeted swab may be taken of any discharge for microbiology culture and sensitivity testing (Fig. 23.1).

Inspection and percussion of the teeth may reveal a dental source of maxillary ARS; however, if the dental nerve has died, the tooth may not be sensitive. Evidence of dental caries may suggest an odontogenic source for maxillary sinus infection, though when both occur simultaneously it can be difficult to tell which came first. Toothache in the upper teeth is a good predictor of ABRS [14]. Palpation of the neck for lymphadenopathy is a must.

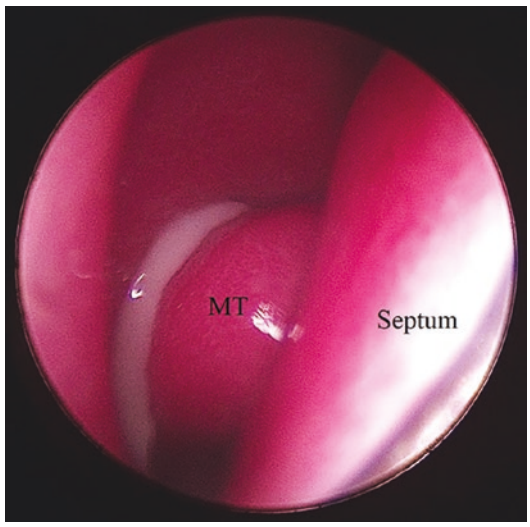

Fig. 23.1 Mucopurulent discharge from the right middle meatus (*MT* middle turbinate)

Diagnosis

Those criteria defined by EPOS determine the diagnosis of ARS in adults and require an acute onset of two or more symptoms, at least one of which should be nasal blockage, obstruction or congestion; anterior nasal discharge or post-nasal drip; with or without facial pain or pressure, or a reduced sense of smell [1]. Once ARS is diagnosed, a determination of the subtype is made: viral ARS, post-viral ARS or ABRS. These are summarised in Table 23.1.

Most cases of ARS are viral, self-limiting and mild, and last less than 5 days. The diagnosis is clinical and no further investigation is required. Often, viral ARS is self-diagnosed as the 'common cold' and managed with supportive measures. Post-viral ARS is diagnosed when symptoms worsen after 5 days, or persists longer than 10 days. ABRS is diagnosed when three or more of the following features develop: worsening of symptoms, severe local facial pain, a high fever more than 38 °C, purulent discharge and raised inflammatory markers such as CRP or ESR [1]. Contrary to common belief, purulent nasal discharge *alone* does not necessarily equate to ABRS [14].

Differential Diagnosis

If the diagnosis is unclear at presentation, a ranked list of the most likely diagnoses will direct further investigation. Other diagnoses, often attributed to ARS, lack the prime features of an acute onset of nasal obstruction and discharge. Or, the 'lesser' features of ARS, such as facial pain, pressure or a reduced sense of smell, carry much more emphasis in the history than expected for ARS.

Facial pain or pressure *alone* creates many diagnostic traps. The trigeminal nerve conveys

Table 23.1 Summary of definitions

ARS condition	EPOS (2020) definition	AAO-HNS (2015) definition
ARS: Acute ARS = a single episode <12 weeks Recurrent ARS: ≥4 ARS episodes/year, with symptoms-free intervals	In adults: Acute onset of ≥2 symptoms, including one of: (a) nasal blockage, (b) obstruction or (c) congestion, (d) anterior nasal discharge or (e) post-nasal drip; with or without facial pain or pressure, or a reduced sense of smell	ARS ≤4 weeks of purulent nasal discharge accompanied by: (a) nasal obstruction or facial pain, (b) pressure or fullness, or both
	In children: Acute onset of two or more symptoms of: (a) nasal blockage, (b) obstruction or (c) congestion, (d) discoloured nasal discharge or (e) cough	
Viral ARS	Viral ARS = 'common cold' is a mild, self-limiting episode of ARS lasting less than 10 days	
Post-viral ARS	An episode of ARS with an increase in symptoms after 5 days or persistence of symptoms for more than 10 days (without symptoms or signs of bacterial sinusitis)	
Acute bacterial rhinosinusitis (ABRS)	An episode of ARS with at least three additional symptoms or signs of: (a) discoloured mucous, (b) severe local facial pain, (c) fever more than 38 °C, (d) raised CRP or ESR, or (e) a deterioration of symptoms after an initial milder phase of acute rhinosinusitis	ABRS is defined as symptoms worsening within 10 days or lasting more than 10 days (similar to EPOS Post-viral ARS)

the sensory innervation of the face from the skull-base to the neck, and facial discomfort may arise from any structure between these levels, e.g. the dura, teeth, gums, palate, eyes, pinnae and face. These areas must be considered to avoid being misled. Dysaesthetic pain may be attributed to ARS, but a clue indicating a different diagnosis is the absence of nasal obstruction and discharge, and this pain is severe and chronic, not acute. Diagnostic boundaries become blurred when a dysaesthetic sensation is exacerbated by ARS, but correct management of the ARS will allow the dysaesthetic sensation to be managed with more optimism. However, be aware that surgical trauma to drain-infected sinuses may exacerbate a dysaesthetic sensation. This is a dark and gloomy situation. The patient should be given a detailed explanation, on several occasions, of this most difficult possibility, and only when all involved have agreed that medical treatment has failed should surgical intervention be considered. If medical treatment fails, surgical drainage is the lesser of two evils, as the inflammation of undrained-infected sinuses may continue to drive the dysaesthetic pain.

A space-occupying lesion of the maxilla may be indicated by facial swelling, numbness and epiphora, with a unilateral nasal discharge and is a sinister trap for the unwary. It is difficult to imagine how this could be misdiagnosed as ARS, but it can. In addition, a unilateral foul-smelling discharge, often in a child, rarely in an adult, is a retained foreign body in the nose until proved otherwise (Table 23.2).

Additional symptoms of itching, watery eyes and sneezing suggest an allergic aetiology, rather than ARS, especially if a triggering allergen can be identified. Patients with allergic rhinitis, how-

Table 23.2 Summary of features that help to clarify an ARS diagnosis

Clinical question	Features to aid assessment
Does the patient have ARS?	**ARS likely if:** ≥2 of the following[a]: Nasal obstruction/congestion Discharge/post-nasal drip Reduction/loss of sense of smell Facial pain/pressure
Could the diagnosis be something other than ARS?	**Differential diagnoses:** Odontogenic Fungal ball Neoplasm Allergic rhinitis Foreign body Non-sinogenic facial pain or headache
If the patient has ARS, what subtype does the patient have?	**Viral ARS:** Mild, self-limiting, ≤10 days **Post-viral ARS:** Increase in symptoms after 5 days or persistent >10 days **ABRS[b]:** Additional features of: Worsening of symptoms, severe facial pain, fever >38 °C, discoloured mucous, raised CRP/ESR
Does the patient have a complication of ABRS?	**Red-flag symptoms:** Periorbital oedema/erythema Proptosis Double vision Ophthalmoplegia Reduced visual acuity/colour vision Severe headache Frontal swelling Signs of sepsis Signs of meningitis Neurological signs

[a]According to EPOS 2020, at least one of the two symptoms should be nasal obstruction/congestion or discharge/post-nasal drip
[b]According to EPOS 2020, ABRS is associated with greater than, or equal to, three additional symptoms

ever, may also develop ARS at the same time. Allergies are always worth excluding.

Complications

Uncomplicated ABRS may be diagnosed and managed in primary care; however, patient information, advice and close monitoring are required to watch for the development of symptoms or signs of complications. Should these occur, referral to a specialist centre is imperative.

Complications occur when ABRS progresses beyond the bony boundaries of the nose and paranasal sinuses into adjacent areas, either directly or via thrombophlebitis in diploic veins. Although the bone is thin at the lamina papyracea, the cribriform plate and the inner table of the frontal sinus, it can still be an effective barrier to the spread of infection. Spread of infection through the bone into the skin, orbit or intracranial cavity is heralded by increasing pain and a spiking temperature trace and requires urgent treatment. Drowsiness and a falling Glasgow Coma Score/Scale (GCS) suggest intracranial sepsis.

Osteomyelitis of the frontal bone with subgaleal or subperiosteal abscess, from frontal sinusitis, presents with swelling and inflammation, known as Pott's puffy tumour, which becomes a discharging fistula. This seems to be more common in ENT practice than intracranial sepsis, even though the inner table is thinner. This may be due to spread anteriorly via thrombophlebitis in diploic veins, or that patients with intracranial sepsis go directly to neurosurgery. In a feverish patient with ABRS, intracranial sepsis must be excluded if the patient develops headache, neck stiffness, nausea or vomiting, changes in their mental state (drowsiness, confusion), focal sensory or motor neurological deficits, ataxia or grand mal seizures. A raised blood pressure and bradycardia occurs with raised intracranial pressure. Papilloedema is a late sign.

Infection spreading into the orbit is associated with periorbital swelling and inflammation, suggesting either periorbital (pre-septal) or orbital cellulitis. The ophthalmology team will help assess the urgency for surgical intervention by documenting colour vision, visual acuity, ophthalmoplegia and proptosis.

Facial swelling due to maxillary osteomyelitis from isolated maxillary sinusitis is rare and other causes should be sought. More likely causes would include an odontogenic abscess, or a neoplastic process.

General sepsis, in otherwise healthy patients with ABRS, is rare, but is life-threatening and requires emergency medical care. Sepsis is suggested by an altered mental state, increased pulse

or respiratory rate, dysrhythmia, inadequate urine output, temperature <36 °C, mottled or ashen appearance and a non-blanching rash [15], and should be managed in an acute hospital setting. There are some prime suspects for sepsis, who need extra vigilance. Patients with a compromised immune system may develop sepsis early that accelerates swiftly and is associated with unexpected organisms, e.g. acute invasive fungal rhinosinusitis (AIFRS). Prime suspects for sepsis are those receiving chemotherapy, who have had an organ transplant, with HIV infection, or who have uncontrolled diabetes [16].

Investigations

Swabs

A targeted swab of purulent discharge taken from the middle meatus, or spheno-ethmoidal recess, with the help of an endoscope, may guide antibiotic therapy accurately; a non-targeted swab may not be helpful.

Bloods Tests

A full blood count may show a raised white cell count in bacterial infection.

A raised CRP increases the likelihood of bacterial rather than viral ARS [17]. It correlates well with radiological signs of rhinosinusitis and positive bacterial culture of sinus puncture material [18]. A raised ESR is also a good marker of ARS and correlates well with CT findings [18]; however, CRP is a more sensitive marker of acute phase inflammation than ESR [19]. CRP increases within 24 h of inflammation and, having a constant half-life, its level decreases, returning to normal in about a day if the inflammatory process resolves. A rise in ESR is only seen days after the start of inflammation and may be raised several days after the process of inflammation has ceased.

Imaging

Radiological investigations have become so complex, with advances in technology, that time spent in the Radiology Department talking to the radiologists is never wasted.

Plain sinus radiographs do not show sufficient detail and are not recommended; an opaque sinus may be revealed equally by trans-illumination or an ultrasound scan. A diagnosis of acute ARS may be made without radiological imaging and the use of CT scans should be judicious. When there are signs and symptoms suggesting a complication, however, imaging is essential to plan surgical intervention and a CT scan of the paranasal sinuses is the first choice. It shows the bony anatomical detail for surgical planning, and also useful soft-tissue information. Sections in the coronal, sagittal and axial planes, with soft tissue and bony windows without contrast are usually sufficient. However, if there is suspicion of intra-orbital or intracranial complications, or a soft-tissue mass, or a need to differentiate fluid from polypoidal tissue, then both contrast and specific imaging settings are helpful [20]. It is important to raise your concerns with the radiologist, so the use of appropriate settings and contrast can be applied to confirm, or exclude, possible complications.

CT findings must be used in the context of the clinical history and examination findings, since a CT scan alone is not a good diagnostic tool. Up to 30% of asymptomatic patients, and up to 80% of patients with minor upper respiratory tract infections, which do not require treatment, have paranasal sinus abnormalities on a CT scan [20, 21]: an abnormal scan, in the absence of the clinical information, may misdirect treatment.

Those sinuses involved in uncomplicated ABRS show homogenous opacification. Heterogeneity, such as hyperdense central material surrounded by a hypodense rim, or microcalcification, suggests fungal infection, and bony erosion suggests complications or a neoplastic process.

When intraorbital or intracranial complications of ARS are suspected, or identified on CT, additional magnetic resonance imaging (MRI) scanning may be useful. Due to its better soft-tissue definition, an MRI scan is better at delineating intraorbital or intracranial extensions of disease, and differentiating soft-tissue masses, e.g. polyps or tumours, from fluid and inflamed mucosa. MRI is also better at evaluating sinus content and discharge, and the extension of soft-tissue inflammation in AIFRS. MRI findings of fungal infection include signal voids on T2 sequences due to high concentration of metals such as iron, manganese and magnesium, in addition to highly proteinaceous secretions that restrict diffusion.

Treatment

Viral ARS

Since most cases of viral ARS are mild and self-limiting, many patients do not require treatment. However, symptomatic treatment is available over-the-counter at the high-street pharmacy. Paracetamol and non-steroidal anti-inflammatory drugs (NSAIDs) can help reduce pain, aches and nasal congestion. Vasoconstrictive decongestants, e.g. oral pseudoephedrine or topical oxymetazoline, help reduce nasal congestion during the acute phase, but these should be used for only 7–10 days since long-term use leads to rebound congestion and mucosal hypertrophy. If ARS is concurrent with allergic rhinitis, antihistamines may reduce symptoms of rhinorrhoea and sneezing. Some of the above medications are available in oral antihistamine–analgesic–decongestant combinations.

Topical ipratropium bromide nasal spray may reduce rhinorrhoea if particularly troublesome. Nasal saline rinsing (also called nasal douching or irrigation), with or without sodium bicarbonate, may be helpful in reducing nasal blockage and clearing nasal discharge. Vitamin C or zinc lozenges may reduce the length of symptoms in some patients [1].

Antibiotic treatment for viral ARS is not recommended as multiple randomised controlled trials have shown that they do not reduce the length or severity of disease. Furthermore, antibiotics can bring about adverse side effects and are associated with the development of resistant strains of bacteria, which are difficult to treat.

Post-viral ARS

Post-viral ARS treatment is the same as for viral ARS, although corticosteroid nasal sprays, available over-the-counter, may help reduce post-viral ARS symptoms [22], but there is insufficient evidence that they help in viral ARS.

In post-viral ARS, oral corticosteroids and antibiotics are not beneficial, and antihistamines are not recommended unless there is concurrent allergic rhinitis.

ABRS

The above symptomatic treatment is helpful in patients with ABRS. Antibiotics, in addition, are beneficial at reducing the severity of symptoms and speeding up the resolution. A Cochrane review suggests that antibiotics are more beneficial in ARS cases with purulent discharge [23], but only, it seems, in those with severe pain [24]. Studies have shown a significant benefit of Penicillin V and Amoxycillin in ABRS, but there is less evidence to suggest their efficacy in children [25]. And yet, antibiotics do not appear to prevent the occurrence of complications of ABRS. If infection persists, despite medical treatment, the diagnosis should be reviewed since other diseases may present similarly, e.g. maxillary sinusitis of odontogenic origin, fungal ball or tumours.

Treatment of ABRS is medical. Surgical treatment is needed if there is persistent infection in

Table 23.3 Summary of treatment options for ARS

ARS subtype	Treatment options
Viral ARS	Analgesia—paracetamol, ibuprofen Decongestants—oral pseudoephedrine, topical oxymetazoline (limited course to avoid rhinitis medicamentosa) Antihistamine Oral antihistamine–decongestant–analgesia combination Topical ipratropium bromide Nasal saline rinsing Vitamin C Zinc
Post-viral ARS	As above with the added option of: Topical corticosteroids
ABRS	In addition to the above symptomatic treatment, systemic antibiotics may be beneficial Surgical treatment may be required if a complication arises
Recurrent ARS (≥4 per year)	May benefit from endonasal sinus surgery or balloon sinuplasty (once other potential causes such as immunodeficiency and odontogenic causes have been ruled out)

immunocompromised patients, or antibiotic resistance, or complications develop. Surgery releases pus from, for example, a subperiosteal orbital abscess, an orbital abscess, a subperiosteal abscess of the frontal sinus wall (Pott's puffy tumour) or from an intracranial abscess (Table 23.3).

Clinical Vignette

A 30-year-old woman presents with a 1-week history of nasal blockage, a reduced sense of smell, severe pain over her cheeks, purulent nasal discharge and intermittent pyrexia of 38.5 °C. Her GP diagnoses ABRS and prescribes oral antibiotics, nasal saline rinsing and a 7-day course of topical oxymetazoline.

Take Home Message

This is likely to be ABRS, rather than viral ARS, as the patient has at least three of the diagnostic features of ABRS, which include: (1) worsening of symptoms, (2) severe facial pain, (3) high fever >38 °C, (4) purulent discharge and (5) raised inflammatory markers, e.g. CRP or ESR. Antibiotics should improve symptoms and reduce illness duration. This case of ABRS can be managed in the community, provided complications have been ruled out.

Recurrent ARS

Patients with recurrent ARS should have an odontogenic cause ruled out and immune testing. A low IgA may be found by immunoglobulin electrophoresis, and functional antibodies may reveal a poor immune response to respiratory pathogens, e.g. *Streptococcus pneumonia* and *Haemophilus influenza*, and vaccination against these organisms is helpful. Once these have been ruled out or treated, cases of recurrent ARS (≥4 cases of ARS per year) may benefit from endonasal sinus surgery or balloon sinuplasty to improve sinus ventilation and drainage [26].

Clinical Vignettes

The following vignettes highlight the importance of identifying patients with complications and of being aware of other diagnoses that may mimic ARS.

Vignette 1: Complicated ABRS

A 12-year-old girl with a 2-week history of nasal obstruction and purulent nasal discharge develops a painless swelling of the forehead and a change of personality. She was referred for urgent care on that day, was admitted to hospital and started on intravenous antibiotics and nasal decongestants. CT and MRI scans revealed acute frontal sinusitis, a subperiosteal abscess of the frontal bone and a small subdural empyema. Her frontal sinus was trephined and flushed daily through a sinus cannula. The neurosurgical and infectious diseases teams guided management of the subdural empyema, which included intravenous antibiotics for at least 6 weeks.

Take Home Message

The examination findings of a forehead swelling and neurological signs are strong indicators of complicated ABRS, which in this case is a Pott's puffy tumour and an intracranial abscess requiring a multidisciplinary team approach with systemic antibiotics and surgical drainage.

Vignette 2: Dysaesthesia and Non-sinogenic Facial Pain

A 45-year-old woman has an intermittent feeling of pressure and heaviness across her nasal bridge and cheeks occurring on most days over the past few months. Antibiotic treatment has not helped. Her nose feels blocked, but she has no other rhinological or red-flag symptoms. Nasendoscopy revealed healthy mucosa throughout the nasal cavity. Midfacial segment pain was suspected and she was started on amitriptyline 10 mg nocte for 6 weeks. Her symptoms improved, supporting the diagnosis.

Take Home Message

Facial pain, pressure and headaches have many causes apart from ARS [27]. Patients with midfacial segment pain may complain of nasal blockage despite no identifiable obstruction in the nose [28]. The absence of other rhinological signs and normal nasal endoscopy makes ARS highly unlikely. Further investigation, e.g. an MRI scan to exclude neuro-vascular conflict, or a trigeminal nerve lesion, should be considered.

Vignette 3

A 65-year-old man, on chemotherapy for acute myeloid leukaemia, presents with a 3-week history of nasal congestion and progressive right facial pain, headache and intermittent pyrexia. Nasal endoscopy revealed pale discoloured nasal mucosa on the right. CT and MRI scans were consistent with fungal infection of the right maxillary sinus. The patient underwent urgent endoscopic debridement and was commenced on systemic antifungal treatment. Histology confirmed invasive aspergillosis consistent with AIFRS.

Take Home Message

AIFRS may mimic bacterial ARS and it may be difficult to tell them apart. The immunosuppression is a strong clue to invasive fungal disease. Other conditions include diabetes mellitus, HIV infection, and immunosuppressive medication, e.g. following organ transplantation or chemotherapy. Patients with AIFRS require urgent assessment, both medical and surgical treatment [29, 30], since it carries a high risk of mortality if not treated promptly. Coronavirus infection may increase the risk of invasive mucormycosis.

Be alert to look for red-flag symptoms and signs indicating complications, such as periorbital swelling or inflammation, facial or forehead swelling, eye signs such as periorbital cellulitis, decreased visual acuity, diplopia, ophthalmoplegia and proptosis, severe headache, signs of meningitis and focal neurological signs.

Areas of Controversy

- Antral washout in acute rhinosinusitis
- Maxillary antral washout is a procedure that aims to flush out mucopus from the maxillary sinus and clear obstructive particles from its ostium. Although commonly performed in some centres for ABRS, there is no significant evidence to show that it conveys additional benefit to medical treatment in uncomplicated ABRS. It is, however, simple and quick to perform with little morbidity and allows a means of obtaining a pus sample for microbiology culture and sensitivity.
- Antral washout compared with endoscopic middle meatal antrostomy
- When more rapid source control of maxillary sinusitis is required, such as in a septic immunocompromised patient, maxillary antral washout is a simple and quick procedure. Endoscopic middle meatal antrostomy is another option, although may take longer with the likelihood of a bloody field in the presence of acute infection, but allows direct inspection of the sinus and biopsies to be taken, and anatomically widens the drainage pathway. Both of these procedures can be done under local or general anaesthesia, with an antral washout being a better-tolerated procedure.
- Which procedure for recurrent ARS?
- Balloon sinuplasty is an effective alternative to endoscopic sinus surgery in treating select cases of recurrent ARS and can be done as an ‘in-office/clinic’ procedure under local anaesthesia. It widens the ostia without removal of tissue and thus is only suitable for primary localised sinusitis of the frontal, maxillary or sphenoid sinuses [31]. When performed for recurrent maxillary sinusitis, maxillary antral washout is another option

but may have a higher rate of recurrence when compared to endoscopic middle meatal antrostomy.

Key Learning Points

- Antibiotics are not beneficial in patients with viral or post-viral ARS. However, there are many treatment options that aid symptomatic relief.
- In the small proportion of patients with ABRS, antibiotics may be beneficial by reducing symptoms and duration of illness.
- Orbital, neurological, local or systemic red-flag symptoms are indicative of complications that require urgent referral to secondary care for further investigation and treatment that may involve intravenous antibiotics and surgical treatment.
- Patients are at a higher risk of complications if they have poorly controlled diabetes, or if they are immunocompromised, and are at a higher risk of acute invasive fungal rhinosinusitis, which requires urgent surgical treatment.
- Patients with recurrent ARS (≥4 per year) may benefit from endonasal sinus surgery or balloon sinuplasty but only once other potential causes such as immunodeficiency or odontogenic causes have been ruled out.
- Facial pain, pressure and headaches have many potential causes including non-sinogenic diseases, which should be considered as differential diagnoses in addition to ARS to avoid misdiagnosis.

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24 Clinical Assessment and Management of CRSsNP

Sietze Reitsma

Introduction

Chronic rhinosinusitis (CRS) has been traditionally divided into 'with nasal polyps' (CRSwNP) and 'without nasal polyps' (CRSsNP). As explained in Chap. 21, this division leads to two clinically distinct diagnoses, although both encompass many disease entities. In terms of the new CRS classification, based on localization of the disease (localized/unilateral vs. diffuse/bilateral), CRSsNP usually coins patients with diffuse CRS. Localized CRS in the absence of polyps is strictly speaking also CRSsNP, but as its treatment is usually surgically driven (see Chaps. 21 and 22), we will not focus on localized conditions in this chapter.

Differences Between CRSsNP and CRSwNP

The disease entities encompassed within the CRSsNP and wNP diagnoses are far more different than only the appearance of polyps upon nasal endoscopy. In Western countries, the main distinction stems from its underlying endotype: CRSsNP mainly has a non-type 2 inflammatory endotype, whereas in the majority of CRSwNP, it is type 2 (see Chaps. 21 and 25). This has important implications for clinical practice and patient management. For the rest of this chapter, CRSsNP is to be understood as primary diffuse non-type 2 CRS, unless clearly stated otherwise.

Patient History

Even before looking into the nasal cavity, an ENT surgeon should have a clear idea about the probable endotype simply by asking the right questions. Of course, there will be overlap in patient presentation, but the patterns to be recognized are essentially different. They are summarized well in 2020 edition of the European Position Paper on Rhinosinusitis and Nasal Polyps (EPOS2020) [1]. Both groups complain most of nasal obstruction. Patients with CRSsNP complain more of headache/facial fullness/facial pain, and less of loss of sense of smell than those with CRSwNP. The reaction to systemic corticosteroids, such as short courses of prednisone, is also less pronounced in CRSsNP. Comorbidities suggesting a type 2 inflammatory propensity, such as adult-onset or late-onset asthma and atopic dermatitis, are less common in CRSsNP. In contrast, childhood-

S. Reitsma (✉)
Department of Otorhinolaryngology and Head and Neck Surgery, Amsterdam University Medical Centres, Amsterdam, The Netherlands
e-mail: s.reitsma@amsterdamumc.nl

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onset asthma is more prevalent in CRSsNP. The presence of non-steroidal anti-inflammatory drug (NSAID)-exacerbated respiratory disease (N-ERD), which presents with an allergic reaction to NSAIDs, points towards CRSwNP. See Table 24.1.

There is conflicting literature regarding gender, age, and smoking differences between CRSsNP and CRSwNP. Generally, CRSsNP patients tend to be younger. Male gender is associated with an increased risk for CRS in general, but no definitive conclusions about gender differences between sNP and wNP can be drawn [1].

Exposure to air pollutants and irritants is associated with the development of CRS in general.

Table 24.1 Patterns of patient history for CRSsNP and CRSwNP

Item	CRSsNP	CRSwNP
Nasal obstruction	++	++
Loss of sense of smell	+/–	++
Facial fullness/pressure/headache	++	+/–
Early-onset asthma	+	–
Adult/late-onset asthma	–	+
N-ERD	–	+
Response to OCS	+/–	+

N-ERD non-steroidal anti-inflammatory drug-exacerbated respiratory disease, *OCS* oral corticosteroids

However, there is evidence that they promote disease progression especially in CRSsNP patients [2].

Nasal Endoscopy

The hallmark difference between CRSsNP and CRSwNP obviously is the appearance of fleshy polyps in the middle meatus and beyond. The most 'typical' form of CRSsNP will present with mucopus from the middle meatus with mildly oedematous mucosa.

However, there can be a wide variety of mucosal changes such as cobblestone mucosa, local or general oedema, granulations, congestion, etc. that can hamper a definitive endoscopic differentiation (Fig. 24.1). Also, anatomical variations, such as an everted uncinate process, can be mistakenly judged as being nasal polyps. After surgery, scarring and synechiae might also obscure the endoscopic view. Despite all these possible challenges, it is unlikely that the underlying inflammatory process will change over the course of the disease. This means that a CRSwNP patient, once diagnosed with and treated for nasal polyps, will not become a CRSsNP case in the absence of polyps. Conversely, a CRSsNP case that shows polypoid mucosa in the wound healing after surgery does not become a CRSwNP patient at that point.

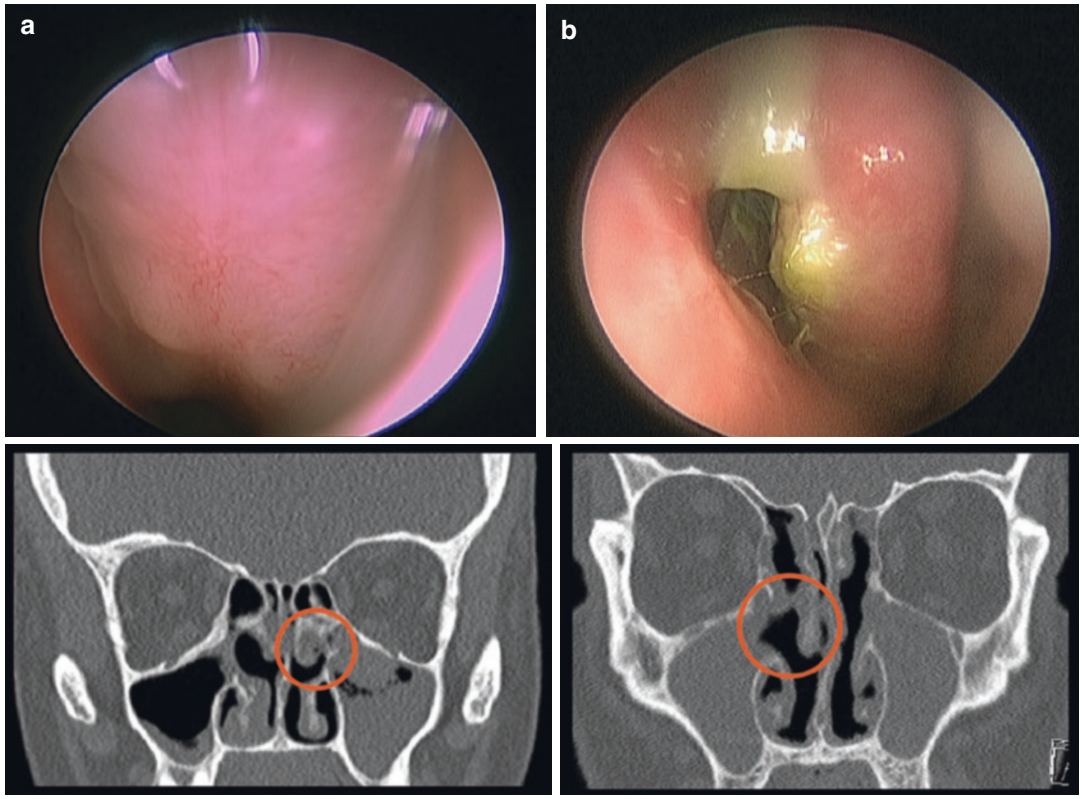

Fig. 24.1 Endoscopic and computed tomography images from two CRSsNP patients. (**a**) Endoscopic view from the left nasal cavity showing an oedematous middle turbinate with thick mucus from the middle meatus. The coronal section from the CT scan shows patchy opacification in the ethmoid sinuses, partial opacification of the left maxillary sinus, and near-total opacification of the right maxillary sinus. The red circle indicates the field of the endoscopic image. Note the opacification at the floor of the right nasal cavity, suggesting stasis of mucus here. (**b**) Endoscopic view from the right nasal cavity from a previously operated patient, showing pus and crusting in the middle meatus. The coronal section from the CT scan shows patchy opacification in the ethmoid sinuses and total opacification of both maxillary sinuses. The red circle indicates the field of the endoscopic image

Endotyping/Additional Investigations

Endoscopy: Because of the challenges that can arise when 'differentiating by endoscopy', EPOS2020 has introduced a more sophisticated classification system (see Chap. 21) which depends on the underlying endotype instead of the endoscopic endonasal appearance. This will greatly help especially in those cases where the clinical picture points towards a CRSsNP (Table 24.1), but nasal endoscopy show polyps or polypoid mucosa.

Eosinophils: There currently is a lack of biomarkers, resulting in the rather rough distinction between type 2 and non-type 2 endotypes. Clinically, the distinction can be made on the level of serum eosinophils (with cut-offs ranging from 150 to 300 cells/μL) or tissue eosinophils (with debatable cut-offs [3]; EPOS2020 suggests ≥10 per high-powered field).

Total Immunoglobulin E: A serum total IgE of ≥100 is indicative of a type 2 endotype.

Allergy testing: Although there is no clear link between allergic sensitization and CRSsNP, a skin prick test or blood test (RAST or ISAC) is advised in the workup of CRSsNP as allergic rhinitis is a treatable trait, and its presence might affect overall disease control/complaints.

Early differentiation between type 2 and non-type 2 is advised, or at least when a patient with CRS fails to respond to 'basic' medical therapy such as intranasal corticosteroids and rinsing.

Medical Management of CRSsNP

Although there is a clear distinction between CRSsNP and CRSwNP, the first line of treatment is similar for both, especially since many CRS patients are seen by primary care physicians. Moreover, a definitive diagnosis in primary care is likely to be challenging given the differential diagnosis (allergic rhinitis, non-allergic rhinitis, etc.) and the lack of facilities for nasal endoscopy and/or imaging.

Thus, the differentiation between CRSsNP and wNP will mostly take place in secondary care or beyond. Therefore, the initial 'basic' medical therapy should consist of intranasal corticosteroids (INCS) and the use of nasal rinsing. For additional steps, evaluation by an ENT surgeon is strongly advised. An overview of the various therapeutic options is explained in detail below (summarised in Table 24.2).

Appropriate Medical Therapy

Local/Intranasal

Rinsing

A cornerstone treatment of CRS, be it CRSsNP or CRSwNP, is nasal rinsing, next to intranasal corticosteroids (see below). Nasal rinsing is cheap, fast, patient-friendly and can be applied at every level of care, including self-care or primary care. A large number of trials have been performed to evaluate its efficacy. However, due to tremendous variations in rinsing properties (concentration of NaCl, use of other minerals or additives, rinsing volume, rinsing pressure, devices used, frequency, etc.), and due to methodological limitations, much remains to be elucidated at this point. However, there is solid enough evidence for nasal rinsing with isotonic saline or Ringer's lactate in CRS [1].

Table 24.2 Medical therapies for CRSsNP

Therapeutic option	Remarks
Nasal rinsing	Cheap, fast, patient-friendly. Evidence for isotonic saline or Ringer's lactate
Intranasal corticosteroids	Less effective than in CRSwNP but still supported by evidence in CRSsNP
Xylitol as rinsing additive	Reduces biofilms. Limited evidence (small studies) shows positive outcomes
Antibiotics (short courses or long term/ macrolides)	Very limited evidence and risk of cardiovascular morbidity Not supported or advised
Oral corticosteroids	No solid evidence. Not advised

Intranasal Corticosteroid (INCS)

Next to rinsing, the use of INCS in CRS is cornerstone treatment and should be considered 'mandatory' before any other step (including surgery) is considered. Many studies have addressed the value of INCS for CRS in general, but only four double-blind placebo-controlled randomized clinical trials (DBPCRCT) have assessed CRSsNP specifically after 1990. In 1992, Qvarnberg et al. described a randomised, double-blind study of 40 CRSsNP patients with chronic/recurrent maxillary sinusitis underwent a trial of a budesonide 200 μg b.i.d. aerosol ($n = 20$) or placebo ($n = 20$). All patients had saline antral irrigation and erythromycin. After 12 weeks, facial pain and sensitivity were improved in the budesonide group, but nasal blockage, discharge, and postnasal drip were comparable [4]. With the new classification of CRS in mind, it is quite possible that a component part of the patient cohort had localized disease, and not primary diffuse non-type2 CRS.

Twelve years later, Lund et al. published on a double-blind placebo-controlled randomised controlled trial (DBPCRCT) containing 167 CRSsNP patients without previous surgery, divided into two groups: budesonide nasal spray 128 μg b.i.d. ($n = 81$) or placebo ($n = 86$). After 20 weeks, a greater number of responders favoured budesonide over placebo with significant improvement of symptom score, whereas disease-specific quality of life was not different [5].

In 2010, Hansen et al. reported the results from their DBPCRCT on a small sample of 20 CRSsNP patients, all with previous sinus surgery. Fluticasone propionate 400 μg b.i.d. delivered

with a special device (n = 10) was compared to placebo (n = 10) for 12 weeks and showed a greater number of responders, an improved combined symptom score and less oedema (endoscopy score). Disease-specific quality of life and nasal discharge (endoscopy score) were not different [6]. Finally, in 2011, Mösges et al. performed a DBPCRCT in 59 CRSsNP patients without sinus surgery using mometasone furoate nasal spray 200 μg b.i.d. (n = 29) or placebo (n = 30) for 16 weeks. The number of responders favouring mometasone, symptom scores, and endoscopy scores all improved significantly compared to placebo [7].

Taken together, the studies support the use of INCS in CRSsNP, although the effects are less pronounced than in CRSwNP patients [1]. Given the excellent safety, availability, and ease of use, INCS should be considered a first-line treatment for CRSsNP together with nasal rinsing.

Xylitol

If saline rinses and INCS are not sufficient to gain disease control, one might consider the addition of xylitol to the rinsing fluid. This is especially true when thick, sticky discharge is found upon nasal endoscopy, which are signs of biofilm formation. Xylitol is a naturally occurring sugar alcohol with the ability to reduce biofilms. There is some limited evidence that rinsing with xylitol reduces patient-reported outcome measures such as a visual analogue scale (VAS) or the 22-item SinoNasal Outcome Test (SNOT-22). See Chap. 22 'New innovations and treatments' for more details.

Systemic

Antibiotics, Including Long-Term Antibiotics/Macrolides

Although short courses (<4 weeks) of antibiotics are prescribed frequently for (exacerbations of) CRS, both in primary and in secondary care, there is a lack of high-quality studies justifying such prescriptions. It is unclear whether patients actually benefit from them when compared to the natural course of an exacerbation, while there is a fair chance of adverse events, mostly gastrointestinal. For long-term courses of antibiotics, the same is true: there is limited evidence supporting its use. Despite a large number of open studies suggesting efficacy of long-term antibiotics, placebo-controlled studies, or studies comparing long-term antibiotics with INCS or surgery, hardly show positive outcomes [1]. However, most studies contain relatively small groups of CRS patients both wNP and sNP. Moreover, there is a variety in previous surgery, concomitant use of INCS, etc. hampering a good comparison.

The study by Wallwork is interesting because it evaluated only CRSsNP patients treated with macrolides (roxithromycin, n = 29) or placebo (n = 35) and showed significant effects on patient-reported outcomes and endoscopy, especially in patients with a low IgE [8]. This would suggest that in patients with primary diffuse non-type2 CRS, macrolides might be effective. However, they carry a significant risk of cardiovascular morbidity. As such, the use of long-term antibiotics/macrolides is not advised in CRSsNP until high-quality data is available. Such studies are currently being undertaken [9].

Oral Corticosteroids

Short courses of oral corticosteroids are often used in CRSwNP and have proven to be effective, albeit for short periods of time only [1]. This is in line with the steroid-responsiveness of the type 2 inflammatory endotype most seen in CRSwNP in the Western world. For CRSsNP, however, no PCDBRCTs exist on the use of oral corticosteroids. It is therefore not advised to use them regularly for CRSsNP, especially given the adverse effects [10]. Should there be doubt about the endotype of a CRS patient without nasal polyps with conflicting or borderline lab results concerning the endotype, one could try a course of oral corticosteroid to test for responsiveness. This situation will be the exception rather than the rule.

Surgical Management of CRSsNP

Should medical treatment fail to attain sufficient disease control, endoscopic sinus surgery (ESS)

might be necessary. Although randomized controlled trials comparing surgery with medical therapy are lacking for CRSsNP, there is a large body of literature regarding the role of ESS in CRSsNP. For a comprehensive overview, please refer to Chap. 6.2 of EPOS2020 [1]. It would be beyond the scope of this chapter to mention all of the studies here, but a few are worth discussion.

- The National Comparative Audit of Surgery for Nasal Polyposis and Chronic Rhinosinusitis in England and Wales followed 3128 patients who underwent ESS for CRS [11]. A significant and clinically important improvement of the mean SNOT-22 score was found, with greater improvement found in patients with CRSwNP compared with CRSsNP, although in both subgroups the effect was large. These effects were maintained up to 5 years after ESS [12].
- In a large systematic review, Smith et al. found 45 studies reporting on the effect of ESS for CRS. Although the majority consisted of low-level studies, all of them support the fact that ESS brings about significant changes in symptom scores and/or quality of life [13].

The goal of surgery, especially in CRSsNP, is to create a more open paranasal sinus cavity to which medical therapy can be more effectively distributed. It is therefore current and common practice to prescribe post-operative INCS and/or rinsing for CRSsNP. Patient counselling should at least include the expected reduction in symptom burden, the risk of complications (which is generally low), the rationale for surgery, and, hence, postoperative therapy, and the possibility of revision surgery. Headache is generally a poor indicator for surgery (see below).

Treatable Traits

Patients with CRSsNP can have comorbidities and/or traits that contribute to a worse disease outcome. Appropriate treatment of the CRS component should include addressing these comorbidities/traits. If a patient with CRSsNP fails to attain disease control with appropriate medical therapy (at least INCS and rinsing), attention should be given to the following:

- **Smoking**: smoking including second-hand smoking is a well-known risk factor for the development and maintenance of CRS [14]. Patients should be strongly advised to stop smoking and be offered sufficient help to do so.
- **Allergic rhinitis**: although the treatment of CRS consists of a number of steps also treating allergic rhinitis (AR), such as INCS, uncontrolled AR might hamper effective disease control in CRS. Test for the presence of sensitization to aero-allergens, and treat accordingly. If needed, allergen immunotherapy might be used to reduce the disease burden of AR [15].
- **Occupational exposure**: continued exposure to pollutants and irritants will lead to a reduction of disease control in CRS(sNP). There is evidence that patients with important exposure need surgery more often [2, 16, 17]. Inform about the occupational exposure of a patient with poor disease control, and counsel about its impact.
- **Asthma**: although CRSsNP only associates with early-onset asthma, and a large proportion of CRSsNP patients have no asthma at all, it is wise to inform about pulmonary complaints, especially when nasal symptoms persist despite treatment. When in doubt, refer the patient to a pulmonologist for further work-up.

Important Differential Diagnostic Considerations in CRSsNP

Secondary CRS

It is of utmost importance to consider a secondary aetiology in CRSsNP, at the first encounter when the diagnosis of diffuse CRS is made, and especially during follow-up in those cases that:

– Do not respond (properly) to therapy
– Have bleeding, crusting, pain, and/or loss of tissue as symptoms

– Are associated with symptoms in other organ systems (pulmonary infections, cough; skin rashes; joint pain, swelling; eye infections; etc.) or more generalized symptoms such as weight loss and fatigue

In such cases, additional investigations are warranted, which can be performed by the ENT specialist or can be performed by referring the patient to the proper specialty.

In case of a suspected underlying immunodeficiency, a full blood count, erythrocyte sedimentation rate, serum levels of IgA, IgG, and IgG subclasses should be determined. Additionally, functional antibody titres and vaccine responses could be assessed. If there is suspicion of a vasculitis, the presence of antinuclear or antineutrophil cytoplasmic antibodies should be measured, as well as organ-specific tests (e.g. kidney function) depending on patient history. Nasal tissue biopsies are advised as well, both from diseased mucosa as from areas with apparent normal mucosa. In such cases, beware of a possible abuse of cocaine. See also Chap. 44 'Granulomatous vasculitis and the cocaine nose'. In rare cases with (central) loss of tissue, a midline or natural killer/T-cell lymphoma can be diagnosed, although the histopathologic confirmation can be difficult and might require multiple biopsies.

The Patient with Headache

As CRSsNP patients often present with headache or facial pressure, a basic understanding of neurological headache syndromes is pivotal for an ENT surgeon. A thorough discussion of the full differential diagnosis of headache is beyond the scope of this chapter. Rather, a few clinically helpful hints are given:

1. If a patient complains of headaches and has no other sinonasal symptoms whatsoever, a non-sinonasal cause is most likely. This is also true when a patient can point to the exact location of the pain, and when this location happens to be in the region of some paranasal sinus.
2. Even if headache is accompanied by other symptoms such as nasal obstruction or discharge, it is only likely to be sinonasal in origin if the intensity of the headache is linked to that of the other symptoms and responds to nasal medical treatment.
3. Patients can have multiple simultaneous diagnoses: CRSsNP, headache from overuse of analgesics, and a primary headache syndrome (e.g. migraine) can occur together. This means that abnormalities upon nasal endoscopy and/or imaging are not an explanation for headaches per se.
4. Therefore, be very reluctant to perform surgery when headache is the most prominent symptom.
5. Some (rare) headache syndromes also present with nasal complaints such as congestion, rhinorrhoea, and lacrimation. These usually come in attacks/episodes and are predominantly unilateral. This is true for trigeminal neuralgia, paroxysmal hemicrania, and cluster headache. The last two are mostly seen in men, and the pain is experienced as very severe.
6. Always advice a patient who is regularly using analgesics for headaches to stop these drugs for a longer period of time to rule out medication overuse headache.
7. When in doubt, refer patients to a neurologist specialized in headache/neuropathies/facial pain. Often, a non-specialized neurologist will perform imaging, and if a (partial) opacification of one or more of the paranasal sinuses is found, the patient will be sent back because of a sinonasal cause.

Short Summary of Areas of Controversy or Uncertainty

- There is a great need for high-quality evidence on the effect of long-term antibiotics in patients with CRSsNP.

Key Learning Points

- Chronic rhinosinusitis without nasal polyps (CRSsNP) is an umbrella diagnosis; for bilateral disease, it roughly correlates with primary diffuse non-type2 CRS in the Western world

- The clinical picture and management of CRSsNP is distinct from CRS with nasal polyps
- Caution is advised for the use of antibiotics in CRSsNP
- Treatment-resistant CRSsNP might point to an underlying cause (secondary CRS) which warrants clinical suspicion and work-up
- Headache is a challenging symptom in CRSsNP and has a broad differential diagnosis; ENT surgeons should acquaint themselves with a basic understanding of neurological causes for headache. Be very reluctant to perform surgery when headache is the main complaint.

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25

Clinical Assessment and Management of Chronic Rhinosinusitis with Nasal Polyposis

Claire Hopkins and Jo-Lyn McKenzie

Introduction

The epidemiology of CRSwNP is regionally variable but is a globally prevalent disease. The incidence of nasal polyps increases with age to a peak in the sixth decade. The prevalence, based on endoscopic examination in a Swedish population, is estimated at 2.7% of adults and is twice as high among men as among women [1]. A South Korean study identified a population rate of approximately 5%.

Nasal polyps are very uncommon before the third decade of life; a diagnosis of polyps in childhood should prompt investigation for cystic fibrosis.

Although there is similar prevalence of CRSwNP in Sweden and South Korea, their inflammatory endotypes are distinct. CRSwNP in Western countries commonly presents with type 2 inflammation, whereas type 1 and 3 inflammation is more frequent in Asian countries despite polyposis [2]. Interestingly, reports have indicated that the incidence of type 2 inflammatory CRSwNP has increased during the past decade in some regions of Asia, together with an increase in nasal colonisation of *Staphylococcus aureus,* which has been postulated to drive inflammatory expression towards type 2 [3].

Risk Factors and Comorbidities

Comorbid respiratory conditions are commonly found in patients with nasal polyposis. Up to 60% of patients with polyps have lower airway disease, including coexisting asthma, typically with onset in adulthood [4].

The association between nasal polyps and allergic rhinitis is complex; nasal polyps are reported to be less common in those with allergic rhinitis and childhood-onset allergic asthma than in the general population. Allergic rhinitis and childhood asthma are strongly correlated with central compartment allergic disease, where polyps may be seen growing from the middle turbinate and septum [5].

Occupational exposure to dust has been described as a risk factor particularly in textile workers. Smoking does not seem to be a strong risk factor for CRSwNP, though alcohol may be associated with increased symptom burden. There are described genetic associations with higher rates of first-degree relatives affected [6].

C. Hopkins (✉)
ENT Department, Guy's Hospital, London, UK

J.-L. McKenzie
Royal Brisbane and Women's Hospital,
Brisbane, QLD, Australia

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Diagnosis and Assessment

CRSwNP is a diagnosis made through clinical symptoms and signs corroborated with imaging and nasendoscopic findings supportive of a local inflammatory process [7]. Hallmark symptoms are nasal congestion and hyposmia as well as nasal discharge, and to a lesser extent, facial pain and pressure. The symptoms must persist for more than 12 weeks and be supported by nasendoscopy findings of mucosal inflammation, discharge and polypoid changes to the mucosa, and/or computerised tomography (CT) imaging demonstrating nasal polyps [6, 7].

The clinical history is focused on the duration, frequency and severity of sinonasal symptoms and their impact on quality of life and ability to perform normal daily activities. Nasal obstruction is common, particularly when polyps are large and may be associated with sleep disturbance. Hyposmia or anosmia is also common. Nasal discharge anterior or posterior is variably present. Facial pain and pressure can be present but are not alone enough to make a clinical diagnosis [7].

Quantification of symptoms using a patient-rated outcome measure may facilitate assessment. The SNOT-22 is a widely used clinical scoring system considering common sinonasal and associated symptoms [8]. Assessment routinely determines the quality-of-life impact of the condition and response to interventions and also can be used to predict likelihood of benefit from interventions including surgery [9].

History needs to consider comorbid conditions such as allergic rhinitis and lower respiratory disease such as asthma and bronchiectasis. Establishing a respiratory diagnosis and the control of their disease is important in guiding therapy [4]. NSAID-induced wheeze or asthma exacerbations are an important point of history to help diagnose NSAID-exacerbated respiratory disease (N-ERD) for treatment and prognosis [10]. Patients may also report symptom exacerbation by alcohol.

Prior treatments trialled and the response of the patient to these can be informative for diagnosis and making management decisions. CRS with nasal polyps is often responsive to systemic steroids, whereas CRS without nasal polyps is less steroid responsive. It is important to assess the duration of response and level of control of the patients' symptoms in making treatment decisions. Identifying patients with poor disease control can inform progression to surgery or, after surgery, the need for revision or to consider other systemic treatment options such as corticosteroids and biologicals [7, 11]. Many patients may have already undergone surgery—the extent of prior surgery is usually apparent on CT imaging; a short duration of benefit is predictive of future risk of recurrence [9].

Clinical examination is focused on assessing the nasal airway patency and the presence or absence of polyps. Anterior rhinoscopy can establish severe polyposis and any concomitant anatomical cause of nasal obstruction. Expansion of the nasal bridge or orbital signs may be present in very severe CRS with nasal polyposis [12].

Routine Investigations

Nasendoscopy to examine the nasal mucosa is essential. The presence of pale to translucent nasal polypoid masses is the hallmark of CRSwNP, and mucopurulent discharge may also be present [12]. The degree of polyposis can be recorded by sites and grading of the polyps in relation to the middle turbinate and the nasal floor [7]. The most widely used scoring system is that described by Lildholdt et al., with each side of the nose being scores separately and graded from 0 (no polyps) through to 3 (large polyps reaching below the lower edge of the inferior turbinate) (Fig. 25.1).

Nasal endoscopy is essential in the rhinological examination and can inform of diagnosis as well response to therapy. It is a simple and well-tolerated part of the examination.

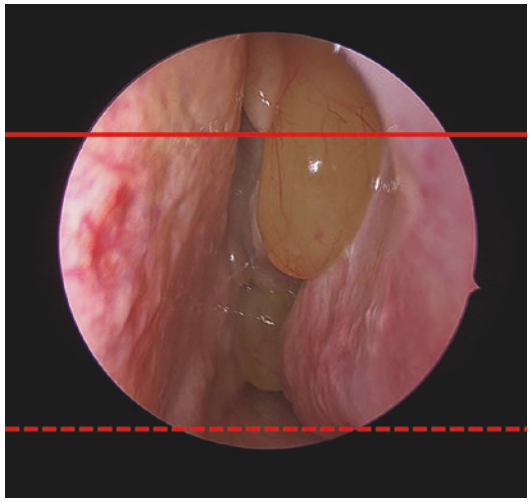

Fig. 25.1 Endoscopic image of left nasal cavity showing grade 2 nasal polyps, reaching below the lower border of the middle turbinate (solid red line) but not reaching below lower border of inferior turbinate

Imaging

Imaging is an important tool in CRS. It may be used to confirm the diagnosis when endoscopy is equivocal, assess the severity or extent of disease and guide treatment decisions. However, in order to minimise exposure to ionising radiation, it is usually reserved for patients in whom medical treatment has failed and when surgical intervention or biological therapies are being considered. It reveals anatomy and its variants for surgical planning and may alert to the possible diagnosis of allergic fungal disease and other diagnoses. Nasal polyps are usually bilateral – in the setting of unilateral nasal polyps, imaging should be considered at an early stage to exclude the rare occurrence of sinonasal malignancy or more common benign tumours such as inverted papilloma [12]. Computerised tomography (CT), usually without contrast, is the gold standard investigation for CRSwNP [7].

CT findings of importance include extent and severity of nasal polyps and mucosal changes. The most used scoring system is the Lund-Mackay which is based on the degree of opacification for the compartments of the sinuses and the ostiomeatal complex. This scoring system has been validated in several studies. The disease subtype can be suggested by CT findings particularly in allergic fungal disease with bony remodelling and double densities. The degree of osteoneogenesis in CRS indicates long-standing disease and poorer prognosis of treatment. Opacification of the olfactory cleft is common in patients with hyposmia [7, 12] (Fig. 25.2).

The anatomy revealed on CT sinus imaging reveals essential details for planning safe surgery including the presence of sphenoethmoidal cells, location of the optic nerve and anterior ethmoidal arteries and the position and integrity of the lamina papyracea and cribriform plate. CT is essential for safe and effective sinus surgery, and the scan should be available in the operating room [8].

MRI can reveal the presence of sinonasal inflammation. It is most useful in CRSwNP in the setting of allergic fungal disease or advanced disease with dehiscence of the skull base or orbits. MRI does not however provide the spatial and bony definition required for surgical planning [7, 13].

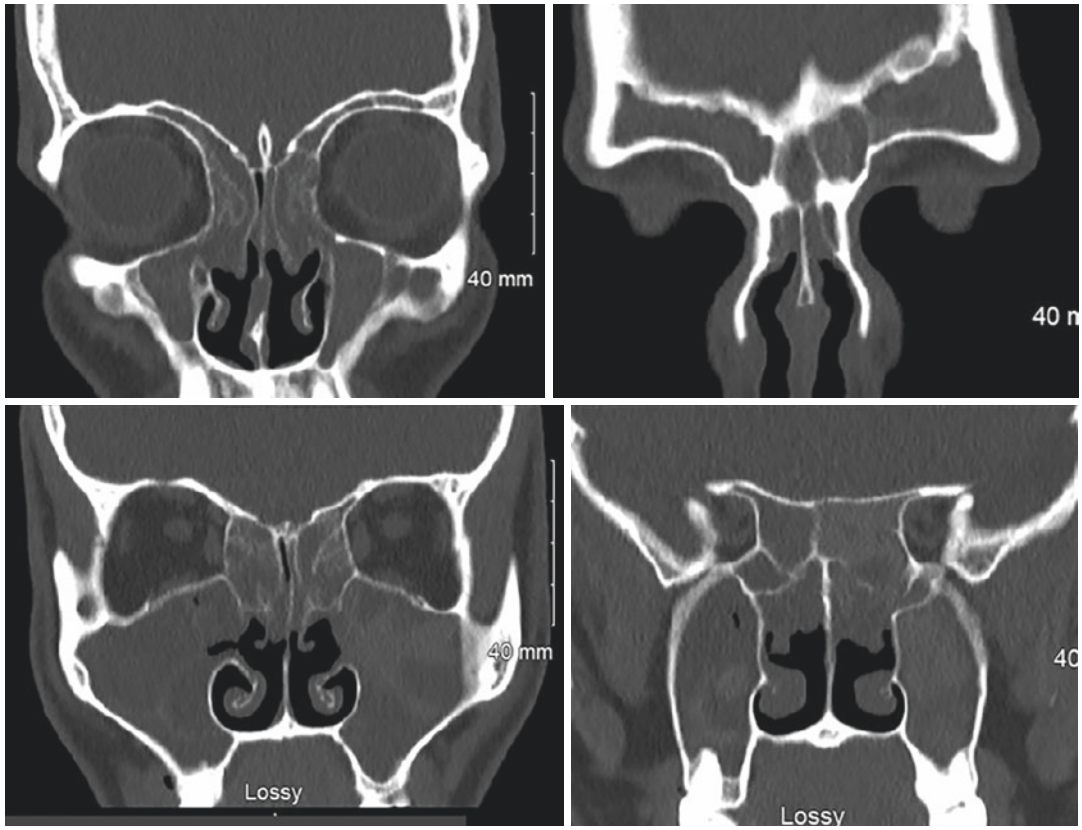

Fig. 25.2 Coronal CT demonstrating extensive opacification of all sinus groups in conjunction with nasal polyps

Supplementary Investigations

Peak nasal inspiratory flow can be measured to establish severity of nasal congestion and to follow treatment response with an objective measure. It is a low-cost and reliable clinical measurement [7]. Rhinomanometry is also available and computational methods under investigation. However, these measures do not predict response to treatment and are largely reserved for clinical trials.

Standardised testing of olfactory function can also be useful in the assessment of CRSwNP; psychophysical testing can assess identification, discrimination and threshold levels of olfactory function.

Nasal polyp biopsy performed in clinic or intraoperatively can help with disease endotyping and potentially informing prognosis and treatment. Patients with apparent CRSwNP occasionally have a different pathology such as inverting papilloma, sarcoidosis and even malignancy. Polyp biopsy helps avoid mismanagement of this rare but significant patient group and should be considered in the setting of unilateral polyps [12]. Diagnosing eosinophilic CRS (eCRS) requires quantification of the numbers of eosinophils, i.e. number/high-powered field (HPF) [3]. The amount of eosinophilic infiltration and the overall intensity of the inflammatory response were closely related to the prognosis and severity of disease [14]. With a move to disease endotyping to guide treatment, this may become a more standard part of patient management and may help guide treatment decisions (Fig. 25.3).

Blood tests are not always required in primary workup but should be done in patients with treatment-resistant disease or a suspicion of underlying inflammatory disease such as eosinophilic granulomatous polyangiitis or sarcoidosis.

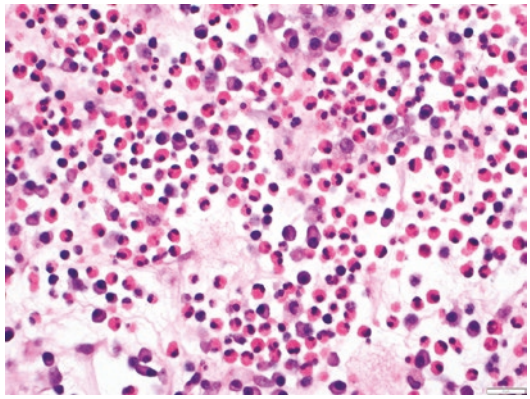

Fig. 25.3 Histological examination of nasal polyp removed from patient in Fig. 25.2, demonstrating more than 100 eosinophils per high-powered field

Patients with high blood eosinophils and IgE tend to demonstrate more aggressive and resistant disease, and there is a strong correlation between serum and tissue eosinophilia in CRS patients. Serum eosinophils are more readily assessed than tissue eosinophils; however, levels may reflect both upper and lower airway disease and can be supressed by recent steroid usage [3, 15]. Nasal nitric oxide measurements have been shown to aid diagnosis of cystic fibrosis and primary ciliary dyskinesia and similarly can be of utility in treatment-resistant or severe disease where these diagnoses are being considered [7].

Assessment of Comorbidities and Subgroups of CRSwNP

There are some distinct pathological subgroups of nasal polyps which can be observed in a group of related but distinct conditions, and which should be considered during assessment.

Central Compartment Allergic Disease

In the patient with allergic rhinitis, a central compartment allergic polyposis (CCAP) affecting the septum and middle turbinate is observed. This centralised anatomical pattern of nasal polyps is observed in those with inhaled allergen sensitivities and is distinct from wider sinus cavity polyposis of CRSwNP [5]. Skin prick testing or measurement of specific IgE can help identify potential targets for immunotherapy. The relationship between inhalant allergies and nasal polyps is less clear in other subtypes, but allergies may increase the severity of symptoms and therefore should also be controlled [4].

Allergic Fungal Rhinosinusitis

Allergic fungal rhinosinusitis (AFRS) is a form of a non-invasive fungal rhinosinusitis with IgE-mediated hypersensitivity to fungal hyphae in eosinophilic mucin. It appears an immunologically distinct subtype of CRS and is characterised by severe nasal polyposis and recidivist disease. The diagnosis is based on the criteria proposed by Bent and Kuhn: (1) production of eosinophilic mucin without fungal invasion into sinonasal tissue; (2) positive fungal stain of sinus contents; (3) nasal polyposis; (4) characteristic radiographic findings (with expansion of sinus cells and bony remodelling, and heterogenous opacification of the sinuses caused by eosinophilic mucin; and (5) allergy to fungi [16].

Asthma

Up to 60% of patients with CRSwNP have comorbid asthma; late-onset asthma is strongly suggestive of a type 2 inflammatory profile [1]. Asthma may be overlooked if cough is attributed to post-nasal drip. Uncontrolled nasal polyps may be associated with frequents asthma exacerbations; close co-management with respiratory specialists is important to optimise outcomes [17].

NSAID-Exacerbated Respiratory Disease

Non-steroidal anti-inflammatory drug-exacerbated respiratory disease (N-ERD) is characterised by the triad of CRS with severe eosinophilic nasal polyps, asthma and respiratory reactions triggered by the ingestion of substances

that inhibits cyclooxygenase [10]. The disease usually begins in the third decade of life with NSAID-induced reactions generally developing later and including an acute worsening of respiratory symptoms and nasal congestion. The disease in this patient group is usually severe and more rapidly recurrent after intervention [10]. The prevalence of N-ERD increases in patients with multiple surgeries [18].

A diagnosis of N-ERD can be made with a history of two clear reactions to NSAIDS, but many patients with asthma are told to routinely avoid such medications. When the diagnosis is uncertain, the patient could be considered for an aspirin provocation test which is done in an outpatient setting under medical supervision with capacity for resuscitation [10].

Immunodeficiency and Mucociliary Dysfunction

The testing of immune function in all patients presenting with CRSwNP is unlikely to be sufficiently informative to justify routine use.

Cystic fibrosis is commonly associated with polyps, and primary ciliary dyskinesia may also be encountered and should be considered in recalcitrant cases [7, 12].

Treatment of CRSwNP

Medical Management

Intranasal Treatments

Irrigation with nasal saline is a simple and central treatment recommendation for CRS. Despite a lack of high-quality trials, clinical experience suggests symptomatic benefit. It is low risk and therefore widely used and recommended [7, 19].

Topical steroids have robust evidence for improvement of symptoms in CRSwNP. The improvements are demonstrated as quality-of-life improvements as well as endoscopic assessment [20]. They deliver improvement in obstruction, rhinorrhoea, hyposmia and reduce polyp size. They are very well tolerated although can cause nasal irritation and epistaxis. Their long-term safety is well established [20]. New-generation corticosteroids such as mometasone and fluticasone have low systemic bioavailability and have high-quality safety data for long-term use [7]. Patients with high tissue eosinophilia have been demonstrated as the most responsive [14]. For moderately or severely symptomatic nasal polyps, clinical experience suggests that intranasal delivery of glucocorticoids may be improved using topical drops or, in patients who have had previous sinus surgery with open cavities, by high-volume irrigations [20].

The effectiveness of topical glucocorticoids is believed to be enhanced after surgery, likely owing to improved access. The delivery of glucocorticoids with high-volume nasal irrigation has been shown as more effective in reducing endoscopic evidence of recurrence than delivery of an equivalent dose by means of nasal spray after sinus surgery [21]. Other modes of delivery, such as breath activated exhalation delivery devices, may also enhance effectiveness [12]. Nasal steroid formulations are widely underutilised with a database study showing only 20% of CRS patients regularly use a nasal steroid [7]. Patients should be educated regarding appropriate delivery techniques and the need for long-term adherence to therapy.

Steroid-eluting stents have been developed for use before and after sinus surgery, with the aim of delivering higher local concentrations of steroids than other delivery methods and overcoming compliance issues. They have been in research and development without a significant uptake to date in clinical practice. In support of these stents, one trial showed significant reductions in polyp score and need for surgery following placement of a mometasone-eluting implant in patients with CRSwNP who were considered candidates for surgery, while other trials have shown no change in progression to requiring ESS [7]. Their use has been investigated postoperatively where improvement has been demonstrated in endoscopic and imaging scores but not in terms of symptoms of quality of life [20].

Systemic Therapy

Glucocorticoids

Glucocorticoids have a long history of use in airway inflammation; oral steroids have a body of strong evidence in this setting. They are effective in the management of CRSwNP reducing symptoms at least in the short term [22]. However, the immediate benefits of systemic glucocorticoid therapy need to be balanced with the long-term potential adverse effects which are significant. Therefore, systemic steroids should not be considered as a first line of treatment for CRSwNP (23)s. They can be used in a short course during 2–3 weeks as a last resort of treatment when combinations of other medications are ineffective [7].

The potential for adverse effects of glucocorticoids is well established. Severe outcomes include suppression of hypothalamic pituitary axis, hyperglycaemia, diabetes and Cushing's syndrome [23]. There are data to assess specific adverse effects in sinonasal patients. Multiple studies have shown injection of steroid or repeated courses to cause osteopenia. The effect of bone loss is well demonstrated in asthma literature. A recent consensus document has considered the wider range of potential side effects for OCS but still concluded that a clear assessment of the risks associated with oral steroid use in upper airway disease cannot be made. However, there is growing evidence from studies in asthma that patients receiving >2.5 short courses of OCS per year suffered significantly higher loss in bone density and a dose-dependent increase in all adverse effects, with as little as four courses over a lifetime being associated with harm [23].

Perioperative use of glucocorticoids has been explored and has mixed data. Some studies have shown benefit to reduce perioperative bleeding and improve surgical conditions for the surgeon during endoscopic sinus surgery; however, the reduction of blood loss is limited, and the risk of repeated systemic steroid use needs to be carefully considered; topical vasoconstriction and modern anaesthetic techniques usually mean preoperative treatment is of limited additional value. Only one of five studies on this topic found a conclusive benefit. This application is therefore to be considered with caution, given the growing evidence of cumulative risk of harm [7].

Antibiotics

The practice of using short-term antibiotics in CRSwNP is widespread in primary care despite a lack of evidence. Short-term doxycycline has demonstrated a small but statistically significant reduction in nasal polyp endoscopic scores and rhinorrhoea in one study. Long-term (>4 weeks) antibiotic use has been investigated and has limited utility in this disease group. Macrolides have not been demonstrated to improve symptom scores in CRswNP patients [24].

Anti-leukotrienes

Anti-leukotriene medications target the inflammatory pathway driven by leukotrienes. They have been investigated in CRSwNP and appear to have little added benefit in terms of symptom improvement when used as an add-on to intranasal corticosteroids [7]. There are described neuropsychiatric adverse effects, and so their use is not currently recommended. Some may have a role in N-ERD but have not been formerly evaluated in RCTs [10].

Biological Therapy in CRSwNP

Biologic therapy using monoclonal antibodies (Mabs) that block the action of interleukins (IL) or other targets central to type 2 inflammation now plays an important role in the management of difficult-to-treat asthma. Many of these treatments have also been shown to be useful in the management of severe CRSwNP [25]. Their placement in the therapeutic pathway for CRSwNP is in evolution as experience with the medications evolves. Consensus guidelines are

available and suggest they should be considered for patients with at least moderate symptoms or a moderate Lund-MacKay score who fail conventional medical and surgical treatment [26]. Their role in specific subsets of CRSwNP, such as AFRS and N-ERD, is yet to be clearly defined.

IL4/IL13 pathway activation is targeted by dupilumab, an IL4 receptor subunit Mab. It has been shown to improve symptom scores, nasal polyp scores, olfaction and imaging scores. The most common reported adverse events (nasopharyngitis, worsening nasal polyps and asthma, headache, epistaxis, injection-site erythema) were more frequent with placebo. The agent seems well tolerated in available trials [25].

Anti-IgE therapy with omalizumab has shown improvements in nasal polyp burden and symptoms scores. Associated adverse effects have been reported as anaphylaxis, arterial and venous thromboembolic events and an increase in common colds [26].

Both dupilumab and omalizumab have been approved by regulatory bodies for use in severe CRSwNP. Head-to-head comparisons are not available, but indirect comparison data currently favours dupilumab [27].

IL5 is targeted by the agents mepolizumab, benralizumab and reslizumab. Only mepolizumab currently has available evidence for reduced symptoms and decreased revision surgery in CRSwNP patients. There are no serious noted adverse effects [25]. More data is becoming available, although these drugs are currently only approved for use in asthma.

Although biologicals have been shown to reduce the need for surgical intervention for CRSwNP, their high costs and the need for long-term treatment mean that this is unlikely to be the most cost-effective treatment across the whole population with CRSwNP, even if superior in terms of long-term symptom control in the difficult-to-treat groups, such as those with severe asthma and N-ERD [26].

It is likely that there will be continued developments in this field, both in terms of the development of new monoclonal antibodies and understanding of response rates, and where in the treatment pathway, these should be optimally placed. In the future, biomarkers may allow us to personalise patient care by identifying which endotype would respond best to one monoclonal therapy over another resulting in substantially better clinical outcomes with fewer side effects than present treatment options. At present, biologics are being positioned as an alternative to repeated surgery, but in the future, they may be given much earlier in the disease process in an attempt to alter the natural history, or in combination with surgery, either in the immediate pre- or post-operative period [25].

Surgery for CRSwNP

Surgery for uncomplicated CRSWNP is usually restricted to those patients who fail to achieve adequate symptomatic benefit from a trial of adequate medical therapy [17]. What constitutes failed medical therapy is variable in the literature but at a minimum requires a sustained trial of intranasal saline and topical steroid, usually in conjunction with a trial of systemic corticosteroid [28]. In patients who fail medical treatment, surgical intervention acts to reduce the volume of inflammatory tissue, remove obstruction and optimise delivery of topical medication. It can be conceived as an adjunct to maximise effect of medical therapy but is not considered curative [8].

Several studies have shown the positive impact of surgery on improving symptoms, particularly in those patient groups with high baseline symptom scores [28]. More severe imaging scores are also associated with greater benefit from surgery [7]. Older patients benefit more with asthmatic and aspirin-sensitive patients having less improvement [9]. There is some data that earlier intervention with surgery relative to when symptoms started leads to better outcomes with more sustained improvements in symptom scores [7]. There is also some suggestion that earlier surgery reduces subsequent development of asthma [17].

Nasal congestion, obstruction and less so smell seem particularly improved by surgery. However, revision surgery is not uncommonly required even in tertiary centres. Prospective cohort studies report revision rates of 11% at 3 years and 19% at 5 years [9]. Female gender, older age at first surgery, the presence of nasal polyposis, comorbid asthma, allergy and family history of chronic rhinosinusitis all appear to be associated with high revision rates [17, 29].

The extent of primary surgery for CRSwNP is debated. Approaches can be described as minimally invasive, complete and extensive. A functional approach based on the ostial drainage pathways is well established as beneficial [7]. Heterogeneity between studies and lack of large randomised trials makes assessment difficult, but there is some evidence for more extensive sinus surgery especially in revision surgery [13]. Many series have more complete surgery applied to more extensive or recurrent disease introducing a significant confounder. Lower revision rates and greater improvements in symptoms have been demonstrated in complete sinus surgery cohorts such as those by Masterson and Deconde [9, 30]. Primary frontal sinus drill-out or a modified endoscopic Lothrop has been shown to decrease symptom burden and polyp recurrence in revision surgery and has some advocates for the primary setting of CRSwNP in selected cases, such as those with N-ERD [13, 31]. Most recently, there has been a proposal for removal of diseased mucosa, described as a sinonasal mucosal reboot, as opposed to mucosal sparing techniques, but further evidence is required to support efficacy [14]. The balance of extent of surgery must be discussed with and tailored to each individual patient.

Surgery carries a risk of potential severe complications including meningitis, intracranial or intra-orbital bleeding, leading to potential neurological deficit or blindness; one study identified the risk of such severe complications as 0.04%; however, significant bleeding or cerebrospinal fluid leak may occur in 0.9% of patients. The UK sinonasal audit reported the following complication rates; excessive bleeding 5% intraoperatively and 1% post-operatively, intra-orbital complications in 0.2% and CSF leak in 0.06% [7, 8].

Post-operative Care

Post-operative care of patients with CRSwNP undergoing endoscopic sinus procedures is important for optimisation of outcomes. Nasal saline irrigation 24–48 h after surgery has low risk and a good evidence base for improving postoperative symptoms and medium-term symptomatic outcomes [7]. Budesonide added to the postoperative irrigation has an increasing evidence base to support its use [21]. Post-operative debridement has shown to reduce synechiae formation but increases postoperative pain. Debridement improves post-operative endoscopic examination, reducing granulation and potential restenosis. This is especially true in patients with significant mucosa and bone removal with extended approaches. It is unclear if it has any long-term positive effects on symptoms or disease severity. Post-operative antibiotics have not demonstrated a benefit, and oral steroids have shown improved polyp scores but not symptom scores to date [7].

Management of specific subgroups requires a tailored approach. Those with a specific diagnosis such as granulomatous disorders, cystic fibrosis and ciliary dyskinesia require a multidisciplinary systemic treatment paradigm. Allergic fungal rhinosinusitis requires early and extensive surgical treatment to the affected compartments. There is no role for topical or systemic antifungals. Clearing the allergic mucin and releasing obstruction for irrigation topicalisation is the mainstay of treatment [16]. The need for more extensive and revision surgery is common. There is uncertainty around the role of medical management in this group, but oral as well as topical steroids can be an adjunct to post-operative treatment [7].

In the N-ERD group, there is some support for the use of adjunctive treatments such as aspirin desensitisation and leukotriene modifiers [10].

N-ERD patients suffer from poorer surgical outcomes compared to their non-N-ERD CRS counterparts, with shorter time to revision and a greater number of revision sinus surgeries in the N-ERD population. There are advocates for more extensive primary surgery including a modified Lothrop approach in N-ERD [31]. Surgery may be followed by aspirin desensitisation to reduce recurrence rates and improve symptom control [18].

Controversies: Current Pathways and Position of Novel Treatments

There is more data needed to guide optimal treatment of CRSwNP particularly with regard to the role and timing of surgery and new agents such as biologicals.

Better intranasal delivery of medication may further reduce the need for both surgery and systemic treatments; devices and drug-eluting stents continue to evolve. Long-lasting stents may overcome poor patient compliance that limits the effectiveness of such treatments.

There is a growing awareness of the risks of repeated use of systemic glucocorticoids which means that these cannot usually give more than occasional, temporary relief.

Surgery is effective in relieving symptoms in the short term and has a disease-modifying effect in that it may achieve better long-term control of disease by facilitating better delivery of topical steroids, particularly with more extensive surgery. Surgery therefore should be considered in patients who remain uncontrolled on INCS and in whom systemic glucocorticoids provide only short-term benefit.

Due to the costs, the need for ongoing treatment and unknown long-term side effects, at the current time, it seems reasonable to consider biologic therapy only in those patients with recurrent nasal polyps after surgery and adequate postoperative medical treatment; in those unfit for surgery; or where it may be predicted that surgery is unlikely to achieve adequate control. However, patient preference is an essential component to shared decision-making, and the risks and benefits of all options should be discussed.

There is some evidence to suggest that early surgery may achieve better long-term symptomatic improvements; similar analysis is required to assess the ideal time to introduce a biologic.

Disease endotyping and developing reliable biomarkers to guide treatment are further evolving as ways to create precision medicine to benefit patients suffering this common condition. It is likely that in the future, surgery will play only a limited role in the management of CRSwNP as we better learn how to address the underlying inflammatory disease.

Key Learning Points

- CRS is a common disease, and those patients with polyposis commonly have a type 2 inflammatory pattern with more difficult to treat disease.
- Diagnosis is formed based on history and examination revealing nasal polyps.
- Disease endotyping characterising the type of inflammation may guide treatment and prognosis of CRSwNP. Specific subgroups can be defined and receive tailored management strategies.
- The mainstay of medical therapy is intranasal corticosteroids. Oral steroids provide short-term benefit but have attendant risks.
- Biological drugs are emerging as effective if expensive agents in the management of difficult treat CRSwNP.
- Surgery is effective in CRSwNP and is generally reserved for patients with persistent symptoms despite medical management.

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Further Reading

Fokkens WJ, Lund VJ, Hopkins C, Hellings PW, Kern R, Reitsma S, et al. European position paper on rhinosinusitis and nasal polyps 2020. Rhinology. 2020;58(Suppl S29):1–464.

Primary Atrophic Rhinitis

26

Isma Z. Iqbal

Introduction

Atrophic rhinitis (AR) was first described by Fraenkel in 1876 [1, 2]. The condition is also known as atrophic rhinosinusitis, rhinitis sicca, rhinitis fetida and ozaena [1]. It is commonly found in tropical climates, Mediterranean areas, Latin and South America and Eastern Europe [3]. The incidence is between 0.3 and 1% in countries with higher prevalence [4]. There is a predominance in young and middle-aged adults. The condition is commoner in females with a ratio of 5.6:1 [5]. There is also an association with poverty and low social economic status. It is a chronic condition characterised by thick nasal discharge, dried crusts with a foul odour and paradoxical nasal blockage.

Aetiology

AR can be subdivided into primary and secondary:

Primary atrophic rhinitis (PAR): The aetiology is poorly understood. The commonest theory for development of PAR is chronic bacterial rhinosinusitis caused by *Klebsiella ozaenae*.

Secondary atrophic rhinitis (AR) is due to granulomatous conditions, radiotherapy to the head and neck, Sjogren's and previous surgery (empty nose syndrome).

The symptoms are secondary to progressive destruction of the ciliary mucosal epithelium due to atrophy of the exocrine sero-mucous glands and loss of underlying bone structures [1].

The factors blamed for its genesis are specific infections, autoimmunity, chronic sinus infection, hormonal imbalance, poor nutritional status, heredity and iron deficiency anaemia [6].

Primary atrophic rhinitis (PAR) has been reported in families where females are affected with a positive family history in about 15–30% of the cases [4]. Some studies have revealed either an autosomal dominant (67%) or autosomal recessive penetrance (33%) [7].

Iron and vitamin A deficiency have also been implicated. Oestrogen deficiency has also been suggested which may be consistent with the female preponderance.

Progressive metaplasia and atrophy of all mucosal components (epithelium, vessels, and glands) takes place because of increased osteoclastic activity, resulting in a volumetric decrease of sinonasal structures [8]. The histopathological picture consists of patches of squamotransformation of the normal respiratory epithelium which is pathognomonic for atrophic rhinitis seen in more than 80% of cases [9].

I. Z. Iqbal (✉)
The Newcastle Hospitals NHS Foundation Trust, Freeman Hospital, Newcastle upon Tyne, UK
e-mail: isma.iqbal1@nhs.net

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Whilst most cases have been attributed to *Klebsiella ozaenae*, other bacterial agents involved in the etiopathogenesis of atrophic rhinitis are *Pseudomonas aeruginosa*, *Coccobacillus foetidus-ozaenae*, Diphtheroids bacillus, *Haemophilus influenzae*, *Bacillus mucosus* or pertussis, and Proteus species [6].

Diagnosis

Symptoms

Patients typically present with progressively worsening nasal dryness and congestion, crusting and reduction in sense of smell with foul smelling nasal crusting. Less common symptoms include anosmia, headache and epistaxis. The anosmia is due to the atrophic process involving the olfactory epithelium as well as insufficient air reaching the olfactory areas due to crusting. Nasal obstruction is a combination of loss of pressure receptors in the nasal epithelium as well as large crusts blocking the air blast to the olfactory area in the roof of the nose. Epistaxis may occur as the crusts dislodge.

Signs

Endoscopic examination reveals a markedly large and wide nasal cavity, visibly dry mucosa and reduction in turbinate size [1]. There may be detectable fetor. Greenish yellow and black crusts of various sizes may be noticed lining the nasal cavities [4]. Palpation of the nasal mucosa may reveal loss of sensation. Nasal septal perforation and saddle nose deformity may occur in severe cases [4].

Other rare causes with similar presentation such as tuberculosis, leprosy, scleroma and syphilis should be excluded. If the disease progresses, chronic pharyngitis, otitis media with effusion or nasal deformity can also occur [10].

Blood Investigations

A full blood count may reveal a microcytic hypochromic picture (iron deficiency anaemia). A raised erythrocyte sedimentation rate (ESR) as well as raised autoimmune markers (ANCA, angiotensin converting enzyme, rheumatoid factor, anti-Ro, anti-La) are important in ruling out other diagnoses (granulomatous conditions, Sjogren's). The serum protein and plasma vitamin level estimations are necessary to exclude malnutrition.

Mucociliary Clearance

The mucociliary clearance with saccharin transit time (STT) demonstrates a prolonged time in PAR. Bist et al. reported the mean value of nasal mucociliary clearance in a control group was 9.92 ± 2.25 (mean ± SD) minutes, whereas in PAR, it was 42.82 ± 11.52 (mean ± SD) ($P < 0.0001$) [6].

Imaging

Because of the high incidence of concurrent sinusitis, CT is frequently included in the diagnostic evaluation of atrophic rhinitis [6]. The maxillary sinus is the most affected in PAR.

Pace-Balzan et al. [11] reported the following CT features in PAR:

1. Mucosal thickening of the paranasal sinuses
2. Loss of definition of the ostiomeatal unit (OMU) secondary to resorption of the ethmoid bulla and uncinate process
3. Hypoplasia of the maxillary sinuses
4. Enlargement of the nasal cavities with erosion and bowing of the lateral nasal wall
5. Bony resorption and mucosal atrophy of the middle and inferior turbinate

Management

The treatment of atrophic rhinitis aims to reduce the volume of the nasal cavity, promote normal mucosa regeneration using a Young's or modified Young's operation, lubricate the nasal mucosa or improve the vascularity of the nasal cavity.

Treatment is aimed at reducing the impact of the condition and preventing further deterioration rather than an intent to cure as this is unlikely to be possible.

Medical

Topical treatment is aimed at improving nasal dryness, crusting and overall symptom control. Several topical treatments have been advocated which are summarised in Table 26.1.

Local or systemic antimicrobial treatment should be commenced following nasal culture for bacteria or fungi [12]. Ciprofloxacin as well as rifampicin have been used to good effect. Frequently, these patients have colonisation of *Klebsiella ozaenae*. Commonly rifampicin 600 mg daily for 12 weeks or ciprofloxacin 500–750 mg for 8 weeks is utilised [12]. A randomised controlled trial comparing nasal submucosal injection of placentrex (human placenta) with oral rifampicin showed objective, subjective and histopathological improvement with maximum disease-free interval on regular follow-up with rifampicin [13]. Awad et al. [14] found rifampicin with mitomycin-C in alkaline saline wash has significantly better improvement in degree of crustations, severity of epistaxis and normalization of secretion than rifampicin and saline nasal rinse alone.

There is one study reporting successful treatment of PAR in a paediatric patient with antibiotic prophylaxis (trimethoprim–sulfamethoxazole) and saline irrigations for 6 months with no evidence disease recurrence or new infectious complications at 1 year [15].

Placental extracts injections inside the nasal mucosa may have the effect of narrowing the nasal fossae and to stimulate vasodilatation, but their effects disappear in approximately 8 weeks after the treatment [13].

Dexpanthenol spray, in a saline product, for patients with atrophic rhinitis was efficient, but

Table 26.1 Topical nasal treatment

Treatment	Action
Saline douche—alkaline, hypertonic, isotonic	Removal of crusts, allergens, inflammatory mediators
Glycerine-glucose (25%) drops	Inhibition of bacterial growth (lactic acid effect of glucose) stimulates commensal bacteria Glycerine anti-inflammatory, stimulates cell maturation, stimulates vasodilation and reduces crusts
Sodium bicarbonate and sodium diborate (Equal combination of the two) in Sodium chloride	Antiseptic and bactericidal effect as well as removing crusts
Dexpanthenol (ointment or spray)	Reduce transepidermal water loss, to activate in vivo and in vitro fibroblast proliferation, and accelerate the re-epithelialisation process
Sesame oil	Nasal moisture, improvement in the nasal ciliary beat frequency
Vitamin A oil	
Liquid paraffin nose drops	Lubricates nasal mucosa and removal of crusts. Long-term use not recommended due to reports of paraffin granulomas and inhalational lipoid pneumonias
Oestradiol in arachis oil (10,000 units/mL)	Vasodilator effects of oestrogen therapy
Kemicetine anti-ozaena solution (90 mg of chloramphenicol, 0.64 mg of oestradiol dipropionate, 900 IU of vitamin D2 and propylene glycol in each millilitre)	Antibiotic, vasodilatory and immunostimulant
Topical vitamin E	Anti-inflammatory, antioxidants, immunostimulants, stabilizing the cell membrane and promoting the skin barrier function

not superior in efficacy compared to placebo [16]. However, assessment of nasal breathing resistance and the extent of crust formation did improve with dexpanthenol.

Topical a-tocopherol acetate (vitamin E) in a study of 44 patients with PAR showed an improvement of the nasal dryness sensation and increased inspiratory nasal flow [17]. Rhinomanometric examination showed increase of nasal airflow at follow-up ($P < 0.05$); nasal mucociliary clearance showed a reduction in mean transit time ($P < 0.05$); and endoscopic evaluation showed significative improvement of hydration of nasal mucosa and significative decreasing nasal crusts and mucous accumulation ($P < 0.05$) [17].

A nasal obturator can reduce nasal dryness with minimal cosmetic implications. These can be made from a material called dimethylpolysiloxane or from an acrylic resin [18].

Surgical

Surgery is considered in patients that do not improve with medical treatment. Decreasing the nasal cavity size would prevent drying of the mucosa and crusting. Reducing the size of the nasal cavity or closure of the nasal cavity also promotes regeneration of normal tissue by reducing or removing exacerbating factors. Stellate ganglion injections to block its activity to cause nasal congestion and secretions have been reported. However, this technique is not currently used [4].

Reduction in Size of Nasal Cavity

Young's procedure as well as implants have been described. The implants may be autologous (bone, cartilage, muscle, fat), homologous (lyophilized bone, fat, human placenta extract) or synthetic (Teflon, acrylics, silicone, silastic). The major problems of their use are implant rejection, leakage and chronic infection of the implant [19].

Young described closure of the nasal cavity for AR [20]. However, this has an impact on quality of life and the risk of wound breakdown. A modified Young's technique was therefore introduced and has demonstrated a complete recovery in 50% ($n = 10$) patients [21].

In a study of 17 patients with AR whose nostrils were closed using a septal mucoperichondrial flap, 15 patients were cured of symptoms, but the exact outcome parameters were not specified [22].

Symptoms resolved in six patients following implantation of two plastipore plates into the floor of the nose and septum of both nasal passages in eight patients [19]. One plate extruded, but symptoms resolved with reimplantation.

Turbinate reconstruction with autologous costal cartilage implants in patients with PAR was effective in improving the SNOT-25 score (108 to 8/125) and CT sinus findings [8]. SNOT-25 is a modification of SNOT-22 and includes additional empty nose syndrome specific questions.

Regeneration of Nasal Tissue

An improvement in nasal symptoms, Sino-Nasal Outcome Test-25 (SNOT-25) scores and endoscopic findings has been reported following intranasal injection of platelet-rich plasma (PRP), but histology remained unchanged [23]. Injection of PRP in AR led to improvement in Nasal Obstruction Symptom Evaluation (NOSE), Sino-Nasal Outcome Test-22 (SNOT-22) scores and nasal mucociliary function [24] .

Conclusion

PAR is characterised by the formation of thick dry nasal crusts on a background of paradoxical nasal obstruction and foetor. It is common in tropical countries. Treatment is aimed at reducing symptoms and encouraging regeneration of tissue. Surgical treatment is considered once medical treatment is unsuccessful. Numerous surgical procedures have been described to

reduce nasal cavity size, promote regeneration of normal mucosa and increase lubrication of the dry nasal mucosa.

Key Learning Points

- Primary atrophic rhinitis (PAR) is a progressive chronic degenerative condition of unknown aetiology
- PAR is characterized by progressive nasal mucosal atrophy, wide nasal cavities with paradoxical nasal congestion and formation of viscid secretions and dried crusts with characteristic foetor
- Treatment of PAR aims to reduce the nasal cavity size, promote mucosa regeneration lubricating the nasal mucosa and improve vascularity of the nasal cavity
- Topical treatment to reduce nasal crusting and nasal drying is first line of treatment

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Fungal Sinus Disease

27

Christopher de Souza, Aishan Patil, Anish Patil, and Rosemarie de Souza

Introduction

Fungi are made up of several thousand species of eukaryotic spore-bearing organisms. More than 60,000 species of fungi are known. Fungi reproduce by both sexual and asexual means. Fungi are eukaryotic and are usually filamentous; they have no chlorophyll; cell walls are made of chitin. Two major groups of organisms make up fungi.

(a) Unicellular fungi are called yeasts.
(b) Filamentous fungi are called moulds

Yeast is unicellular and reproduces by budding; moulds coalesce as colonies of intertwined hyphae referred to as mycelia.

C. de Souza (✉)
Lilavati Hospital, Holy Family Hospital, Mumbai, India

Department of Otorhinolaryngology, SUNY Brooklyn, New York, NY, USA

Department of Otorhinolaryngology, LSUHSC, Shreveport, LA, USA

Mumbai, India

A. Patil
Specialist Registrar, Vascular Surgery, Dundee, UK

A. Patil
Royal Wolverhampton NHS Trust, Wolverhampton, UK

R. de Souza
BYL Nair Hospital, Mumbai, India

Of the 60,000 fungal species, only about 300 have been documented as playing a definitive role in causing disease in humans. These fungal pathogens largely belong to three major groups. They are (1) Zygomycetes, (2) Aspergillus species and (3) various Dematiaceous genera.

Fungi are ubiquitous organisms and reside primarily in the entire respiratory tract. Microscopic colonisation by fungi of the nose and paranasal sinuses can be found in both the normal and in the diseased states.

Diagnosing Fungal (Mycotic) Infections

Confirmation and identification of mycotic infection may require a combination of diagnostic studies (Table 27.1). Fungi are difficult to culture, and growth is often negative. However, PCR (polymerase chain reaction) of the sinus mucus is much more likely to detect and identify a pathogenic fungus [1, 2].

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Table 27.1 Diagnostic methods for detecting and identifying fungi

Investigation	Comments
Microscopy of fresh clinical specimens	Potassium hydroxide (KOH) preparations or Calcofluor white stains help identify the presence of fungi
Histopathology	Tissue samples retrieved from the affected area Frozen section should be considered for necrotic material and tissue biopsies Evidence of fungal invasion confirms the presence of 'invasive fungal rhinosinusitis'
Culture	Fungal cultures take a considerable period of time A positive culture may be present when invasive fungal infection is absent Cultures will identify a specific fungus and guide antifungal medication
Serology	
Polymerase chain reaction tests	
Radiological imaging	

Mycotic Infection

Fungal infections can pose major medical challenges [3]. The incidence of mycotic infection and the number and diversity of pathogenic fungi have all increased exponentially in recent times.

Five categories of fungal entities are recognised:

- Saprophytic colonisation
- Fungal balls (mycetomas)
- Allergic fungal rhinosinusitis
- Chronic invasive (granulomatous and non-granulomatous disease)
- Acute invasive

True fungal infection is subdivided into noninvasive and invasive, and manifestations may overlap or progress from noninvasive to an invasive form. The latter is a particular risk with a decline in host immunity, and the latter should always be considered and assessed. Compromise of the immune system greatly increases the risk of fungal infection. Immune competent individuals were previously considered as having no risk of progressing to invasive disease, but this is no longer true. In 2020, significant numbers of immunocompetent COVID-19 patients developed serious fungal infection, often caused by *mucormycosis*, especially following the use of high-dose corticosteroids.

How Do Fungi Cause Disease?

To cause an infection, the fungus has to first gain access via a portal of entry, attach to cells and grow within the host. They must be able to replicate at 37 °C, obtain nutrients and evade natural defence mechanisms [4]. For dimorphic fungi, this also means transformation of an initial morphologic conversion to a tissue form of growth.

The outcome of inhaling fungal spores depends upon several factors:

- The number and size of inhaled spores
- The integrity of the nonspecific and specific host defences
- The virulence/pathobiological potential of the particular fungus

Pathogenesis of Inflammation from Fungal Disease

1. Some fungi are capable of colonising epithelial tissues surfaces without causing invasive manifestations. Fungal rhinosinusitis is often characterised by colonisation rather than invasion. Colonisation induces profound inflammatory and immune responses resulting in severe damage to the host.
2. Occasionally, fungi cause serious human disease by producing potent toxins and mutagens.
3. Less potent fungal irritants and enzymes also attack host cells leading to inflammation or immunopathology.
4. Fungal cell wall antigens can also stimulate an allergic response in the host [5].

The status of the host immunity will ultimately determine whether the individual at risk will develop non-invasive or invasive fungal rhinosinusitis, and conditions like diabetic ketoacidosis serve to promote the latter.

Prevention and Prophylaxis of Fungal Infection

Prevention of fungal sinusitis in the immunocompromised patient includes:

- Minimising exposure to the fungi most likely to cause rhinosinusitis
- Using prophylactic antifungal agents to diminish the risk of tissue invasion

Risk Factors

Patients with haematologic disease are at risk during the neutropenic phase. The duration of neutropenia is the most important risk factor in leukaemic patients, but this risk increases with corticosteroids, broad-spectrum antibiotics and the choice of chemotherapeutic agents.

Bone marrow transplant recipients are at greatest risk in the immediate post-transplant period before engraftment and in graft-versus-host disease (GVHD). Chronic GVHD is associated with increased risk of invasive aspergillosis, especially with corticosteroid use [6, 37].

Prevention

The Environment

Fungi are ubiquitous, but exposure levels may increase in certain situations such as building work on old properties.

Hospital outbreaks are associated with direct contamination of the ventilation system, as may occur with demolition or constructive projects in or near to the hospital [7].

Hospital ventilation systems ducts should be cleaned regularly to prevent transmission of filamentous fungi, especially in units caring for immunosuppressed patients. High-efficiency particulate air (HEPA) filtration is recommended, but laminar airflow is not.

Prophylactic Antifungal Medications

Prophylaxis should be limited to patients likely to develop infection and should be given only during period of maximum risk.

The prophylactic drug should target the most likely fungal organism. As *Aspergillosis* species is the most common pathogen, medication should be directed at this pathogen [8]. Patients most at risk are those with haematologic malignancies and prolonged neutropenia and those who undergo bone marrow transplantation. The use of fluconazole to prevent invasive candidiasis in bone marrow transplant recipients has been a hugely successful advance.

Patients undergoing intense chemotherapy or bone marrow transplantation who have suffered a previous attack of aspergillosis are particularly at risk of infection, and whilst secondary prophylaxis is recommended, a third will develop a relapse of aspergillosis [9].

With regard to rhinosinusitis and immunotherapy, it is important to identify, diagnose and treat any sinus pathology before commencing immunosuppressant treatment. Sinus disease should be excluded or identified by radiological imaging scans. Rhinosinusitis following immunosuppressive therapy is more likely to occur with long-term antibiotic use, indwelling catheters, nasal intubation, systemic steroids and metabolic abnormalities [10].

Fungal Balls (Mycetomas)

Fungal balls, previously known as aspergillomas, are composed of matted fungal hyphae, typically within a single sinus.

Pathogenesis

A fungal ball is a non-invasive extra-mucosal condition that is typically unilateral and most often found in the maxillary sinus, followed by the sphenoid sinus. They are more common in older women but not described in children [11].

The histology characteristically shows a non-granulomatous inflammatory mucosal reaction with a tangled mat of fungal hyphae within the debris, most often caused by an overgrowth of *Aspergillus* spp.

This fungal overgrowth begins with persistent germinating fungal spores within the nasal cavity and paranasal sinuses. Aetiological factors include dental paste, amalgam and the presence of ferritin and zinc within the sinus lumen.

Fungal balls can form a community with bacteria to form bacterial or mixed balls; double balls describe a combination of a fungal ball and a bacterial ball coexisting within the same sinus [12]. Mixed balls are more likely in chronic rhinosinusitis and immunocompromised patients. Persistence of a fungal ball, despite adequate surgery, can occur secondary to a biofilm [13].

Patients are generally immune competent, but should they become immunocompromised, the condition can become invasive [14].

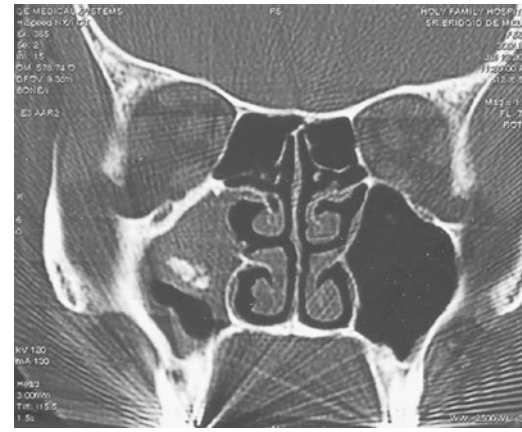

Fig. 27.1 Coronal view of a CT scan showing the typical appearance of a fungal ball in the right maxillary sinus as a hyperintense mass

Clinical Features

Symptoms normally include nasal obstruction, purulent nasal discharge, dysosmia and facial pain, similar to bacterial rhinosinusitis. Bilateral fungal balls have been described but present with symptoms such as foul odour and severe mucopurulent anterior and post-nasal discharge. Inflammatory polyps arise from the ipsilateral affected side of the nose in 10% of patients. A fungal ball may be associated with a mucocele, foreign body or an antrochoanal polyp.

Fungal balls within the sphenoid sinus can induce local inflammatory effects that cause non-specific headaches and occasionally ipsilateral visual symptoms.

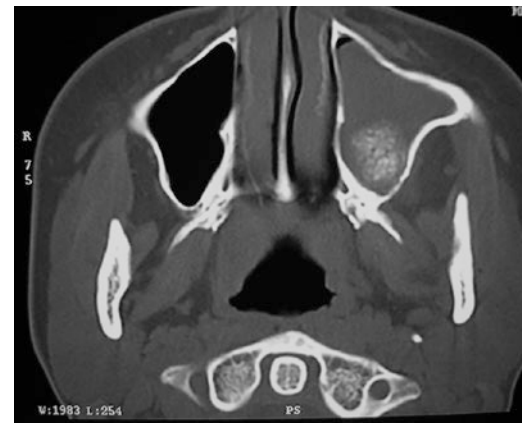

Fig. 27.2 Axial section of a CT scan showing a fungal mass in the maxillary sinus

Radiological Imaging

A CT sinus scan typically shows a heterogenous opacity: radiological features include central radiodense areas, sclerosis of the lateral sinus wall, bone erosion of the inner sinus wall and an irregular surface (Figs. 27.1 and 27.2) [15].

A sinus mycetoma ('fungus ball') may appear on CT as a mass within the sinus, with accompanying features such as erosion and calcification of the sinus [1]. On MRI, hypointense signal may be obtained from the fungus ball on T1- and T2-weighted scans. This is due to the relatively low free water content of the mycetoma.

In invasive disease, specific radiological signs may be seen. In the acute phase, it may be difficult to appreciate signs on CT scanning. If seen, non-contrast CT changes may include hypoattenuation of the mucosa and fat stranding beyond the sinuses. These features are not diagnostically specific, and CT changes should be correlated with the clinical picture. CT scanning is useful for assessing bony involvement. If localised bone destruction has occurred, we may see evidence of intracranial and intraorbital spread.

However, evidence of disease spread beyond the mucosa may be more easily appreciated on

MRI; thus, this is the modality of choice to assess invasion. Fat stranding and soft tissue involvement may be better visualised. Common locations to find fat stranding (on both CT and MRI) include intraorbital, masticator space and pterygopalatine fossa. MRI scanning can also help to identify important complications of invasive disease, such as meningitis, intracranial abscesses and cavernous sinus thrombosis.

Chronic invasive disease may demonstrate iso- or hyperdensity in the sinus spaces on CT, when compared to muscle tissue. Hyperdensity is not usually seen in the acute phase. T1- and T2-weighted MRI imaging may show low signal intensity.

Management

The definitive treatment of a fungal ball is surgical removal and clearance of the fungal debris from the sinus lumen (Fig. 27.3). Endoscopic surgery is usually effective, even if bacterial balls coexist, and is often combined with saline irrigation [16]. Recurrence is rare.

Should a patient be asymptomatic, the need for surgery could be questioned. However, surgery will confirm the diagnosis and prevent later problems should bacterial infection supervene. It may also prevent aggravation of asthma.

Surgery is indicated in symptomatic patients or those with immune suppression where a risk of invasive fungal disease exists.

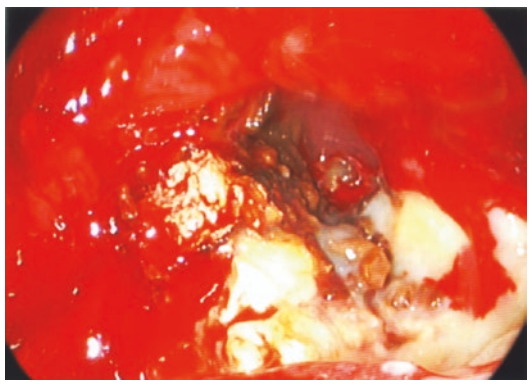

Fig. 27.3 Intraoperative appearance of the whitish mass of the fungal ball being evacuated from the maxillary sinus

Allergic Fungal Rhinosinusitis (AFRS) or Eosinophilic Fungal Rhinosinusitis

Allergic fungal rhinosinusitis (AFRS) was introduced in 1989 to describe a constellation of unusual findings in a unique group of patients suffering from chronic rhinosinusitis [17]. Fungal species of the dematiaceous species are the most common cause of AFRS.

The prevalence of AFRS is approximately between 5 and 10%, especially in younger age groups from 23 to 42 years. Paediatric patients present in a similar way as adults with AFRS. Patients with AFRS are, by definition, atopic; 27% show sensitivity to aspirin; about a third to half of patients have asthma [18, 19]. The condition is much more likely to be seen in hot humid environments and is unusual in cooler temperate climates.

Pathogenesis

AFRS is believed to have an aetiology, similar to that of allergic bronchopulmonary aspergillosis (ABPA).

AFRS is initiated when an atopic individual is exposed to an antigenic stimulus by inhaled fungi. The immunological response induces an intense eosinophilic inflammatory reaction that causes gross mucosal oedema, stasis of secretions and inflammatory exudates, obstructing sinus ostia, creating an ideal environment for fungi to proliferate. Antigenic exposure is thus increased, and the cycle becomes self-perpetuating.

The immunology is very similar to that of ABPA.

- A type 1 (IgE) and type III (IgG-antigen immune complexes) Gell and Coombs reaction takes place [20, 38].
- The Th2 CD4+ subpopulation of T cells, which are prominent in atopic IgE-mediated disease, cause escalation of inflammation.
- Interleukins 4, 5, 10 and 13 are released by the T cells: IL-10 suppresses the alternative Th1 response; IL-4 and IL-13 increase class switching of B cells to produce IgE molecules;

IL-3 and IL-5 enhance eosinophil maturation and activation.

A characteristic of the condition is allergic or eosinophilic mucin that propagates the allergic process. Secondary bacterial infection may occur, but fungi do not invade the underlying mucosa. Charcot Leyden crystals and fungal hyphae within a background of eosinophilic mucus are typical of AFRS.

Aspergillosis also impairs the hosts mucosal defences by suppressing the macrophage and T-cell response.

Clinical Features

Most patients with AFRS are young, atopic and immunocompetent [21]. AFRS is a subset of chronic rhinosinusitis with nasal polyposis in which all affected patients have nasal polyps, and these are typically extensive. Thick inspissated almost solidified eosinophilic mucus is characteristic of the condition. The condition can be exacerbated by septal deviation and turbinate hypertrophy. Unilateral disease is common and has been described in almost half of AFRS patients (now classified as a phenotype of primary localised chronic rhinosinusitis).

The ideal diagnostic criteria for AFRS are as follows:

1. Excessive eosinophilic mucin containing non-invasive fungal hyphae
2. Nasal polyposis
3. Characteristic CT scan radiographic findings
4. Positive fungal stain or culture
5. Type 1 hypersensitivity

Other typical characteristics of AFRS include the presence of asthma, unilateral disease, bone erosion shown on the CT scan, positive fungal culture, Charcot Leyden crystals and serum eosinophilia. Whilst the diagnostic criteria listed above seem clear, in practice, things may be not so simple. Patients often demonstrate all of the clinical characteristics, including the cheesy concretions that suggest fungal disease, but fungi are not always identified on staining or culture. This may be reflective of sampling and laboratory techniques but does cause a diagnostic dilemma and sometimes a pragmatic approach is required. Also, not all patients demonstrate allergy to fungi, but the term 'Allergic' FRS is so well established that it has been retained (EPOS2020).

Salient diagnostic investigations include:

Blood tests:

- Eosinophil count (eosinophilia 500+ cells per microliter; normal 100 - 500 cells/mcl)
- Total serum IgE (normal range 150 - 1000UI/L but commonly accepted normal 150 - 300UI/L)
- Antigen-specific IgE for fungal and other inhalant allergens
- Fungal antigen-specific IgG
- Precipitating antibodies for Aspergillosis (IgG precipitins)

Skin prick:

- Assessment of a range of inhalational allergens including fungal allergens

Histology:

- Microscopic evaluation of the mucin evacuated during surgery

Culture:

- Fungal culture of the mucus/debris evacuated during surgery

Radiological Imaging

The gradual accumulation of allergic fungal mucin gives AFRS a characteristic pattern on the CT sinus scan. As the mucus accumulates, the involved paranasal sinus begins to resemble a mucocele. The central high attenuation can at times be described as 'starry sky', 'ground glass' or a 'serpiginous' pattern. Sinus expansion and bone erosion are common features.

Management

The treatment of AFRS is thorough endoscopic clearance of polyps and eosinophilic mucin, combined with intensive long-term medication. The principle of surgery in AFRS is to provide sinus ventilation and drainage. However, surgery will not completely eradicate disease, and multiple operations may be necessary. This has subsequently led to variations in opinion as to how radical surgery should be.

Whilst some encouraging results have been described with the use of topical antifungal therapy, their use is inconclusive.

Core Message
The goals of surgery are:

- *To remove all mucin and fungal debris from within the sinuses*
- *To create permanent drainage and ventilation of affected sinuses*
- *To preserve the integrity of the underlying mucosa*
- *To provide access to facilitate removal of debris and mucin from previously inaccessible areas within the nose and sinuses*

Chronic Invasive Fungal Rhinosinusitis

Chronic invasive fungal rhinosinusitis typically occurs in healthy immunocompetent individuals. Fungi reside in all sections of the respiratory tract [22]. Some authors [23] have further divided the chronic form into granulomatous and non-granulomatous forms.

Pathogenesis

Whilst there is general agreement that Aspergillus is often a secondary invader of a diseased sinus, it is not clear why certain immunocompetent individuals develop invasive disease. Some speculate that a hot dry climate in individuals with nasal obstruction predisposes to Aspergillus infections. Others believe that anaerobic conditions in the sinus, caused by repeated inflammation, predispose the patient to invasive fungal disease.

The condition can be granulomatous or non-granulomatous. The formation of a granuloma requires an indigestible organism and cell-mediated immunity to be directed towards the inciting agent.

Granulomatous chronic invasive fungal rhinosinusitis: This has been described as granulomas composed of eosinophilic material surrounded by fungus, giant cells, variable lymphocytes and plasma cells [24].

Non-granulomatous chronic invasive fungal rhinosinusitis: This is characterised by tissue necrosis, dense fungal hyphae and scanty inflammatory infiltrate. The fungi in this form may breach mucosal barriers to invade blood vessels or just cause arteritis without vascular invasion.

Ultimately both granulomatous and non-granulomatous forms can result in tissue necrosis.

A new classification, based on mucosal invasion in the absence of angioinvasion, has implications on the use of adjuvant antifungal therapy [25]. Histology of the sinonasal mass typically shows periarterial invasion, without direct involvement of fungal elements or no true vascular invasion. Three histological variants are described:

- Proliferative (granulomatous pseudotubercles in a fibrous stroma)
- Exudative necrotising (with prominent foci of necrosis)
- Mixed

Patients suffering from chronic invasive rhinosinusitis are usually immunocompetent. Extensive investigation to uncover any hidden immunological abnormality has proved negative, and no specific immunological defects have been detected. However, patients with the granulomatous type of disease have been shown to have a cutaneous type 4 hypersensitivity (delayed skin reaction) to aspergillus antigen that is not demonstrated in those with non-granulomatous disease [24].

Clinical Features

Patients typically present with a history of chronic rhinosinusitis symptoms, respiratory tract allergies or nasal polyposis. Symptoms may take months even years to present.

Nasal examination reveals severe nasal congestion, polypoid mucosa, a soft tissue mass that is usually covered with debris or thick inspissated nasal secretions.

Radiological Imaging

An early CT sinus scan is recommended in the initial stages of the disease. Fungal colonisation induces focal or diffuse areas of hyper-attenuation within a sinus. Characteristic features of the invasive process include bone erosion or expansion.

MR imaging is useful to determine if dural involvement or invasion has taken place. Differentiation between a malignant neoplasm and chronic fungal rhinosinusitis may be difficult and should be confirmed by biopsy and histopathology.

Management

The current recommendation is that surgery to remove all diseases where feasible is indicated for both granulomatous and non-granulomatous invasive fungal disease. Surgery should be followed by prolonged courses of amphotericin B and itraconazole.

Whilst the granulomatous form responds well to surgery, it has been suggested that the non-granulomatous form responds best to an aggressive surgical approach [26, 27].

Core Message

There is no general agreement on the extent of surgery necessary to control, arrest or eradicate chronic invasive rhinosinusitis. Neither is it clear if the granulomatous form be treated differently from the non-granulomatous form.

Treatment and outcomes depend on the correct identification of the fungus as well as the specific treatment measures administered.

Invasive Fungal Rhinosinusitis in the Acquired Immunodeficiency Syndrome (AIDS)

The increasing prevalence of AIDS has left patients suffering from this problem at great risk of suffering from fungal infections. Since these patients are immunocompromised, the infections that they suffer are usually serious and have poor outcomes.

Aspergillosis is the most common pathogen in AIDS patients. It usually causes arterial invasion, thrombosis and subsequent necrosis of tissue. *Aspergillus fumigatus* is the most common pathogen isolate in the AIDS population.

Infection by HIV causes selective depletion of CD4 (T helper) lymphocytes. Although impaired cellular immunity predisposes to fungal and intracellular bacterial infections, phagocytic polymorphonuclear cells and macrophages are the primary defences against fungal infections, killing the mycelial and conidial forms of the fungus. However, AIDS patients demonstrate neutrophil and macrophage dysfunction.

Fungal rhinosinusitis has been found to be associated with advanced AIDS and low CD4 cell counts. Neutropenia is the single greatest factor predisposing to the development of invasive fungal sinusitis in patients suffering from AIDS [28].

Core Message

In immunocompromised patients suffering from AIDS and invasive aspergillosis infection, the treatment outcomes improve once the infection has been identified and effective treatment has commenced.

Acute Invasive Fungal Rhinosinusitis

Acute invasive fungal rhinosinusitis is a term used when vascular invasion is the predominant histopathological feature, and the duration of the disease is less than 4 weeks [29]. Patients present with acute invasive rhinosinusitis and are frequently found to be immunologically compromised. A new phenomenon seen during the COVID-19 pandemic was a significant rapid increase of mucormycosis in India, caused probably by the temperate climate, over-the-counter systemic steroids, diabetes mellitus and other immunosuppressants.

Aspergillosis

Aspergillosis refers to several forms of disease caused by dissemination of airborne fungal spores in the genus *Aspergillus* spp.

Pathogenesis

Aspergillosis spores enter the body primarily through inhalation but can also lodge in the eye and ear. Immune suppression is crucial in the susceptibility of this disease, and the increase in organ transplantation has greatly increased the number of patients vulnerable to fungal infections. Transplant recipients, particularly those receiving bone marrow and heart transplants, are highly susceptible to infection by aspergillosis.

Clinical Features

The condition lacks distinctive symptoms and is probably underdiagnosed and under-reported. It primarily affects the lungs but can lead to disease in the nose, paranasal sinuses, eyes and ears. The severity of illness is variable, but it can be significant and lead to death.

Radiological Imaging

Affected patients will need the usual combination of CT scans and MRI scans.

CT scanning is the imaging modality of choice. Typically, radiodensities with calcification in it are very suggestive of aspergillosis [30]. Bony erosions are also seen. Frequency sites involved are the maxillary sinus, nasal cavity, ethmoid sinuses and last the orbit and cavernous sinuses. Cone bean CT scans used by dentists have been found to be useful in the diagnosis of asymptomatic aspergillosis infections that are discovered as incidental findings [30, 31].

Management

Treatment of aspergillosis will depend upon the form of aspergillosis. In patients with a mycetoma, amphotericin B is the first line of treatment, and surgery is likely to be indicated.

Serum galactomannan measurements facilitate early diagnosis and also helps discriminate various fungal species, with levels being high in aspergillosis but not in mucormycosis [32].

The prognosis will depend on the underlying medical condition: if the problem is primarily an allergic response, then the patient should respond to systemic steroids, but the prognosis of invasive aspergillosis is quite poor.

Mortality rates range from 50 to 95%, with the higher mortality risk affecting patients with bone marrow transplants those with AIDS.

Mucormycosis

Mucormycosis is a term used to refer to any fungal infections of the order Mucorales which belong to the class of Zygomycetes. *Rhizopus oryzae* is the predominant pathogen and accounts for 60% of all forms of mucormycosis. It accounts for 90% of rhinocerebral mucormycosis.

Mucormycosis rarely affects a healthy individual but is likely to affect diabetics or immunocompromised patients [33].

Pathogenesis

All fungi of the order Mucorales reproduce sexually as well as asexually. Members of the family Mucoraceae have characterised sporangia which envelops numerous asexual spores.

Mucormycosis may have an acute fulminant course or a slower indolent invasive course. When immunocompromised is not easily reversible, then the course of the disease is aggressive and rapid.

Diabetics presenting with ketoacidosis are disproportionately affected [34]. Rhizopus organisms have an active ketone reductase system and thrive in high glucose acidotic conditions. Diabetics also have decreased phagocytic activity because of an impaired glutathione pathway. Normal serum inhibits the growth of *Rhizopus*, whereas diabetic ketoacidosis stimulates growth [35].

Patients on dialysis treated with deferoxamine B(DFO), an iron and aluminium chelator, are more susceptible to mucormycosis.

Other risk factors are prolonged neutropenia, long-term systemic steroid therapy, protein calorie malnutrition, bone marrow transplantation, immunodeficiency, leukaemia and intravenous drug users.

The relative infrequency of mucormycosis in AIDS reflects the ability of neutrophils to prevent growth of the fungus.

Histological Investigations

Blankophor and Calcofluor white are fluorescent whiteners that bind to chitin and cellulose and fluoresce when exposed to ultraviolet light.

A diagnosis of mucormycosis can be made on histological examination of specimens from a diseased patient but can be difficult and challenging. Histopathology demonstrates that the fungus has a distinct predilection for vascular invasion and predominantly arterial invasion.

Broadband ribbon like hyphae 10–20 microns branched haphazardly along with the absence of septations. Mucor stains easily with haematoxylin and eosin stains. To confirm the presence of a fungal infection, nonpigmented hyphae showing tissue invasion must be demonstrated. This can be seen on tissue sections stained with haematoxylin-eosin (HE), periodic acid Schiff (PAS) or Grocott-Gomori methenamine-silver (GMS) stains. The historically described 90° branching angle of Mucorales in tissue versus the 45° branching angle of septate moulds can at times be difficult to identify because of tissue processing during staining.

Clinical Features

The leading symptom is fever. This is quickly followed by ulceration in the nose followed by necrosis, periorbital, facial swelling or decreased vision (Figs. 27.4 and 27.5). Ultimately, approximately 80% develop a necrotic lesion on the nasal mucosa. Facial numbness is also present in some patients. The significance of anaesthesia of the affected facial areas is an early sign of invasive mucormycosis. Cutaneous and soft tissue involvement by mucormycosis is a common manifestation of the disease in immunocompetent patients.

Headache, fever, proptosis and blackening of tissues in and around the nose are very typical of Mucor infections.

In addition to the clinical features, the diagnosis of Mucor is dependent on radiological imaging, mycological investigations and biopsies for histology.

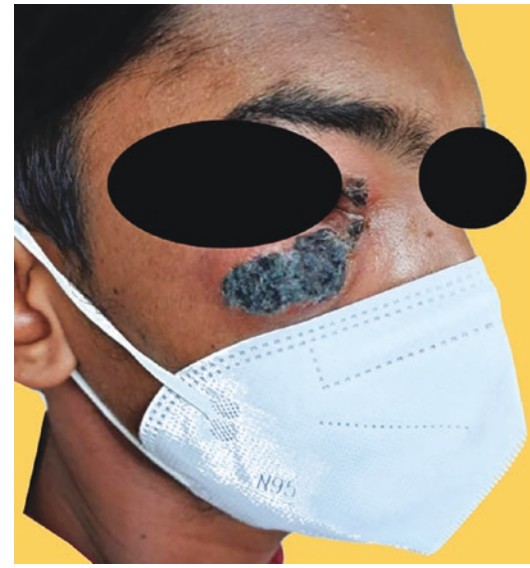

Fig. 27.4 Mucor involving the skin of the cheek and nasal cavity and also extending into the eye. The patient is not obviously obtunded. The patient had COVID 19 and was treated with high doses of steroids for a prolonged period of time. Surgical debridement along with antifungal medication was the treatment modality given

Fig. 27.5 A patient suffering from extensive mucormycosis. The patient suffered from COVID-19 and was treated with high doses of steroids. The patient succumbed to the disease

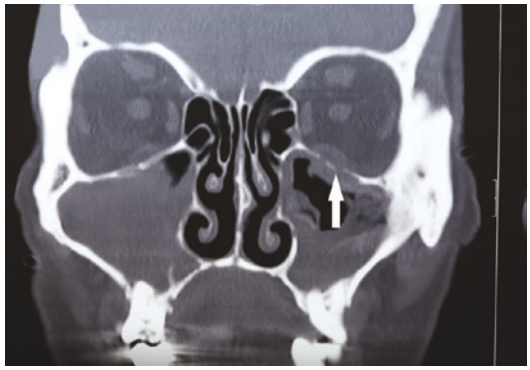

Fig. 27.6 CT scan of a patient suffering from mucormycosis. The white arrow points to the erosion of the orbital floor by the fungus. Of note is the normal looking nasal cavity even though both maxillary sinuses are involved by mucor

Radiological Imaging

CT scanning is imperative though MRI is much more sensitive (Fig. 27.6).

Management

Surgery alone is not curative, and a combined approach is necessary, including:

- Reversal of immunosuppression
- Systemic amphotericin B, isavuconazole, posaconazole as salvage or second-line treatment
- Repeated aggressive surgical debridement until infection and tissue destruction resolves

Hyperbaric oxygen: This has also been reported to be a useful adjunct and reverses ischaemic acidotic conditions that cause fungal infections to perpetuate. Hyperbaric oxygen is usually given daily for 1 hour at 2 atmospheres and may require up to 30 sessions. Hyperbaric oxygen limits the area of deformity by decreasing the required area of debridement without affecting mortality.

Amphotericin B is fungicidal and the drug of choice but also very nephrotoxic. However, liposomal amphotericin is not nephrotoxic and also well tolerated.

Recently, isavuconazole has been used as first-line medication with good results and posaconazole as a second-line treatment for salvage [36].

Mortality in diabetic patients is dependent on diabetic control; survival ranges from 60 to 90% but decreases to 20% unless impaired immune competence is addressed.

Core Message

The mainstay of therapy is:

- *Reversal of Immunocompromisation*
- *Systemic high dose of amphotericin B with isavuconazole using posaconazole for second-line salvage treatment.*
- *Surgical debridement/nasal toilet of nonviable tissue. This may need to be performed several times.*

Key Learning Points

- Fungi are ubiquitous microorganisms, exposure cannot be avoided, and spores are easily inhaled.
- Host exposure is critical if the immune response is compromised.
- Full assessment requires radiological imaging by CT and MRI scans.
- Invasive fungal rhinosinusitis is typically caused by aspergillosis or mucormycosis.
- The treatment for invasive fungal rhinosinusitis is a combination of repeated surgical debridement and antifungal medication.
- Repeated endoscopic clearance of necrotic tissue and fungal debris is effective.
- Amphotericin B is a nephrotoxic fungicidal, but liposomal amphotericin is safe and not nephrotoxic.
- Isavuconazole and posaconazole are new antifungal azoles.

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Frontal Sinusitis

28

Cara Morris and Richard J. Harvey

Introduction

The concept of frontal sinusitis is exceptionally broad. Describing its presentation, aetiology and management is as extensive as describing the concept of a mucosal disease of the lung apex. There are many varied presentations and aetiologies.

Frontal sinusitis can occur as an isolated phenomenon, generally from anatomical compromise, but much more commonly as a part of a broader condition involving other anatomical subsites of the paranasal sinus cavity. In this chapter, we set forth the authors' philosophy and approach to the frontal sinus in acute rhinosinusitis (ARS) and in chronic rhinosinusitis (CRS) by each of the subtypes defined in the EPOS2020 classification system [1].

Definition and Concepts

Acute Frontal Sinusitis

ARS of the frontal sinus can be considered in three groups: the most common (80%) being acute viral rhinosinusitis, likely as a result of the common cold [2]. Typically, this is a self-limiting disease lasting approximately 10 days.

A second group (18%) suffers from acute postviral rhinosinusitis whereby symptoms typically exceed 10 days but not lasting 12 weeks [3].

The final much smaller group identified (0.5–2%) is acute bacterial rhinosinusitis, which presents with fevers, severe pain, almost always unilateral involvement, raised inflammatory markers and a characteristic second peak of illness [1, 4]. Complications of acute frontal sinusitis, from

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C. Morris
Rhinology and Skull Base Research Group, St. Vincent's Centre for Applied Medical Research, University of New South Wales, Sydney, NSW, Australia

Department of Otolaryngology, Head, Neck and Skull Base Surgery, St. Vincent's Hospital, Sydney, NSW, Australia

Sydney ENT clinic, Darlinghurst, NSW, Australia

R. J. Harvey (✉)
Rhinology and Skull Base Research Group, St. Vincent's Centre for Applied Medical Research, University of New South Wales, Sydney, NSW, Australia

Faculty of Medicine and Health Sciences, Macquarie University, Sydney, NSW, Australia

Department of Otolaryngology, Head, Neck and Skull Base Surgery, St. Vincent's Hospital, Sydney, NSW, Australia

Sydney ENT clinic, Darlinghurst, NSW, Australia
e-mail: Richard@richardharvey.com.au

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infective thrombophlebitis, if not adequately managed may be serious and life-threatening.

Chronic Frontal Sinusitis

The classification and management of CRS, with or without frontal sinus involvement, are moving away from a polyp-phenotype to a system based on presumed pathophysiology. This in turn streamlines management to focus on the causative mechanisms. This is outlined in the EPOS 2020 guidelines and better directs management pathways for long-term control.

Primary and Secondary CRS

Pathogenesis of CRS may be characterised as primary or secondary causative mechanisms. Primary CRS is defined as a primary inflammatory disorder which is limited to the respiratory system, which results in sinonasal mucosal disease (Fig. 28.1).

In secondary CRS, sinonasal disease is secondary to another process (Fig. 28.2) [5]. Here it is more about managing the underlying condition rather than the sinus, and thus the focus in this chapter is on primary CRS.

Localised or Diffuse

Both primary and secondary CRS are further defined by its anatomical distribution (localised or diffusely involved).

Anatomically localised CRS demonstrates isolated involvement of the functional anatomical unit whilst sparing the contralateral and sometimes adjacent sinus cavities. In frontal sinusitis, this often incorporates the osteomeatal complex (OMC), ipsilateral anterior ethmoid and maxillary sinus. It is almost always a unilateral phenomenon and highlights that these patients are likely to have an anatomical issue at the frontal recess or OMC in pathogenesis.

In anatomically diffuse CRS, changes observed do not follow functional anatomical groups but instead are diffuse in nature. They are related to inflammation rather than anatomical abnormalities. Diffuse CRS is almost always bilateral and across multiple unrelated functional units in the paranasal sinuses.

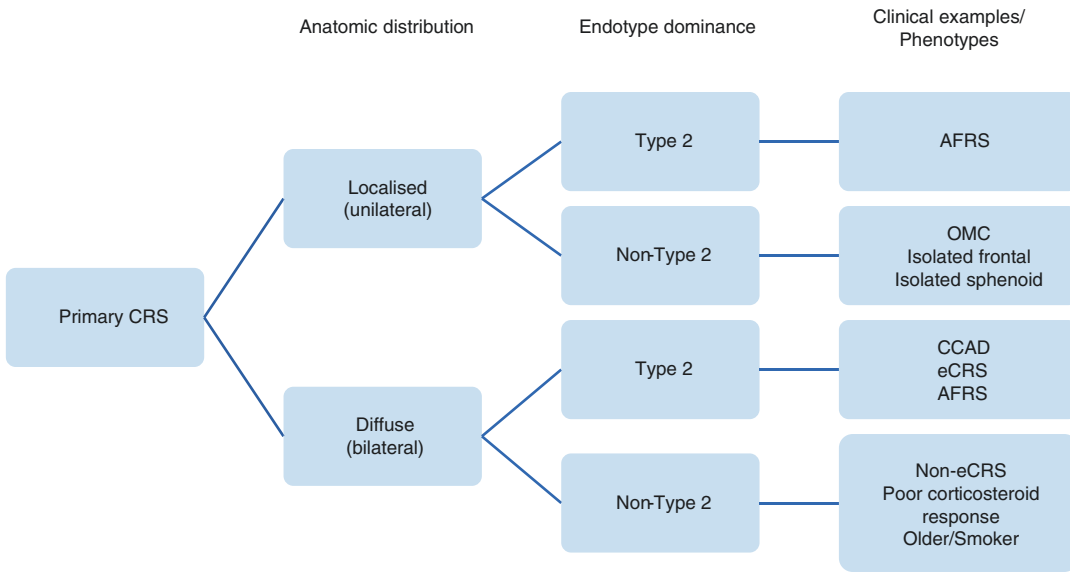

Fig. 28.1 Classification of primary CRS (adapted from Grayson et al. [5])

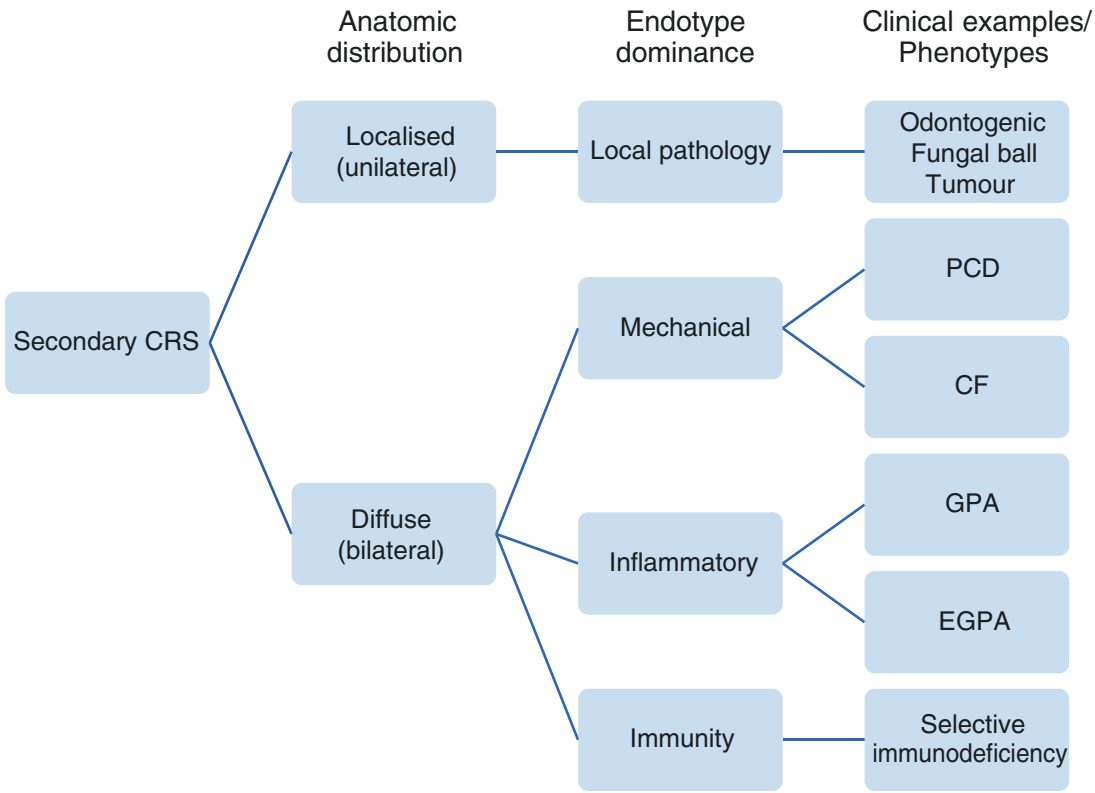

Fig. 28.2 Classification of secondary CRS (adapted from Grayson et al. [5])

Endotype Dominance

CRS is then further characterised at the mucosal level by the dominant type of immune response triggered by the causative antigen. Inherently, immune responses across mucosal barriers trigger alternate molecular pathways to address specific pathogens; Type 1 responses target viruses, Type 2 parasites and Type 3 extracellular bacteria and fungi. These responses subsequently produce tissue inflammation and repair. A dysregulation of these immune responses are thought to be the pathophysiological driver behind many diseases.

In CRS, Type 2 immune responses drives severe nasal polyposis most commonly, and resultantly have been the target of much therapeutic research [6]. Thus, the current system divides CRS into Type 2 and non-Type 2 as this also reflects the current range of therapeutic options as well as the knowledge base.

Anatomy

The management of frontal sinusitis is challenging due to its anatomical location which is not readily accessible, proximity to the orbit and brain and the ease of surgical disorientation. It is highly variable in its size and structure, and it relies on the integrity of its drainage pathway through the lower sinonasal cavity to correctly function [7]. Understanding and confidently identifying fixed anatomical boundaries is essential for safe frontal sinus surgery. These being the nasofrontal beak anteriorly, the posterior table and ethmoid roof posteriorly, the orbital wall and roof laterally and the middle turbinate/intersinus septum medially. This is the concept of the vertical box (Fig. 28.3a) [8].

Inferiorly, the frontal sinus is funnelled down to an area referred to as the ‘ostium’, but it is really a transition zone between upper ethmoid and frontal sinuses. It is here where the vertical

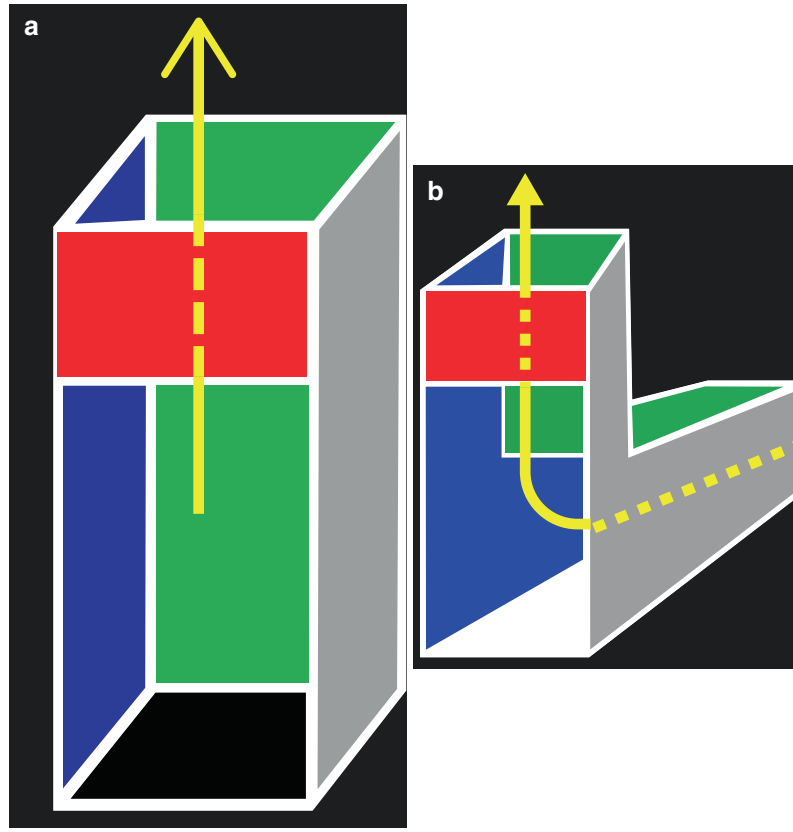

Fig. 28.3 (**a**) Frontal sinus anatomy as a concept of a vertical box. Anteriorly (red) nasofrontal beak, posterior (green) posterior table and ethmoid roof, laterally (grey) orbital wall and roof, medially (blue) middle turbinate/intersinus septum. (**b**) Frontal sinus vertical box and its relationship to the horizontal paranasal surgical box

Table 28.1 International Frontal Sinus Anatomy Classification (IFAC) system

Cell type	Cell name	Definition	Abbreviation
Anterior cells	Agger nasi cell	Most anterior ethmoid cell. Anterior to the middle turbinate origin or above the anterior insertion of the middle turbinate into the lateral nasal wall	ANC
	Supra agger cell	Anterior-lateral ethmoid cell; sits above the agger nasi. Does not extend into the frontal sinus	SAC
	Supra agger frontal cell	Anterior-lateral ethmoidal cell that extends into the frontal sinus	SAFC
Posterior cells	Supra bulla cell	Cell above bulla ethmoidalis. Does not enter the frontal sinus	SBC
	Supra bulla frontal cell	Cell above bulla ethmoidalis. Pneumatises into the frontal sinus	SBFC
	Supraorbital ethmoid cell	Ethmoid cell that pneumatises over the roof of the orbit	SOEC
Medial cells	Frontal septal cell	Medially based anterior ethmoid or the inferior frontal sinus cell, attached to or located in the interfrontal sinus septum	FSC

box of the frontal sinus joins the horizontal paranasal surgical box of the nasal cavity, ethmoid sinus and sphenoid sinus (Fig. 28.3b).

The variable anatomy and relative relationships of the frontal bone partitions arising from the first and second ethmoturbinals have been well classified by the International Frontal Sinus Anatomy Classification (IFAC) and are demonstrated in Table 28.1 and Fig. 28.4 [7]. However, the variability of the anatomy within the frontal

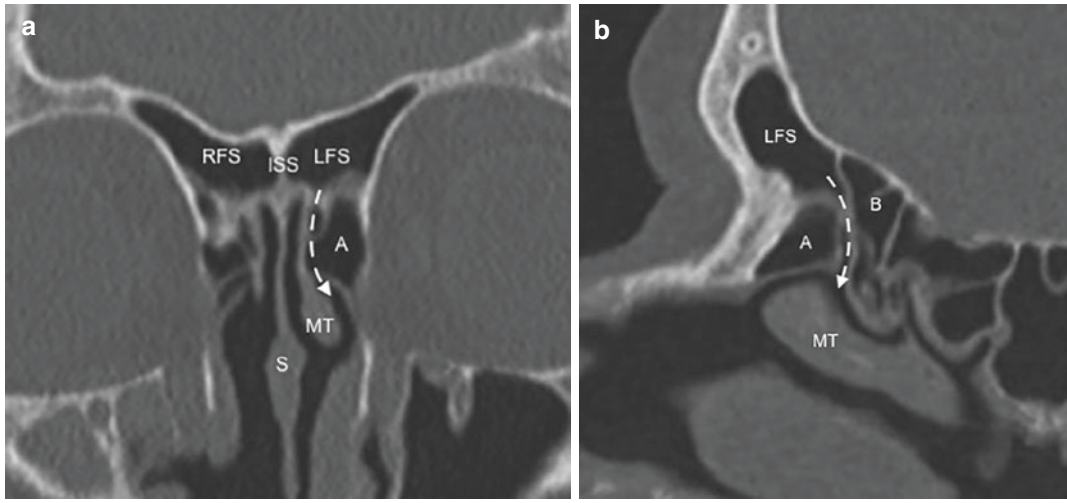

Fig. 28.4 Coronal (**a**) and sagittal (**b**) CT scan images depicting the anatomy of the frontal sinus and surrounding structures. Arrow shows frontal drainage pathway. *RFS* right frontal sinus, *LFS* left frontal sinus, *ISS* inter sinus septum, *A* agger nasi cell, *B* bulla ethmoidalis, *MT* middle turbinate, *S* septum

recess is relatively unimportant surgically, and confident identification of the fixed boundaries of the frontal recess is essential.

Surgical Technique

Mucosal inflammation of frontal sinusitis is usually resolved through a multi-modal approach which may include topical therapy, surgical intervention and systemic medication. Surgery aims to obtain tissue specimen and culture, facilitate the delivery of topical therapy and restore or mechanically facilitate mucus clearance.

Surgical interventions have been well described including endoscopic surgical Draf procedures (Type I, IIa, IIb, IIc, III). External procedures include trephination and, rarely, open approaches [9].

Choice of operation on the frontal sinus is dependent on:

- The nature of the underlying mucosal inflammation
- The goal of subsequent management
- How the proposed anatomical modification helps to achieve this goal

Draf endoscopic sinus procedures are described below, but how they are applied in each frontal sinus phenotype is further discussed later.

Draf I

Draf I procedure involves the removal of cells within the frontal recess, usually the uncinate, ager nasi and anterior ethmoid bulla but does not remove any of the frontal sinus floor (Fig. 28.5).

Draf IIa, b, c

We approach all Draf II procedures in a consistent way, by removing all sinus partitions via a 'Carolyn's window' approach. This involves removing the bone of the frontal process of the maxilla and the nasal process of the frontal bone. This is the 'nasofrontal beak' or the agger-fronto-maxilla bony structure. By removal of this bone, the anteroposterior dimension is extended and aids the dissection. This allows for greater visualisation of the boundaries of the frontal recess ensuring complete clearance of the ethmoids at the junction of the posterior table and against the medial orbit.

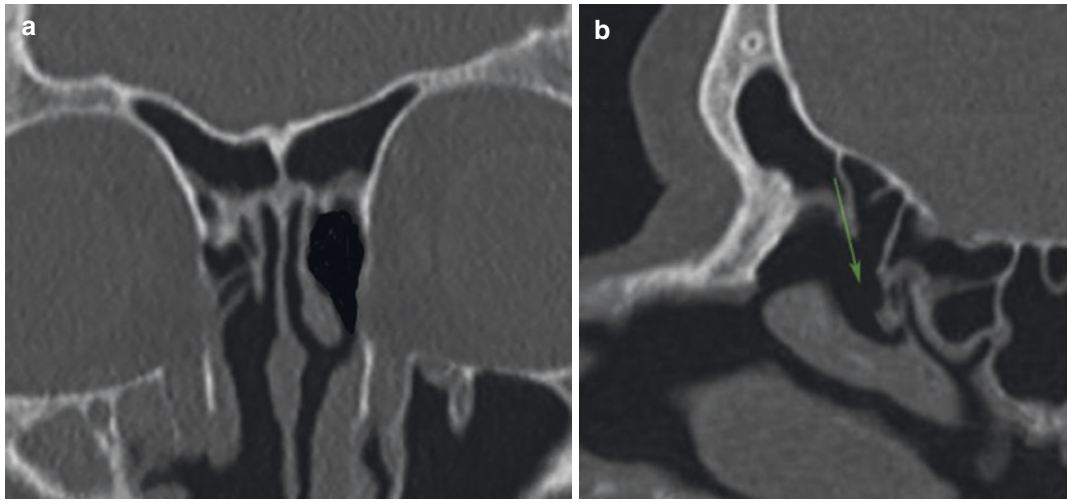

Fig. 28.5 Draf I removal of cells within the left frontal recess without removing the frontal sinus floor, coronal (**a**) and sagittal views (**b**). Arrow depicts frontal drainage pathway

Key principles include the raising an inferiorly based subperiosteal mucosal flap from the lateral wall. The bone of the nasofrontal beak is removed by high-speed drill (Medtronic IPC 30 K 4 mm choanal burr). The lateral limit is the periosteum of the frontal process of the maxilla (Fig. 28.6). The lacrimal sac is exposed. Although the dissection remains lateral to the middle turbinate lamella, the extent of bone removal of the floor of the frontal sinus medial and anterior to the first olfactory neuron defines an extension to a Draf IIb. The Draf IIa is a dissection that remains entirely lateral to the middle turbinate; extension across the nasal septum defines a Draf IIb. The removal of the frontal intersinus septum, opening the contralateral frontal sinus into the surgical approach, defines a Draf IIc, often referred to as a Hemi-Lothrop (Figs. 28.7, 28.8, and 28.9).

Draf III or the Modified Endoscopic Lothrop

The Draf III procedure allows a wide bilateral opening of the frontal sinus by removing the entire nasofrontal beak (periosteum to periosteum), the frontal sinus floor and superior septum (Fig. 28.10). A subperiosteal mucosal flap of lateral wall mucosa over the frontal process of the maxilla is described above or can be extended onto the septum [10]. The first olfactory neuron is always the posterior limit of the dissection.

The septal extension of this flap can be awkward, and the septum is often thickened/polypoid. In this instance, the septal extension of the graft is foregone, and a free mucosal graft is used. The superior septum posteriorly no further than the first olfactory neuron and anterior to inferiorly incorporate the swell body and any high deviation.

Using a 4 mm high-speed drill (Medtronic IPC 30 K 4 mm choanal burr) and a 0 degree endoscope, lateral limits of the periosteum are identified to maximise surgical field and define the lateral limits. Bone is removed medially between these limits using a drill and connected to the frontal recess by a Kerrison rongeur.

Frontal recess partitions and inter-sinus septum are removed. The cavity is squared off by following the orbital wall up to the orbital roof. Mucosa is replaced with a combination of the lateral wall flap, and free mucosa grafts are used to cover any raw bone. Silastic splints are placed in the cavity [11].

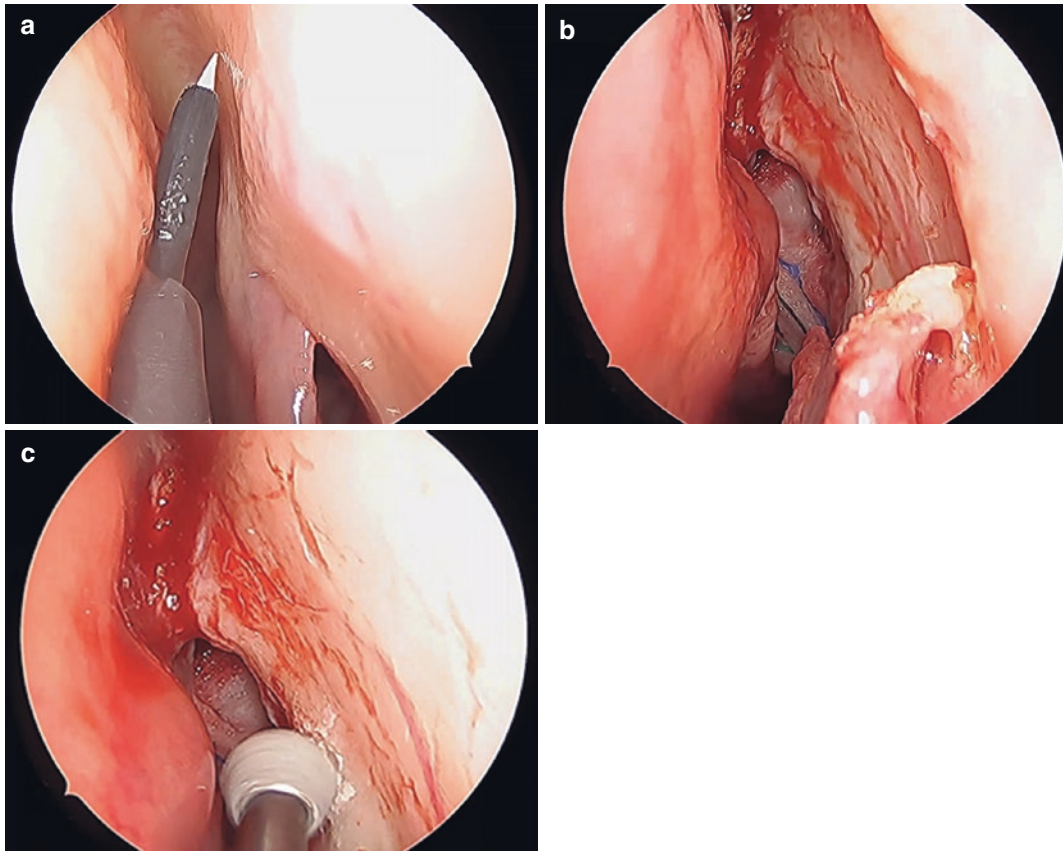

Fig. 28.6 Carolyn's window approach to Draf IIa/b/c, (**a**) Monopolar of mucosal flap, (**b**) Mobilisation of flap, (**c**) Drill to remove the nasofrontal beak

Frontal Mini-Trephine for Culture

Frontal sinus mini-trephination, for obtaining a specimen for culture, is commonly performed with a Seldinger technique (Mini-Trephination Set, Medtronic ENT, Jacksonville, FL) or small incision directly. Optimal placement is 1 cm from midline, at the height of the supraorbital foramina, superior to the superior orbital rim. The skin can be mobilised to place the incision within the eyebrow for optimal aesthetics. A stab incision is made through the skin and widened slightly with blunt dissection to allow for the drill guide to sit flush on the bone. A small drill is then used with gentle irrigation to drill through the anterior table. Using a guidewire, the frontal cannula is placed. Aspiration of air, blood, mucus or pus may confirm position [12]. Using a 20 mL syringe, normal saline is introduced and then aspirated. Resultant fluid can be sent via specimen pot, or if low volume (e.g. 0.5 mL) directly into a paediatric blood culture bottle.

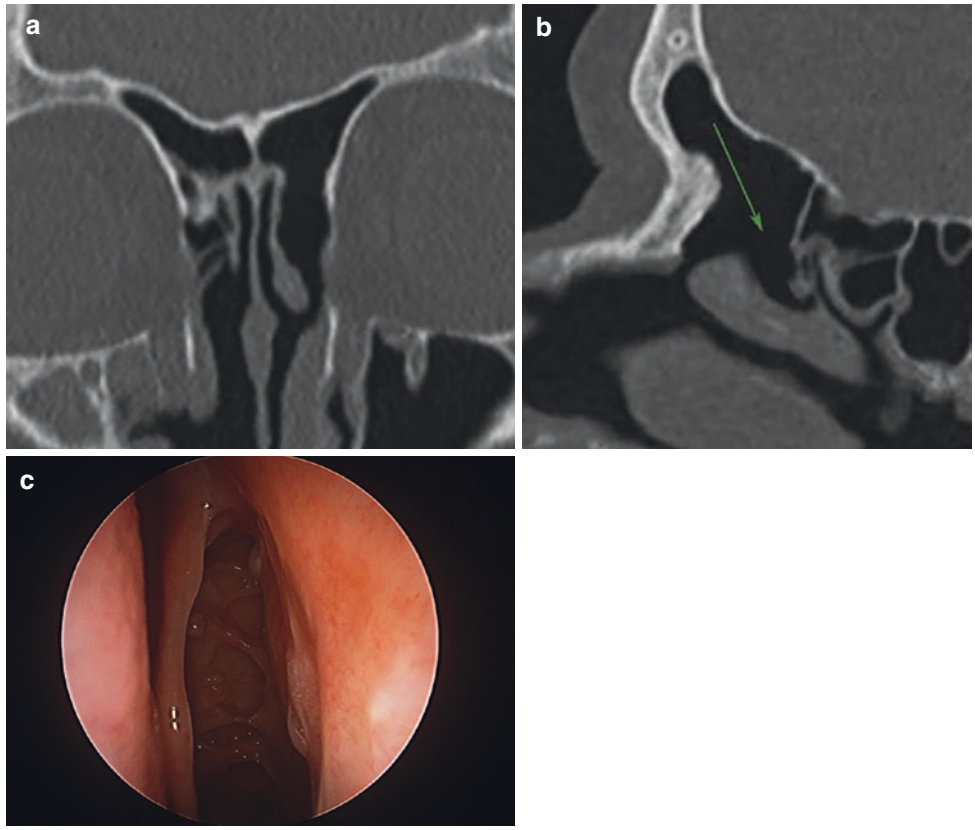

Fig. 28.7 Draf IIa: Limits include the periosteum of the frontal process of the maxilla laterally to the root of the middle turbinate medially. Coronal (**a**) and sagittal (**b**) CT images and endoscopic post-operative photograph (**c**). Arrow depicts frontal drainage pathway

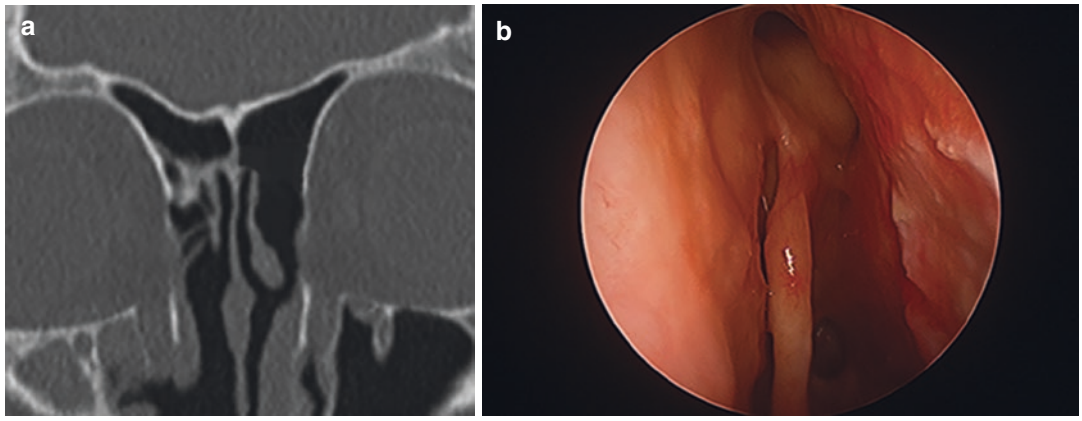

Fig. 28.8 Draf IIb: Limits include the periosteum of the frontal process of the maxilla laterally to the nasal septum medially. Left Draf IIb illustrated by coronal CT scan (**a**) and zero degree endoscopic view (**b**)

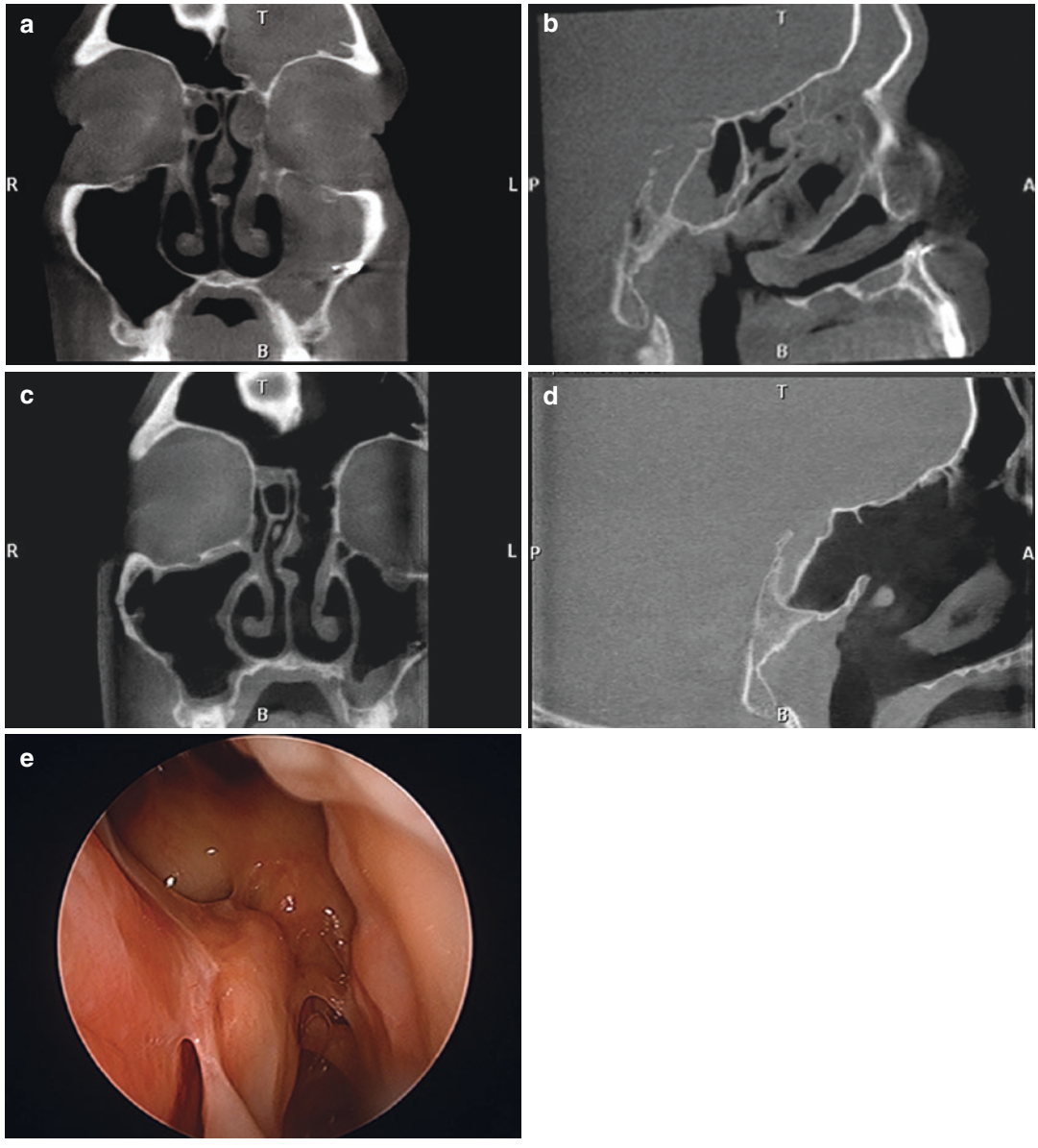

Fig. 28.9 Draf IIc or hemi-Lothrop: Limits include the periosteum of the frontal process of the maxilla laterally, medially the removal of the frontal inter-sinus septum occurs to enter the contralateral frontal sinus. CT scans of pre-operative coronal (**a**) and sagittal (**b**) findings followed by post-operative coronal (**c**) and sagittal (**d**) findings for a patient with AFS. (**e**) demonstrates the post-operative appearance with zero degree endoscope

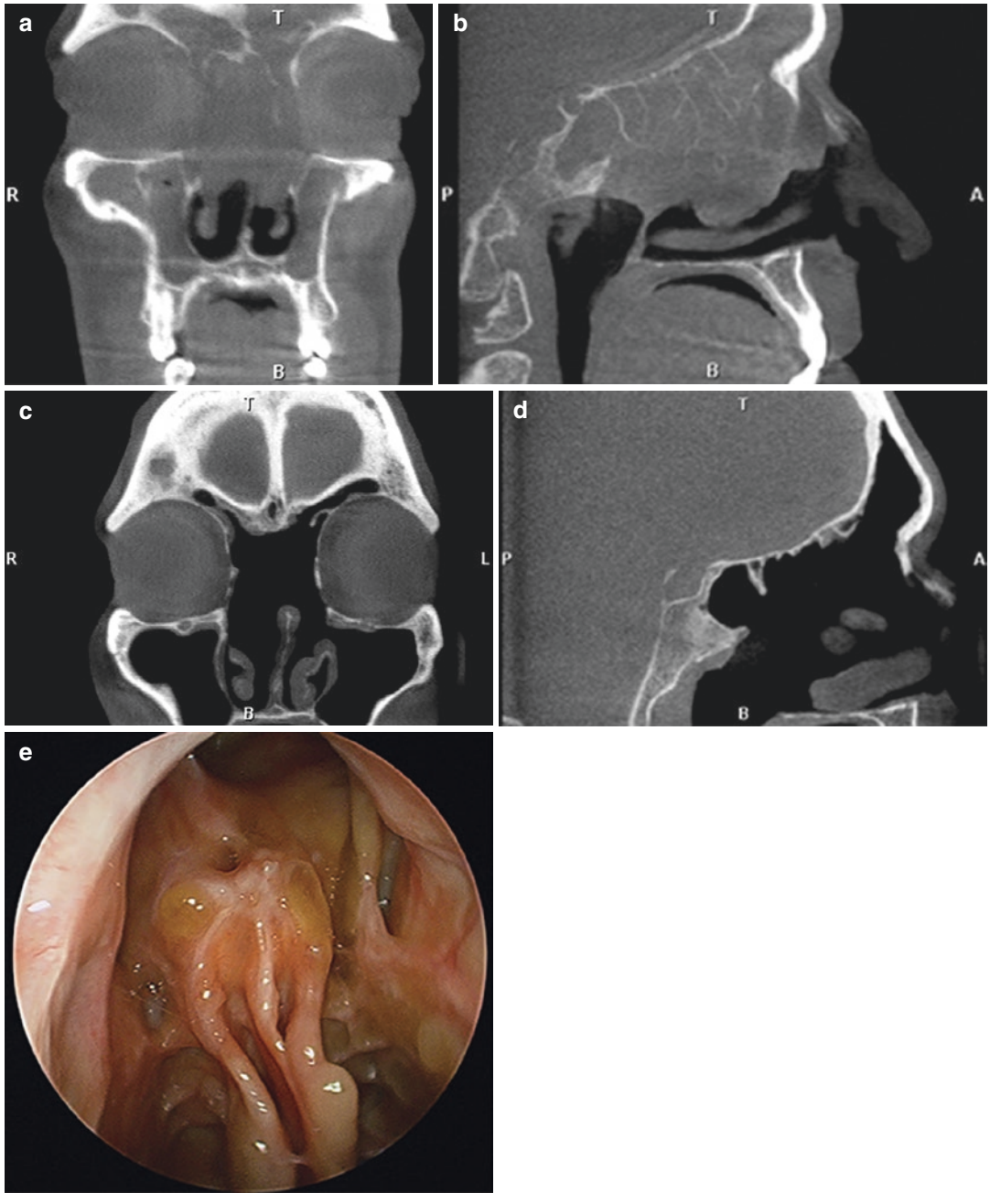

Fig. 28.10 Pre (**a**) and (**b**), and post (**c**) and (**d**), coronal and sagittal CT scans respectively in patient with eCRS who underwent a Draf III procedure. (**e**) Post-operative view with a 0° endoscope into the frontal sinus cavity

The Management of the Frontal Sinus by Sinusitis Disease Phenotype

The management of the frontal sinus differs according to the underlying nature of the frontal sinusitis disease phenotype. There are three principles that guide surgical decision-making when frontal sinus surgery is performed: firstly, to define the nature of the underlying mucosal inflammation. Secondly, to identify the goal of subsequent management and finally, how the proposed anatomical modification through surgery helps to achieve this goal.

Acute Frontal Sinusitis

The vast majority of patients with acute upper respiratory exacerbations, including those with frontal sinus symptoms, especially when bilateral, have a viral, allergy or combination aetiology. Simple symptomatic relief is the mainstay of management. It is important to avoid unnecessary use of antibiotics and subsequent potential side effects in this instance [13].

In the 0.5–2% of patients with a suspected bacterial origin, often those with unilateral symptoms, antibiotics are recommended as the mainstay of therapy. Antibiotics should be culture driven, with the use of broad-spectrum empirical antibiotics covering the most common pathogens (*Streptococcus pneumoniae*, *Haemophilus influenzae* and *Moraxella catarrhalis*) in the interim [14]. A middle meatal swab is the best option for gaining a culture result for treatment purposes [15]. If the middle meatus does not reveal a culture opportunity, the use of trephination for washout and culture may be useful [1].

While obtaining culture information is important in ARS of the frontal sinus, there is little role for acute frontal sinus surgery. Even in the setting of intracranial and orbital abscess formation, surgery on the frontal sinus is not thought to improve outcomes [16]. The spread of bacterial infection is by indirect spread via thrombophlebitis, and the abscess location is often distant to the sinus cavity itself. Even when there is bone loss, this is not the site of 'connection' but an osteomyelitic change and a sign of the need for long-term antibiotic therapy and not for sinus surgery. This is the nature of the development of complications such as 'Potts puffy tumour'. Surgery is often required to evacuate or drain an abscess, and a microbiological sample can be taken from the frontal sinus at the time of managing the complication.

Frontal Sinus Involvement in CRS

Primary-Localised CRS

When a single frontal sinus is involved in CRS, it is referred to as a localised CRS. This may be isolated to the frontal sinus alone or, if it involves the osteomeatal complex (OMC), includes the anterior ethmoid and maxillary sinus, as they share a common drainage pathway. This pattern of localised CRS suggests an issue with the anatomy of that subunit.

The predication for management and extent of surgery required depends on underlying on mucosal factors, namely, their endotype dominance (Type 2 dominant and non-Type 2 dominant). Thus, primary-localised CRS is further characterised.

Localised Type 2 Dominant Frontal CRS: Allergic Fungal Rhinosinusitis

Allergic fungal rhinosinusitis (AFRS) is not simply an inflammatory reaction to fungus; it is a hypersensitivity condition [17, 18]. It is characterised by the presence of fungal hyphae and eosinophilic mucin within sinuses, in which mucus clearance is impaired and a hypersensitivity reaction has occurred in response to fungal contact. It is imperative to be able to remove the fungal burden from the sinus cavity, both at the time of surgery, and provide clearance of fungal-containing mucus in the future. The only way to achieve this is by providing a very large opening.

Surgical principles in localised AFS-related frontal sinus disease should include a Draf IIa (with wide natural dimensions), Draf IIb or IIc to allow for complete removal of fungi, a wider

mucosal drainage pathway and the application of topical corticosteroid therapy (Fig. 28.9).

Peri-operative oral corticosteroids have been shown to be important, with limited evidence on the use of immunotherapy or antifungals in refractory cases [18]. Additional antifungal therapies offer little benefit [1].

Localised Non-type 2 Dominant Frontal CRS: Isolated or Ostial Occlusion Frontal CRS

Isolated sinusitis is typically an infective phenomenon. This is the classic 'ostial occlusion' sinus disease [19]. There are many reasons why the mucosa of the frontal recess or OMC may not respond to medical therapy. There are well-defined mucosal remodelling events, such as subepithelial fibrosis and basement membrane thickening, that may not respond to medical therapy and result in long-term ostial occlusion [20].

For most primary localised non-type 2 dominant CRS patients with frontal sinus involvement after medical therapy, formal modification of the frontal recess itself is often required.

Surgical options include balloon dilatation and Draf IIa. Other modifications can be used depending on the anatomy, but extended openings are not generally required as reventilation and one-off drainage/washout usually resolves the chronic state [19]. Sinus function, in the form of mucociliary clearance, almost always resumes for these patients.

Primary Diffuse CRS

Here, changes are related to inflammation rather than anatomical abnormalities and therefore diffuse in nature. They are further categorised by endotype dominance and subsequently expressed phenotype.

Primary Diffuse Type 2 Dominant: Eosinophilic Chronic Rhinosinusitis (eCRS)

The nature of this condition is characterised by diffuse mucosal infiltration by eosinophils (10>/HPF) and a subsequent inflammatory response [1]. It is important to appreciate that eCRS is a chronic inflammatory airway disease, often with coexistent adult-onset asthma, which will require ongoing maintenance. Hence the general goal of management is to surgically alter the sinuses to produce a simple anatomical box (neo-sinus) allowing for maximal application of topical corticosteroid therapy, and maximal dimensions to prevent mucus plugging in a condition that is both hypersecretory and likely to undergo exacerbations during the course of the disease.

Surgery involves creating a simple neo-sinus cavity, and the frontal sinus is connected by Draf III or extended Draf II if the anatomy is wide and disease severity is low (Fig. 28.10). We rarely apply simple Draf IIa surgery in this condition as the frontal sinus is the most common site of poorly controlled mucosa and recurrent polyps [21]. Corticosteroid irrigations are the mainstay of post-surgical therapy [22].

The recent addition of biologicals (monoclonal antibodies targeting IgE, IL4 and IL5 inflammatory pathways) to the management ladder in recalcitrant eCRS, particularly in the presence of comorbid asthma, is improving the ability to control the condition in its most severe forms where topical corticosteroid irrigations and surgery have failed [23–25].

Primary Diffuse Type 2 Dominant: Central Compartment Atopic Disease (CCAD)

The nature of central compartment atopic disease (CCAD) is an exuberant allergic rhinitis resulting in oedema and polypoid change in the central sinonasal cavity with mucus trapping [26]. This typically occurs in younger patients with a good history of inhalant allergy. Imaging often shows central opacification of the paranasal sinuses, with superior and lateral sparing of the sinus mucosa known as the 'black halo' sign [27].

Left untreated, secondary sinus dysfunction occurs that includes mucosa within the frontal sinus, related to the direct extension of polypoid changes into the sinus outflow pathway or from lateralisation of the middle turbinate [28].

Patients often complain of barotrauma but still retain smell until late in the disease course.

Management is targeted at the inhalant allergy driving these changes, and once the specific aero-

allergens are defined, immunotherapy is commenced early. As the frontal sinus is secondarily involved, a simple Draf IIa surgical opening will suffice for most. Access for topical therapies is less of an important concept, and inhalant allergen immunotherapy is pursued [28].

Primary Diffuse Type 2 Dominant: Allergic Fungal Rhinosinusitis (AFRS)

As previously described, the nature of this hypersensitivity disorder is mucosal dysfunction, oedema and expansile changes in the sinus cavity which often results in the involvement of the adjacent functional unit. Thus, AFRS may be considered diffuse in nature. Management goals include the complete removal of fungal elements and to establish mucus clearance either by restoring mucociliary clearance or by allowing clearance by nasal irrigation. A Draf III frontal sinus opening is almost always required unless the frontal recess has been very widely expanded by the disease already. Removal of fungal debris and delivery of topical corticosteroid therapies require a very large opening.

Primary Diffuse Non-type 2 Dominant: Non-eosinophilic Chronic Rhinosinusitis (Non-eCRS)

The nature of this condition is inflammatory but non-type 2. Non-eCRS patients tend to be older and do not respond well to corticosteroids [29, 30]. The presence or lack of polyps in this defined group does not separate these patients from those of the eCRS group, which is the basis for endotype-based classification and why the subsequent management strategy is important.

The goal of management is to reduce inflammation. Medical management relies on treating the bacterial colonisation and the anti-inflammatory effects of a macrolide (anti IL8) rather than heavy use of corticosteroids [30]. Clinically, non-eCRS is not hypersecretory with thick mucin. Although crusting forms, mucus plugs are uncommon. The principals of surgery are to provide access for nasal irrigations to overcome the secondary mucostasis, provide access to topical antibacterial agents and relieve obstruction. Thus, surgery in the form of a Draf IIa is usually all that is required for ventilation, drainage and the application of topical irrigation.

Frontal Sinus in the Setting of Secondary CRS

Here the sinonasal disease is secondary to another disease process. Anatomical distribution is again characterised into localised and diffuse groups.

Secondary CRS: Localised

When the frontal sinus is secondarily involved because of another localised inflammatory process, the management is usually limited to the management of the inflammatory process.

Fungal Ball

Fungal ball is a good example of a localised foreign body reaction in the form of fungal debris which accumulates in the sinus and causes an inflammatory reaction. Management requires the removal of the entire fungal ball and refashioning of the involved sinus whose function will often return. Accordingly, surgical intervention is limited to either simply treating the maxillary disease and/or a Draf type 1 and OMC procedure. An excellent outline of fungal ball management may be found in EPOS2020 [1].

Odontogenic Sinusitis

Dental infections/periapical abscess of tooth may result in purulent secretions within the sinus cavity causing odontogenic sinusitis. Whilst this is commonly within the maxillary sinus, changes may extend to the frontal sinus. This often resolves following endodontic work/tooth extraction, but surgical intervention is limited to either simply treating the maxillary disease and/or a Draf type 1 and OMC procedure.

Tumours

When tumours are present within the sinonasal cavity, there is often a significant amount of oedema and sinus dysfunction as a secondary component. This dysfunction often self-resolves following tumour removal. Typically, if the tumour is in the ethmoid and maxilla but poste-

rior to the anterior ethmoid artery, the frontal sinus and its pathway are spared, and a Draf I procedure is all that is required.

If the tumour is in the anterior ethmoid or anterior to the anterior ethmoid artery, then a Draf IIa, b or c is the minimum required to ensure that the frontal sinus and drainage pathways are patent and functioning. If the tumour is in the frontal sinus, then a Draf III is almost always required with or without an external approach. Frontal sinus tumours however are no longer within the secondary CRS category, and this is well addressed elsewhere in this book.

Secondary CRS: Diffuse

The nature of secondary diffuse disorders is a failure of the body's defence mechanisms to fight and control mucosal disease. These are broadly separated into three causative groups: mechanical, inflammatory (auto immune) and immunity (immunodeficiency).

Mechanical Cause

Conditions such as primary ciliary dyskinesia and cystic fibrosis demonstrate a mechanical dysfunction of mucociliary clearance. Mucostasis and resultant bacterial colonisation ensue. Management aims are based on creating a cavity that allows for mechanical washout; however, a Draf III is often not useful due to the frontal hypoplasia which is common in these groups.

Inflammatory Cause

Granulomatosis with polyangiitis (GPA) and eosinophilic granulomatosis with polyangiitis (EGPA) are the most common examples of secondary diffuse inflammatory disease. These autoimmune conditions result in a destructive change in the sinus cavity, but this is a broader autoimmune condition involving multiple body systems and which should be managed as such. Frontal sinus surgery rarely plays a role in managing these patients.

Immunity/Immunodeficiency

These disorders include selective IgA deficiency, combined variable immune deficiency and poorly controlled diabetes. Careful management of the underlying immunodeficiency is integral to the care of these patients. Persistent frontal disease, despite maximal correction of underlying immunodeficiency, should be managed as per the guidelines of primary localised CRS.

Perioperative Care in Frontal Sinusitis

Conscientious perioperative care is integral in the success of frontal sinusitis surgery due to the risk of scarring and stenosis.

Draf I procedures are dressed intraoperatively with finger cot dressing or resorbable packing such as hyaluronic acid gel. They are discharged home on the day of surgery and followed up at 3 weeks and 3 months post-surgery.

As the authors' approach to any Draf II is via Carolyn's windows approach, all dressings and follow-up are identical. At the end of the procedure, the lateral wall flap is replaced, and any exposed bone is covered by inferior turbinate free grafts. Glove finger spacers and hyaluronic acid gel are placed to secure the flaps. Patients are discharged the day of surgery and followed up 1 week, 3 weeks and 3 months.

Draf III procedures are completed by replacing the lateral nasal wall mucosal grafts, with or without the septal extension and covering any exposed bone with free mucosal grafts [11]. The grafts and surgical opening are covered by a 0.5 mm silastic sheet (Medtronic, Jacksonville, FL) cut accordingly to allow for contouring to the surgical shape [11]. The silastic is supported by absorbable dressing (Nasopore, Polyganics Groningen, the Netherlands). Patients go home the day of surgery and are followed up in 3 weeks and 3 months post-operatively.

Effective delivery of topical therapy to the frontal sinus is an essential component in the post-surgical management of the frontal sinus. Nasal irrigations allow for lavage of mucus and debris and the delivery of topical pharmacotherapies to the mucosa. All patients commence irrigations the day following the procedure. Draf III frontal sinusotomies allow significantly greater access and flow rate of topical pharmacotherapy compared to Draf IIb followed by Draf IIa, and

this difference should be considered when making surgical decisions [31].

Key Learning Points

- Frontal sinusitis is a broad concept due to its many varied aetiologies of CRS.
- Frontal sinusitis is classified by the EPOS2020 which gives guidance to the underlying disease process.
- Acute frontal sinusitis is most often viral in aetiology, but in unilateral disease, then bacterial frontal sinusitis is likely, and antibiotic use should be culture driven.
- In CRS, frontal sinus surgery techniques achieve an anatomical modification, from surgery, to aid a management plan.
- Surgical techniques, such as the removal of the ager nasi, front maxilla process ('Carolyn's window') overcome the narrow anteroposterior distance and aid in frontal recess surgery.
- Mucosal flaps and grafts should be applied where possible to cover exposed bone as healing is greatly improved.

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Complications of Rhinosinusitis

29

Vasileios Chatzinakis and Christos Georgalas

Introduction

In the era of antibiotics and endoscopic sinus surgery, complications of rhinosinusitis—acute or chronic—are relatively rare. Introduction of widely available, cost-effective computed tomography scanning with intravenous contrast administration has resulted in their earlier diagnosis and management. However, complications do still occur and, in some cases, can prove life-threatening. Hence, the clinician must have a high index of suspicion and be familiar with the appropriate diagnostic algorithm, as well as the principles of their management.

Epidemiology, Microbiology and Pathophysiology

Epidemiology: In almost all large epidemiological studies, orbital complications appear twice as often as intracranial ones and males are significantly more frequently affected than females [1]. ARS was more often the precipitating factor in children, whereas CRS with or without nasal polyposis was more important in adults [2]. There is a clear seasonal pattern in their incidence, mirroring URTIs [3]. The recent restrictions associated with measures to deal with the COVID-19 pandemic have resulted in reduced incidence of URTIs—

V. Chatzinakis
Endoscopic Skull Base Center, Hygeia Hospital, Athens, Greece

C. Georgalas (✉)
Endoscopic Skull Base Center, Hygeia Hospital, Athens, Greece

Medical School, Nicosia University, Nicosia, Cyprus

Athens, Greece

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however, there are no studies showing a corresponding decrease in acute sinusitis cases or their complications [4]. Although orbital complications tend to occur primarily in young children, intracranial complications can occur at any age, albeit with a predilection for the second and third decade of life.

Microbiology: Pathogens involved seem to differ between children and adults. Predominant pathogens in *children* are *Streptococcus pneumoniae*, *Haemophilus influenza*, *Moraxella catarrhalis* and *Staphylococcus aureus* [5]. In *adults*, anaerobic, odontogenic and polymicrobial infections predominate and have a more severe presentation. Pathogens most commonly involved in the pathogenesis of adult intracranial complications are *Streptococcus* and *Staphylococcus* species and anaerobes.

Pathophysiology: Two main mechanisms are involved: direct extension and haematogenous or lymphatic spread. This is more of theoretical rather than practical value, since there is no clinical way of distinguishing between the two mechanisms, and it does not affect management.

Orbital complications are usually the result of direct extension, from the ethmoids to the orbit. The lamina papyracea is the thinnest bone in the body and "cribriform" in structure: multiple minor veins and arteries enter the orbit via lamina papyracea. Cavernous sinus thrombosis, nowadays classified as an endocranial rather than orbital complication [6], is considered a result of retrograde thrombophlebitis via the diploic veins.

Classification Systems

Several different ways of classifying complications of rhinosinusitis have been proposed. The most widely accepted classification is an anatomical one, dividing them into orbital (60–75%), intracranial (15–20%) and osseous (5–10%) [7]. Other authors suggest a classification based in etiology: suppurative versus systematic or "unusual." For this chapter, we chose a more descriptive classification that takes into consideration both the underlying cause and the anatomical area affected.

Complications of Acute Rhinosinusitis

Orbital Complications

The most widely used classification of orbital complications/infections was created by Chandler and included five domains: preseptal cellulitis, orbital cellulitis, subperiosteal abscess, orbital abscess and cavernous sinus thrombosis. Today, "preseptal cellulitis" is considered more of an eyelid than an orbital infection, as the fibrous orbital septum is the anterior limit of the orbital contents [8].

Most orbital complications typically present with chemosis, proptosis, tenderness and restriction of eye movements (Fig. 29.1). However, a subperiosteal abscess (located outside of the extraocular muscles) may cause ophthalmoplegia and impaired visual acuity. An intraconal abscess is likely to form as a result of diagnostic delay. Cavernous sinus thrombosis is a "standalone"

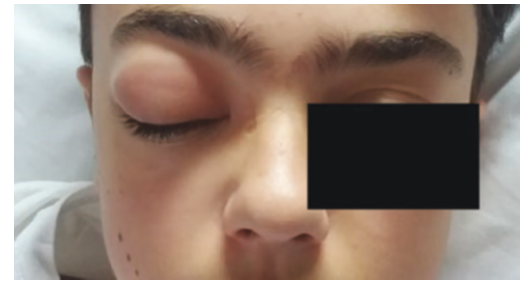

Fig. 29.1 A child with chemosis and proptosis due to orbital abscess of the right eye. Tenderness and eye movement restriction were also present

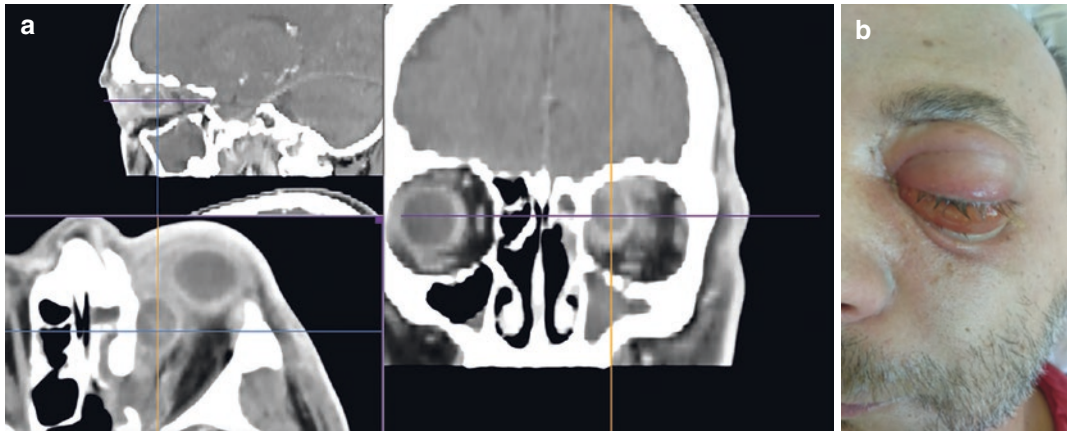

Fig. 29.2 Computed tomography of a subperiosteal abscess of the left eye (**a**). Patient with severe proptosis and oedema (**b**)

intracranial complication, rather than the end stage of orbital infection [9].

CT has been found to have slightly higher predictive accuracy than clinical assessment and is an important diagnostic tool (Fig. 29.2) [10]. In small children with subperiosteal abscesses, there have been a number of studies showing good outcomes with intravenous antibiotics alone, but surgical treatment should never be postponed if vision is affected or response to iv antibiotics is poor after 24 h [11, 12].

Intracranial Complications

Sinus disease is the underlying cause of almost 10% of all intracranial suppuration. Complications include epidural or subdural abscesses, brain abscess, meningitis, cerebritis and superior sagittal and cavernous sinus thrombosis, either alone or in combination (Fig. 29.3). Most patients present with high fever, severe headache, nausea and vomiting, neck stiffness and altered mental state. Subtle behavioural changes often occur.

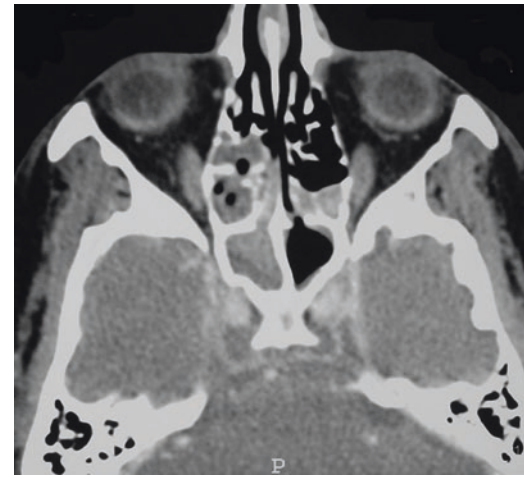

Fig. 29.3 Contrast-enhanced axial CT of a young child suffering from cavernous sinus thrombosis. Note the bilateral at non-fat density filling defect at the cavernous sinuses

Patients with cavernous sinus thrombosis may also display bilateral ptosis, exophthalmos, retro-orbital headache and papilloedema. The diagnosis is confirmed by a "flow void" that is typically demonstrated by a magnetic resonance venogram (MRV). However, an MRI with contrast may demonstrate an enhanced organized thrombus at

an early stage in the disease. Contrast enhanced CT-although not the best option-may also be suggestive of the condition.

Osseous Complications

Osteomyelitis of (mainly) the frontal bone may present clinically with forehead oedema, giving the impression of a soft tissue mass (Pott's puffy tumor) (Fig. 29.4). The infection may disseminate via direct extension or haematogenous spread to cause meningitis or epidural or brain abscess. Drainage of pus by trephination or endoscopic drainage should not be postponed.

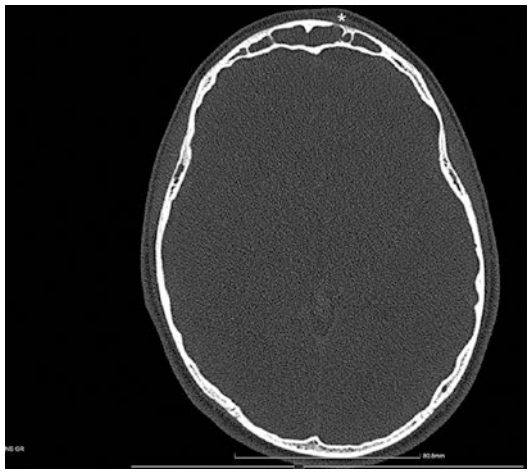

Fig. 29.4 Pott's puffy tumor, secondary to frontal sinusitis. Note the mild oedema over the left frontal sinus and the underlying area of osteomyelitis (*asterisk*). Endoscopic drainage was carried out

Complications of Chronic Rhinosinusitis

Complications of Chronic Rhinosinusitis with Nasal Polyps

CRSwNP can cause complications in two ways: either via direct erosion ~~of~~ the orbital wall and skull base or via sinus obstruction and subsequent mucocele formation. They can also be categorized in anatomic terms: orbital and intracranial complications.

Erosion of the lamina papyracea and anterior skull base can occur with longstanding extensive polypoid disease where CT of the sinuses shows a complete white-out of the sinuses and nasal cavities (Fig. 29.5). Subsequent infections of the lacrimal apparatus have been documented, as well as erosion of the medial orbital wall leading to orbital cellulitis. Involvement of the skull base and lamina papyracea has been described in up to 50% of cases with allergic fungal rhinosinusitis

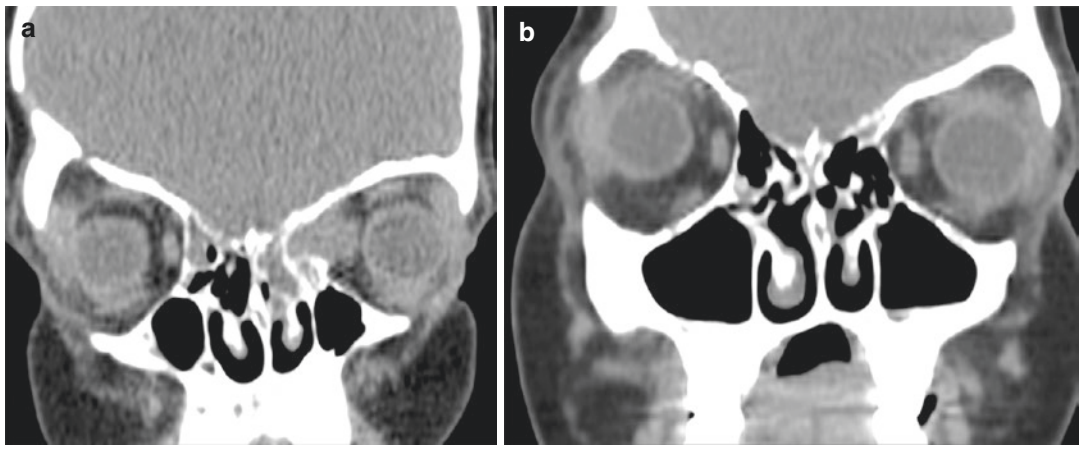

Fig. 29.5 Nasal polyps and multiple mucoceles eroding/remodeling the lamina papyracea of the left orbit. After complete removal of the pathology, the bone appears almost fully restored. (**a**) Pre-op, (**b**) post-op

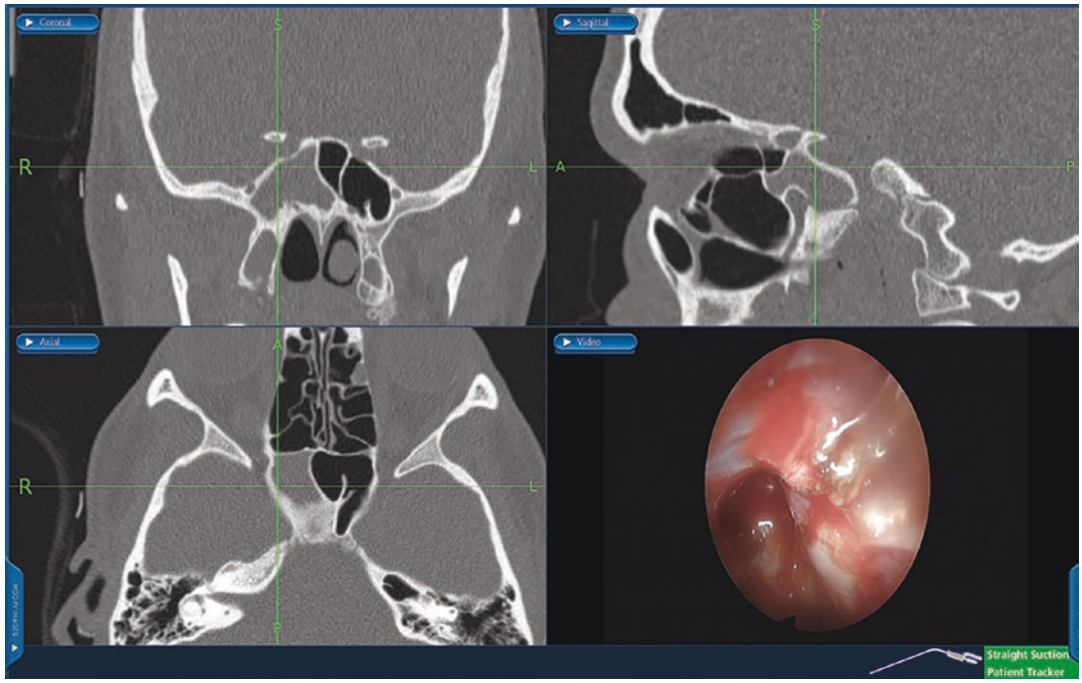

Fig. 29.6 Compressive optic neuropathy due to sphenoiditis

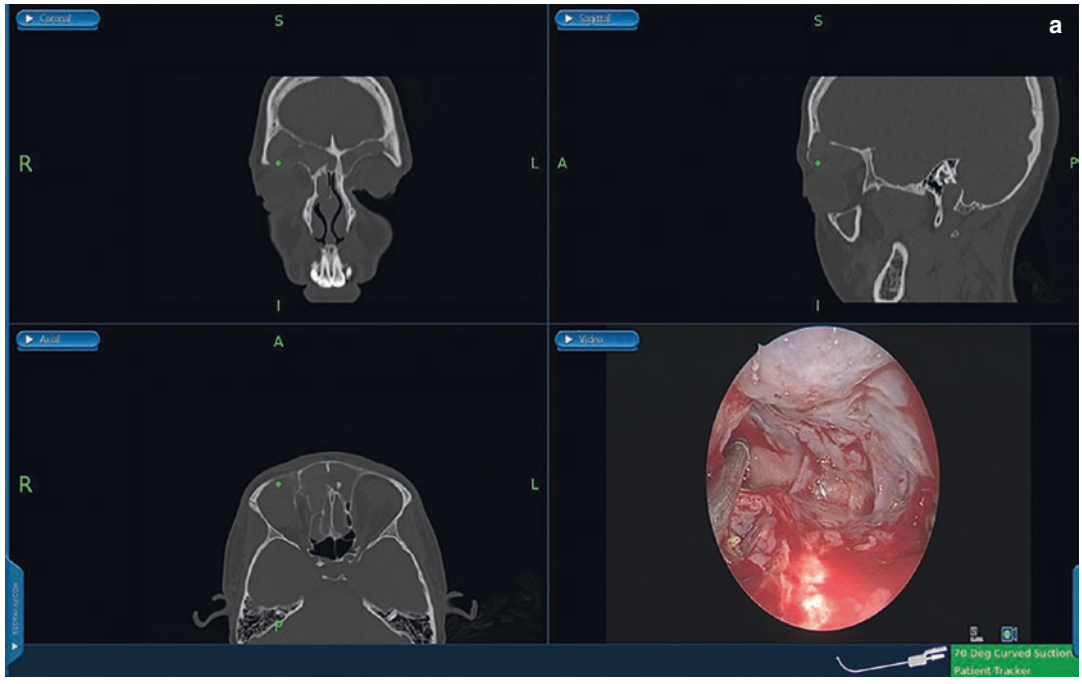

Fig. 29.7 (**a**) Mucocele of the frontal sinus, eroding the roof of the right orbit. (**b**) Note mild exophthalmos preoperatively and upper eyelid oedema. (**c**) Post-op. (**d**) Result of Draf III procedure

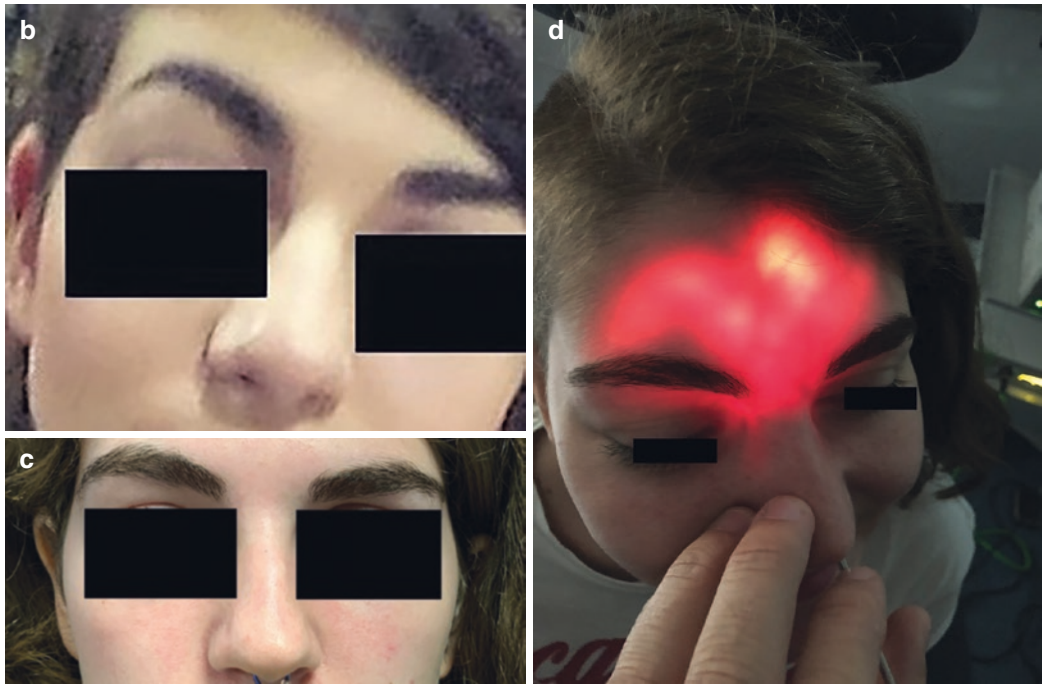

Fig. 29.7 (continued)

[13]. Compressive noninfective optic neuropathy with visual loss can also occur (Fig. 29.6). Nasal polyps usually expand insidiously, remodeling the lamina papyracea or the skull base, without invading the periorbita or the dura. Outflow obstruction, leading to mucocele formation (Fig. 29.7), can also be considered a CRSwNP-associated complication (up to 0.6%). The frontoethmoid region was the most commonly affected area in a series of 82 patients, and patients with aspirin-exacerbated respiratory disease (AERD) were at higher risk [14]. Previous surgery and aspirin sensitivity seem to be risk factors.

Complications of Chronic Rhinosinusitis Without Nasal Polyps

Most complications secondary to CRSsNP are often associated with worsening infection—similar to the complications of ARS—and can involve the eye, brain and lungs. What differs however is the microbiology of these complications.

Chronic inflammatory changes near the orbit can lead to enophthalmos via silent sinus syndrome, epiphora due to obstruction of nasolacrimal duct, proptosis and optic neuropathy as a result of involvement of the orbit and optic nerve accordingly (Fig. 29.8). Fungal or bacterial invasion along the skull base can lead to intracranial complications.

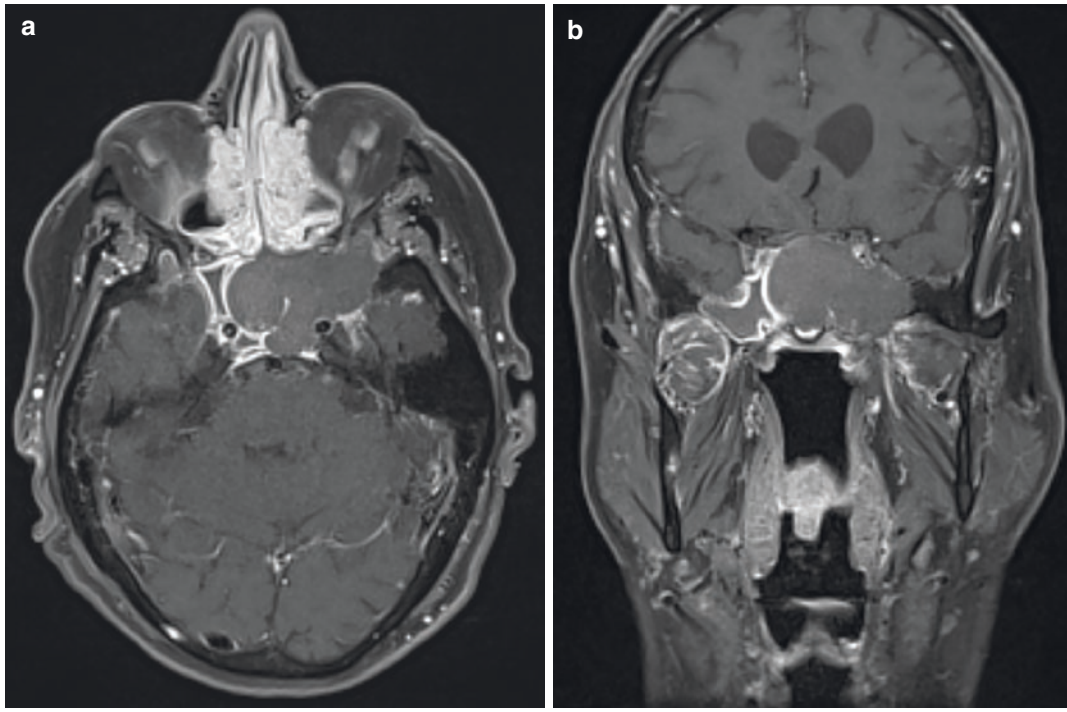

Fig. 29.8 MRI of a large mucocele of the left sphenoid sinus, resulting in abducens nerve palsy of the left eye. (**a**) Axial. (**b**) Coronal plane

The chronic inflammatory response observed in CRS can worsen existing airway pathology or lead to adult-onset asthma [15].

Minor complications associated with CRS tend to occur with local tissue alterations that may lead to osteitis and bone erosion [16].

Medical therapies widely used at treating CRSsNP, including antibiotics and systemic corticosteroids, can also cause various local or systematic complications.

Diagnosis

Physical Examination

Clinical assessment remains the key to diagnosing orbital complications of rhinosinusitis. Visual acuity, ocular motility and colour discrimination should be specifically assessed. Each modality can be affected, but not necessarily in a set order. For example, loss of red and green colour perception due to increased intraorbital pressure may be noted before worsening of visual acuity. Tonometry can prove helpful, but whilst being sensitive, it is not specific. All cranial nerves should be assessed, especially cranial nerves II, III, IV, V_1, V_2 and VI that can be involved in orbital and intracranial complications.

Intracranial complications tend to present in a more "nonspecific" manner with symptoms such as headache or fever—if any at all. More specific signs and symptoms such as neck stiffness, alteration in mental state or vomiting should lead to an earlier diagnosis.

Radiology

To our knowledge, there have been no large randomized, controlled trials, comparing computing topographic scanning to ultrasonography or magnetic resonance imaging in the diagnosis of rhinosinusitis complications. As far as orbital complications are concerned, it is the author's opinion that contrast CT should be the study of choice. It is relatively inexpensive, widely available, quick and detailed and can assess bone erosion and any extension of inflammation. Enhancement of orbital fat usually indicates an intraorbital complication of variable severity. An orbital or subperiosteal abscess can be readily identified from its characteristic appearance of a relatively low-attenuation central necrotic component and a capsular ring enhancement with contrast.

The appropriate use of computed tomography in children with sinus disease has been addressed by a clinical consensus statement. This recommends careful consideration be given to the risk–benefit ratio. A CT sinus scan is however recommended in children who fail to respond to treatment and those with complications of infection [17].

On the other hand, MRI can prove superior to CT in soft tissue differentiation, parenchymal extension or marrow-space involvement without exposing the patient to irradiation. MRI is often performed concurrently with MRA when cavernous sinus thrombosis is suspected. However, MRI is more expensive, is less available, requires sedation/anesthesia in younger children, is susceptible to image degradation by movement and is more time-consuming than a CT scan.

Laboratory Tests

Although not specific, an elevated white blood cell count with a prevalence of neutrophils is very common in complicated acute rhinosinusitis. Leukopenia is also possible, but this is typically related to worse outcome. C-reactive protein (CRP) is an index of inflammation and is usually elevated, but due to its low specificity, it is more useful to monitor the early recovery period rather than to establish the diagnosis.

In intracranial complications like bacterial meningitis, blood cultures and CSF analysis and culture are often helpful in confirming a more precise diagnosis and yielding an infective pathogenic microorganism. Cerebrospinal fluid, acquired via a lumbar puncture, will normally reveal >5 white blood cells/μL, >50 mg/dL of protein and <40 mg/dL of glucose in cases of bacterial infection [18].

If an intracranial abscess is suspected, radiological imaging of the head is mandatory before a lumbar puncture is performed, since brain herniation is a significant risk. Elevation of intracranial pressure to levels higher than 200 mm H_2O is also a potential risk of intracranial infection and must be excluded prior to lumbar puncture.

Treatment

Principles of Management

The principles of treating complicated rhinosinusitis, especially acute infection as described above, follow a common pattern: As a general rule, hospital admission is necessary for diagnosis and treatment. Evaluation from the ENT specialist, an ophthalmologist and/or a neurosurgeon should be considered according to the likely complication. Appropriate intravenous antibiotic treatment should be started as soon as possible once an orbital or intracranial complication is suspected. A second-line antibiotic (usually third-generation cephalosporin) that crosses the blood–brain barrier or a quinolone as an alternative is often instigated as first-line antibiotics, such as ampicillin/sulbactam or amoxicillin/clavulanate, may have already been administered prior to the complication and hospital admission.

Sometimes an antibiotic that is effective against a multiresistant *Staphylococcus aureus*, such as vancomycin, should be prescribed, especially when treating intracranial complications.

Intranasal use of topical vasoconstrictors/decongestants is common practice, but their effectiveness has not been definitively proven. As a general rule, if the patient responds poorly to intravenous antibiotics after 24–48 h, then surgical exploration and drainage should occur without further delay. Whilst

planning the procedure, communication between all subspecialties involved is vital.

Surgical Management

Orbital Complications

Preseptal and orbital cellulitis, and small medially located subperiosteal abscesses (<2 cm diameter), usually respond well to systemic intravenous antibiotics. Larger periorbital and orbital abscesses require surgical intervention and drainage.

Endoscopic transnasal drainage of abscesses is a well-established technique that avoids an external facial scar, shortens hospital stay and has a good outcome. The external approach via a Lynch–Howarth incision is an alternative technique, especially if endoscopic expertise is not easily available. The transcaruncular approach offers the possibility of external drainage without leaving an external scar.

The endoscopic drainage approach commences with a medial meatal antrostomy and anterior ethmoidectomy. The lamina papyracea is identified and partially removed to expose the periorbita. The periorbita may or may not need to be incised with a sickle knife (subperiosteal or intraconal). The subperiosteal abscess is exposed and drained. Pus samples should be obtained and sent for culture.

External or combined approaches are reserved for laterally located abscesses or when the endoscopic approach fails to relieve intraorbital pressure.

Frontal sinus osteitis with a subperiosteal abscess (or Pott's puffy tumor) will require a Draf II/Draf III procedure or rarely an osteoplastic approach to the frontal sinus, if reconstruction of the anterior wall is mandated. Alternatively, a minimally invasive external procedure (such as a trephination of the frontal sinus) may be used, with or without cannulation and topical installation of antibiotics in the frontal sinus.

Intracranial Complications

Intracranial complications are typically associated with frontal sinusitis, ethmoiditis or sphenoiditis, and surgical intervention will generally be necessary in almost all cases. The goal of such an intervention is to address the endocranial complication and treat "en route" the affected sinus whenever possible. In the presence of purulent sinusitis, adequate drainage of the involved sinus should be considered as sine qua non. Whether the drainage of the affected sinus (usually the frontal) will be via an endoscopic approach or an external trephination/exploration is debatable: Whilst some studies have shown potentially better outcomes by using the endoscopic approach [19], the counter-argument involves the risk of a postoperative frontal ostium stenosis as a result of operating endoscopically in a heavily inflamed, oedematous frontal recess. Craniotomy, a transfrontal approach, image-guided aspiration or simple burr-hole drainage may be used to drain epidural abscesses, brain abscesses or subdural empyemas, with the aim of reducing intracranial pressure and lowering the risk of recurrence from residual disease. Meningitis is the sole intracranial complication that has not been associated with better outcomes after endoscopic sinus drainage. The surgical treatment of cavernous sinus thrombosis includes drainage of the primary source of infection in the sinuses: The cav-

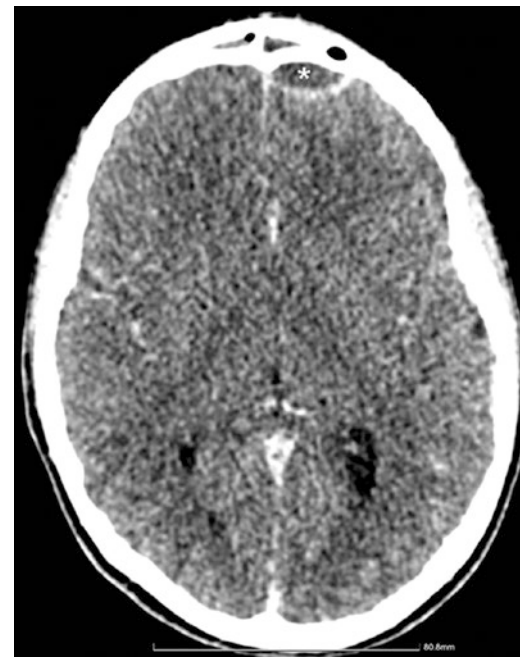

Fig. 29.9 Epidural abscess as a result of osteomyelitis of the frontal sinus (Pott's puffy tumor) showing at Fig. 29.4 (*asterisk*)

ernous sinus itself is not exposed as this has been shown to cause higher morbidity.

Clinical Examples

Case 1: A Case of Pott's Puffy Tumor with Epidural Abscess

A 14-year-old-boy was referred with progressive acute frontal sinusitis. He developed severe headache and nausea over 24 h that failed to respond to iv analgesics. He had tachycardia (108 bpm) and pyrexia (38.6 °C), and the white blood cell count was elevated. Vital signs met the criteria of sepsis.

Examination showed a soft mass on his forehead, consistent with osteomyelitis of the frontal sinus (Pott's puffy tumor). The diagnosis was confirmed by a CT scan, which also revealed an underlying epidural abscess (Fig. 29.9).

The frontal sinus was drained by endoscopic ethmoidectomy and drainage by a Draf II procedure that preserved the bony wall of the frontal drainage pathway. The epidural abscess was drained by a neurosurgical team after completion of the endoscopic procedure.

The patient recovered fully and showed no sign of recurrence over a 3-year follow-up time.

Case 2: A Case of Subperiosteal Abscess of the Left Orbit

A 4-year-old boy presented with acute onset of proptosis of the left eye 10 days after an upper respiratory tract infection. Orbital palpation showed mild tenderness but no restriction of eye movement. The swelling had commenced 3 days ago and had not improved with oral amoxicillin/clavulanate.

Endoscopy showed severe unilateral mucosal oedema but no evidence of mucopurulent discharge.

Intravenous antibiotics were initiated by the paediatricians, but he failed to no improve after

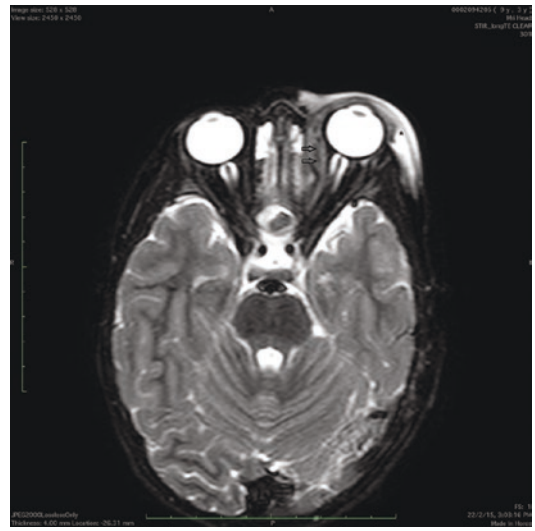

Fig. 29.10 MRI of a left subperiosteal abscess. Note the collection (*arrows*) affecting the medial rectus muscle as well as the eyelid oedema (*asterisk*)

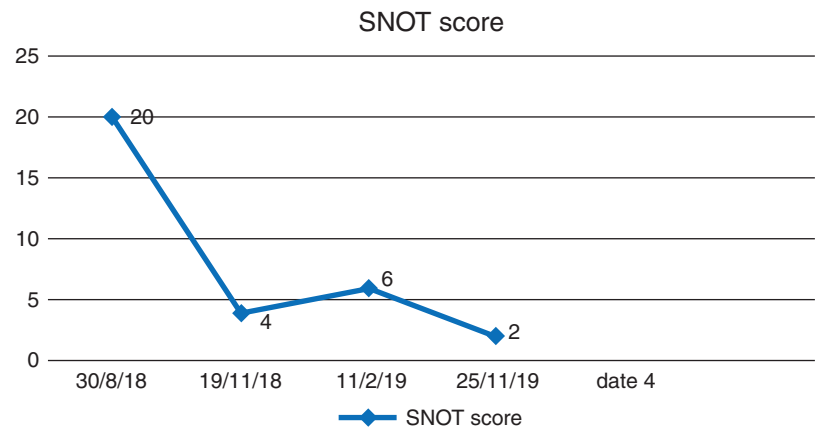

Fig. 29.11 Case 3 SNOT-22 score, over 1 year follow-up

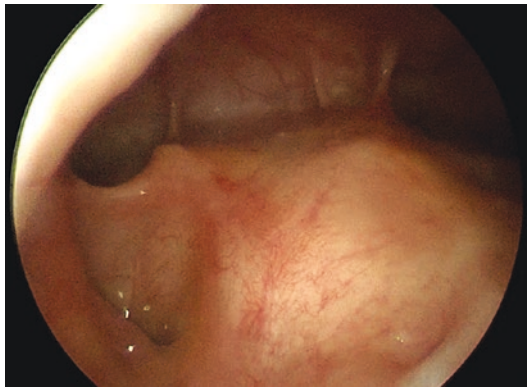

Fig. 29.12 Case 3: Endoscopic view of the patent frontal sinus drainage pathway (Draf 3 neo-ostium), 3 years after surgery

24 h. A scan was planned, but due to parental concern about irradiation, he underwent an MRI scan of the orbits that revealed a subperiosteal abscess (Fig. 29.10).

Ipsilateral endoscopic medial antrostomy and anterior ethmoidectomy were performed, resulting in almost complete resolution of symptoms within the next 48 h.

Case 3: A Case of Chronic Frontal Fungal Sinusitis with Coexisting Mucocele

A 17-year-old girl presented with a 12-month history of nasal obstruction, sleep disordered breathing and mild swelling of the right eye for 6 months (Fig. 29.7b). She was initially diagnosed with allergy. Her SNOT-22 score was 20 (Fig. 29.11).

She had diplopia in downward gaze and nasal endoscopy showed a polypoid mass blocking the anterior ethmoids.

An MRI scan was suggestive of a mucocele of the far lateral region of the right frontal sinus.

She underwent endoscopic surgery and drainage via a Draf III procedure. Nasal polyps surrounded by thick mucus were removed. She had a small defect of the right orbital roof that explained her diplopia.

Histopathology and cultures confirmed the presence of "allergic" eosinophilic mucin consistent with a diagnosis of allergic fungal sinusitis. Three years later, she remains asymptomatic, and endoscopic examination shows a patent Draf III neo-ostium (Figs. 29.7c and 29.12).

Areas of Controversy

1. Endoscopic versus open drainage for the frontal sinus in cases of acute infection with endocranial complications.
2. Is it ever safe to treat medically a well-defined orbital abscess?
3. Do antibiotics reduce the incidence of endocranial or orbital complications of ARS?
4. Do we always need to deal with the sinuses in cases of endocranial complications?

Key Learning Points

- Whilst the clinical presentation may vary between patients, infection can progress rapidly to become severe and dangerous.
- Early orbital periorbital complications of sinusitis usually respond to intravenous antibiotics.

- Early treatment with empiric intravenous antibiotics should be instigated to all patients with suspected complications.
- Antibiotic choice is determined by the most likely pathogens. These pathogens are typically *Streptococcus pneumoniae*, *Staphylococcus aureus* and *Pseudomonas aeruginosa*.
- The threshold for requesting a CT scan of the sinuses, orbit and head should be low.
- Endoscopic sinus surgery (ESS) remains the gold standard for treating most infective complications of ARS.
- Endoscopic surgical drainage should be performed early and not be considered as the last resort.
- Drainage of primary frontal/ethmoid sinus infection via ESS and a Draf II drainage procedure is likely to improve the clinical outcomes in patient with orbital and intracranial complications [19].
- Dexamethasone reduces local oedema and inflammation. The role of dexamethasone has been revised over the past few decades. It is now considered to improve the long-term outcome of sinogenic meningitis [20].
- Orbital abscess and cavernous sinus thrombosis are rare but serious surgical emergencies that require prompt intervention with high-dose broad-spectrum intravenous antibiotics and surgical exploration.

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Section V

Benign and Malignant Sinonasal Tumours

Sinonasal Papilloma

30

Usamah Hadi and Andrew C. Swift

Introduction

Sinonasal papilloma is an unusual benign tumor that can have extraordinary recurrence rates and the potential for transformation into squamous cell carcinoma. As a unilateral nasal mass, it presents as a challenging condition. The unilateral sinonasal symptoms, isolated nasal tumor, polypoid growth, or radiological sinus opacity are common entities that can mimic a host of clinical and other pathologic diseases. This unilaterality increases the burden for the surgeon to establish the correct diagnosis and treat the condition appropriately. The challenges posed during early tumor development result from the lesion forming in closed anatomical spaces without inducing noticeable symptoms. It is only in later stages of the disease when the tumor enlarges that symptom becomes apparent. The mainstay of management is surgical resection of the tumor. However, surgery for inverted papilloma has evolved from basic removal of nasal polypoid masses to extensive but precise endoscopic techniques.

The benign nature of the tumor led to surgical resection being performed by most ENT surgeons, but individual experience was often limited. Once the concept of the "oncological approach" of extensive resection via lateral rhinotomy and medial maxillectomy became fashionable, the operation was often done by surgeons with a head and neck interest.

With the development of endoscopic techniques and a better understanding of the biological behavior, the management has progressed. Most tumors can now be treated very effectively with endoscopic endonasal techniques with much improvement in the postoperative morbidity. There is still a place for external surgery, but this is now used with expert planning, often being combined with endoscopic surgery.

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U. Hadi
Department of Otolaryngology HNS, American University of Beirut Medical Center, Beirut, Lebanon

Rhinology Division, American University of Beirut Medical Center, Beirut, Lebanon
e-mail: uh00@aub.edu.lb

A. C. Swift (✉)
Liverpool Head and Neck Centre, Liverpool University Hospitals Foundation Trust, Liverpool, UK

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Terminology: WHO Definition

The terminology of sinonasal papilloma is confusing and imprecise [1]. Older historical terms such as Schneiderian papilloma and Ringertz tumor are so well established that they continue to be used. The Schneiderian membrane is a historical term for the nasal mucosa, named in honor of a seventeenth-century German anatomist, Professor Konrad Viktor Schneider of Wittenberg (1614–1680), who published his work on the nasal mucous membrane and catarrh, refuting the theory that nasal secretions originated from the pituitary gland.

A sinonasal papilloma is defined as a benign epithelial tumor composed of well-differentiated columnar or ciliated respiratory epithelium with variable squamous differentiation [2].

The nomenclature of papilloma lacks precision, and various terms are used. The World Health Organization classified sinonasal papilloma into three histological subtypes: these include inverted, exophytic, and oncocytic subtypes (Fig. 30.1a–c).

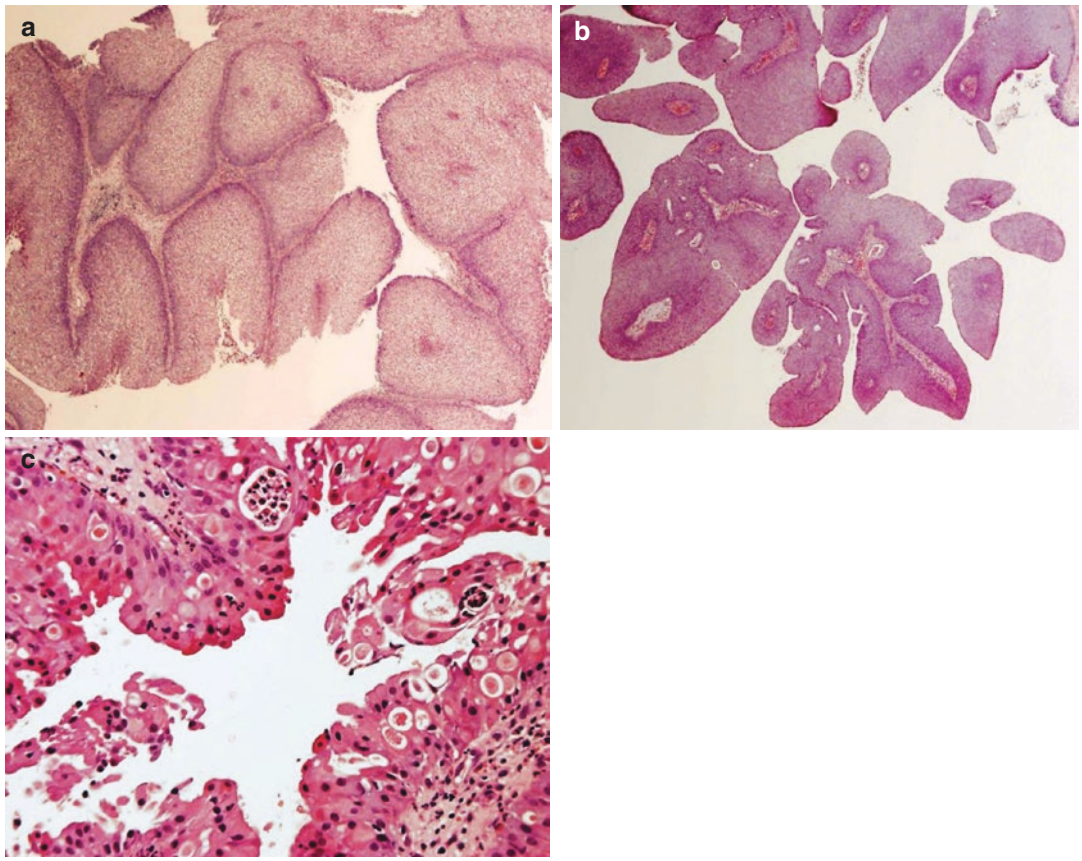

Fig. 30.1 Histological subtypes of sinonasal papilloma: (**a**) Inverted papilloma. (**b**) Exophytic papilloma. (**c**) Oncocytic papilloma

Pathogenesis

Overall, sinonasal papilloma accounts for 16% of all unilateral nasal polypoid lesions [1]. Inverted papilloma (IP) accounts for 0.4–7% of sinonasal cavity tumors [3]. The incidence is uncommon and ranges between 0.6 and 1.5/100,000 per year; the gender ratio is 5 men to 1 women; the peak incidence is 55 years [4]. Inverted papilloma typically originates along the lateral nasal wall or maxillary sinus and has a propensity to recur.

The estimated prevalence of each of the three main histological subtypes is inverted (62%), exophytic (32%), and oncocytic papilloma (6%).

Inverted Sinonasal Papilloma (IP) (Fig. 30.1a)

Histologically, an inverted papilloma appears as thickened respiratory epithelium that protrudes into the underlying stroma. The protrusions do not invade the underlying basement membrane and give the characteristic "inverted" description [1]. The respiratory epithelium may be accompanied by squamous cells or have a transitional cell appearance, but it is strictly not transitional cell epithelium as occurs typically within the bladder. The microscopic appearance of ISP can be combined with exophytic histological features.

Intraepithelial neutrophilic inflammation is a characteristic feature.

In contrast to inflammatory nasal polyps, eosinophils are sparse throughout the stroma of the papilloma.

Exophytic Papilloma (Fig. 30.1b)

The exophytic papilloma has a characteristic histological exophytic growth pattern and is difficult to differentiate from a warty growth, both microscopically and macroscopically.

Oncocytic Sinonasal Papilloma (Fig. 30.1c)

The oncocytic tumor displays columns of cylindrical cells that may have endophytic and exophytic features. The oncocytic papilloma has a characteristic histological appearance; clinically, it behaves in a similar way to inverted papilloma, and the recurrence rate and malignant tendency are about the same for both tumor types. This subtype accounts for 3–5% of sinonasal papilloma. It has been referred to as a microcystic papillary adenoma and may be misdiagnosed as a low-grade adenocarcinoma.

For the purpose of simplicity, the oncocytic papilloma will not be differentiated from the IP within the various sections of this chapter.

Etiology

The etiology of sinonasal papilloma is unknown. However, most research is focused on inverted papilloma.

A viral etiology has been considered, but the evidence for Epstein–Barr virus (EBV) is inconclusive [5]. Evidence for human papillomavirus (HPV) being associated with sinonasal papilloma has been reported but is inconsistent and variable [6]. Recent reports do not support HPV as having an etiological role in the pathogenesis of inverted papilloma, nor in tumor recurrence [7, 8].

Malignant Transformation

The transformation rate of inverted papilloma to malignancy is estimated to be about 7.6% with malignant change being either synchronous (7.1%) or metachronous (3.6%) [9]. However, one substantial review found only 1.9% malignant transformation (740 patients over 10 years), with no specific identifiable risk factors. Most

malignant transformations arose within an existing inverted papilloma, and metachronous tumors were always preceded by recurrence [10].

The most likely malignancy to arise from cell transformation in inverted papilloma is transitional cell carcinoma. Squamous cell carcinoma (SCC) is sometimes associated with coexisting inverted papilloma. However, such tumors are often well advanced at presentation and the coexistence of tumor types may just be a pathological phenomenon due to abnormal development of cell lines rather than malignant transformation from inverted papilloma.

Diagnosis of malignant transformation: The endoscopic appearance of malignant transformation may not be obvious, and biopsies will only be diagnostic if taken from an affected area.

Confirmation of the histological diagnosis may be challenging and is dependent on the specialist expertise of the histopathologist and consideration of tumor behavior. Low-grade malignant cells are not easily identified in the early stages of tumor formation. With time, this leads to an underdiagnosis of squamous cell carcinoma, and once clinically apparent, it is later reported as malignant transformation.

Reasons for transformation: Why transformation occurs is not fully understood. Research into the etiology and risk of malignant change by exploring the whole human genome seems logical but would be extremely challenging and expensive.

Factors that have been considered include the cell cycle, angiogenic factors, environmental and occupational exposure, chronic inflammation, and viruses [11]. Whilst the viral theory for malignant transformation is very topical and seems logical, there is no definite proof that this is the case. However, inverted papilloma is uncommon, and malignant transformation even more uncommon. In order to address this particular dilemma, large meaningful standardized multicenter studies with robust methodology are required. However, a recent meta-analysis does report an increased risk of malignancy in patients infected with HPV 16, 18, 11/16, and 16/18 compared to those with HPV 6, 11, and 6/11 [12].

Biomarkers of Malignant Transformation

There is currently no agreement about the principal biomarkers that will either predict the risk of transformation or identify malignancy (IP-SCC) (see Table 30.1).

Tumors with concomitant positive HPV are often accompanied with biomarkers associated with early carcinogenesis such as elevated epidermoid growth factor receptor (EGFR) and transforming growth factor-alfa (TGF-a).

Mutation of the p53 tumor suppressor gene and increased expression of p21 and p53 have been described in associated malignancy [22, 23]. However, the degree of atypia or dysplasia is not closely associated with malignant change.

Table 30.1 Biomarkers, inverted sinonasal papilloma, and malignancy (references listed in a separate list)

Biomarker	Description	References
P53	Opinion remains inconclusive	[13]
P21 Cyclin-dependent kinase inhibitor Muscle segment homeobox gene MSX2 Tumor suppressor gene PDCD4	Evidence inconclusive	[14]
Serum squamous cell carcinoma antigen	Elevation linked with progression, growth, and recurrence of ISP	[15, 16]
Fascin protein	Levels increased in severe dysplasia	[17]
Survivin	Apoptosis inhibitor higher in malignancy	[18]
COX-2	Possible association with malignancy	[19]
Osteopontin-vascular endothelial growth factor (VEGF)	Affects tumor growth and angiogenesis. Increased in higher stage IP	[20]
Ki-67	Marker of cell proliferation. Possible predictor of prognosis and malignancy	[21]

Clinical Features

A sinonasal papilloma typically presents as a unilateral nasal lesion with nonspecific features.

Exophytic Sinonasal Papilloma (ESP)

The exophytic sinonasal papilloma typically presents as a warty growth within the anterior part of the nasal cavity (Fig. 30.2). These lesions typically occur on the anterior nasal septum in a younger age group. Exophytic papilloma may extend superiorly and inferiorly to the nasal floor. They may be multiple and spread to the posterior nasal cavity. Recurrence is likely, but there is typically no risk of malignant change. Rarely, the tumour may change character to become an inverted sinonasal papilloma, supporting the view that all excised tissue should be sent for histopathological review.

Inverted and Oncocytic Sinonasal Papilloma (ISP, OSP)

Presenting symptoms: Symptoms include nasal obstruction, anterior and/or posterior rhinorrhea, headache, hyposmia or anosmia, epistaxis, and facial pain. Inverted papilloma may mimic any sinonasal disease. Epiphora may occur should the nasolacrimal duct be involved. Isolated sphenoid lesions may present with nonspecific symptoms such as headache, diplopia, and visual anomalies [24]. Sinonasal papilloma can present as an unexpected finding in patients with other pathologies [25].

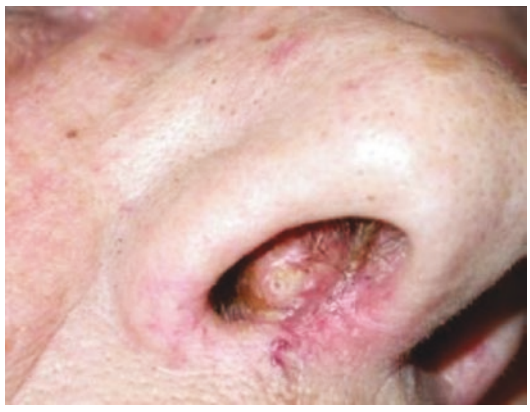

Fig. 30.2 Exophytic papilloma

The duration of symptoms is reported to range from 5 months to 20 years with a mean duration of 3.9 years [26].

Endoscopic appearance: The inverted papilloma typically appears as a polypoid pale gray mass with a grapelike irregular, convoluted, papillary surface with multiple digitations. The endoscopic appearance is variable and can be difficult to differentiate from a "simple" inflammatory nasal polyp; it can also present as an inflamed vascular polypoid lesion (Fig. 30.3a–d). The indistinct appearance makes it even more important to submit all surgically removed polypoid tissue to histological review.

Tumor site: ISP typically arises from the lateral nasal wall adjacent to the middle turbinate (Fig. 30.3a–c).

Tumors can arise from various sites within the sinonasal cavity: ethmoid 48%; maxillary sinus 28%; sphenoid sinus 7.5%; frontal sinus 2.5%; inferior turbinate 2.5%; and nasal septum 2.5% [27].

Sinonasal papilloma may extend beyond the ethmoid to the frontal or sphenoid sinuses [28]. Isolated lesions of the sphenoid sinus are unusual. There are occasional instances of inverted papilloma affecting the nasal vestibule, lacrimal sac, and nasal floor (Fig. 30.3d).

Bilateral sinonasal papillomata are unusual: the incidence of bilateral disease is <1–9%. Malignancy should always be excluded in such cases [29, 30].

Intracranial spread is infrequent but more likely in recurrent tumors that transgress the cribriform plate or ethmoid roof [31].

Intraorbital extension may occur in lesions with extensive ethmoid involvement and typically pushes orbital contents laterally, without invading the periorbita [32].

Differential Diagnosis: An isolated unilateral nasal polyp or mass should raise the suspicion of an inverted papilloma. Unilateral lesions may present as a single small polyp, numerous polyps (Fig. 30.3b), or a single large polyp that looks similar to an antrochoanal polyp.

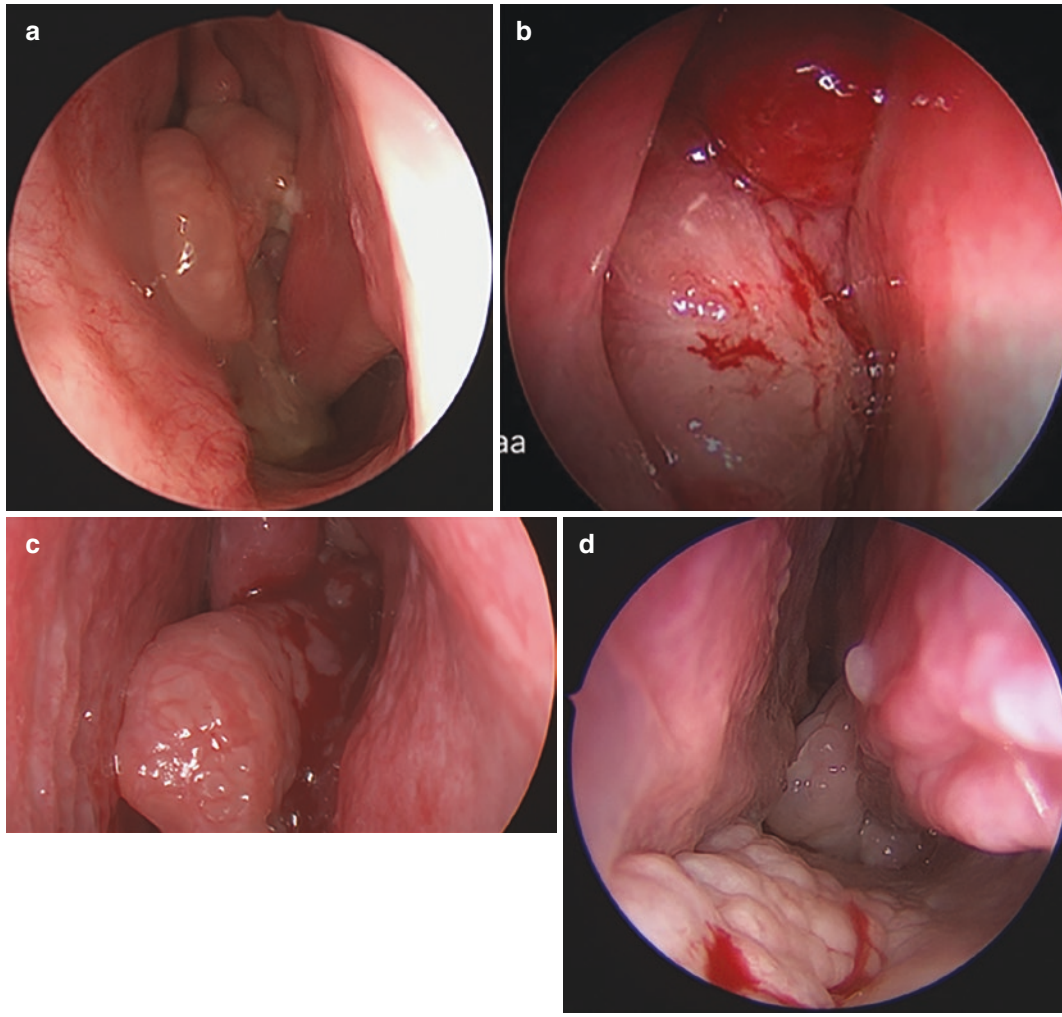

Fig. 30.3 (**a**–**d**) Various endoscopic appearances of inverted papilloma. (**a**) Multiple smooth polypoid lesions. (**b**) Single hemorrhagic polyp. (**c**) Inverted papilloma emanating from middle meatus. (**d**) Endoscopic view of IP arising on nasal floor.

A rare polypoid lesion that can cause histological dispute or confusion is the respiratory epithelial adenomatoid hamartoma (REAH). This is an epithelial proliferation of columnar epithelium in a setting of chronic rhinosinusitis. There is controversy amongst pathologists as to whether this is neoplastic, nonneoplastic, or premalignant.

Other rare lesions to exclude are:

- Malignant tumors such as squamous cell carcinoma, adenocarcinoma, lymphoma, and esthesioblastoma/olfactory neuroblastoma
- Other benign lesions that may be associated with polyp formation, such as mucoceles, dental keratocyst, fibro-osseous lesions, and fungal disease

Association with Nasal Polyps

Inverted papilloma may coexist with chronic rhinosinusitis with nasal polyps (CRSwNP), but the reported incidence is <1%. This reinforces the importance of subjecting all resected polyps to histological review, noting especially the side that the tissue was taken from.

The low reported incidence of ISP with nasal polyps may be due to various factors: many may

go unreported, sampling may be incomplete during surgery and histological analysis, and histological expertise may vary. Histology of polyps is not a precise science; it has been suggested that 17% of papillomas are initially diagnosed as inflammatory polyps [33]. It is also important to appreciate that hyperplastic polyps may be misdiagnosed histologically as inverted papilloma.

Imaging

The combination of CT and MRI scans is complementary to each other and helps to establish a diagnosis and evaluate the extent of the tumor.

High-resolution CT sinus scan: CT is sensitive but nonspecific. The scan typically shows a unilateral lobulated heterogeneous mass with characteristic increased 'calcified' densities in 20% of cases (Fig. 30.4) [34]. The opacity often originates from the middle meatus and extends to the maxillary antrum, nasal cavity, and/or frontal sinus.

CT does not differentiate between trapped mucus and tumor extension, especially in an opaque frontal or sphenoid sinus. CT scans show excellent bone definition that may demonstrate diffuse sclerotic bony thickening or bone dehiscence. Hyperostosis can appear as a central plate-like lesion (or as a "cone-shaped" prominence) [35]. Localized hyperostosis or irregular sclerosis along the sinus wall often correlates with tumor origin and attachment (positive predictive value (PPV) of 89–95%) [36].

Bone remodeling and resorption showing localized bony sinus dehiscence suggest bone destruction from malignant transformation and, whilst not diagnostic, require urgent management and exploration (Fig. 30.5a) [37].

MRI scan of sinuses (see Table 30.2*)*: MRI is particularly helpful in differentiating the tumor interface from retained mucus and inflammatory sinonasal mucosa from tumor (Fig. 30.6) [38]. An MRI scan has a 93–100% positive predictive value of diagnosing inverted papilloma and may also accurately identify tumor attachment.

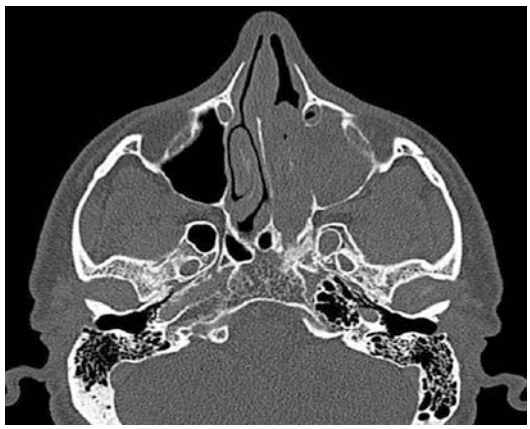

Fig. 30.4 CT sinus scan showing calcified densities

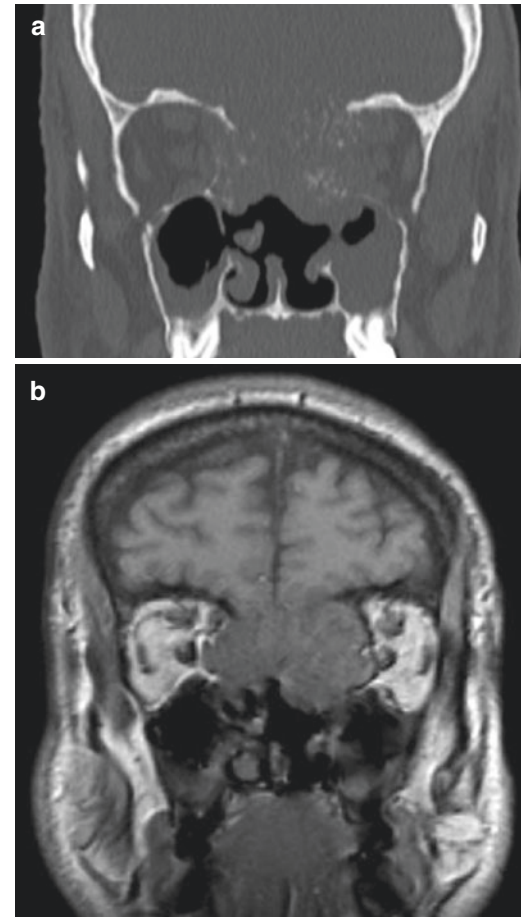

Fig. 30.5 CT and MRI sinus images of malignant transformation to transitional cell carcinoma invading the anterior skull base: (**a**) Coronal CT scan of sinuses. (**b**) MR scan of sinuses/head

Table 30.2 Characteristic features of inverted sinonasal papilloma on MRI scans

T1-weighted MRI sequence	
T1-weighted	IP is hypointense but hyperintense post-gadolinium Hyperostosis appears hypodense
T1 and T2 sequences	Diffuse convoluted cerebriform pattern (CCP)
T2-weighted MRI sequence	
T2-weighted sequences	Tumor iso- or hypointense compared to the normal mucosa
T2-weighted images	Interchanging hypointense and hyperintense bands
Post-gadolinium sequences	
T1-weighted images	Interchanging hypointense and hyperintense bands
Key features	
MRI and CT combined images	Diffuse convoluted cerebriform pattern (CCP) and bone remodeling on CT scan

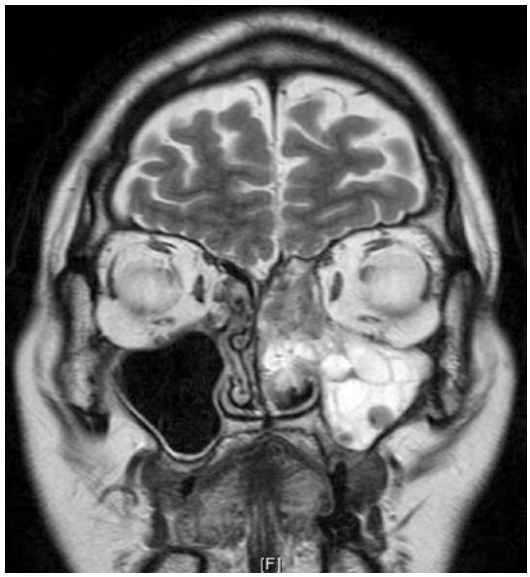

Fig. 30.6 MRI sinus scan showing inverted sinonasal papilloma of left ethmoid and mucus collection trapped in maxillary sinus

MRI may also demonstrate features of malignancy, and transformation should be considered if there is localized disruption of the convoluted cerebriform pattern and bone destruction [39] (Fig. 30.5b).

PET-CT scan: PET-CT studies show a higher maximum standard uptake value (SUV*max)* of FDG uptake by inverted papilloma lesions that is even greater with malignant transformation (IP-SCC) [40].

PET-CT is useful in evaluating patients with IP-SCC but is not a dependable diagnostic modality in those patients without cancer and may erroneously diagnose malignancy should the SUV be high.

Classification

Several staging systems have been described for inverted papilloma, according to radiological signs, tumor site, extent, and origin [4, 41–45].

The Krouse staging system is based on a radiological evaluation of tumor extent and is popular, simple, reproducible, and comprehensive (Table 30.3) [41]. The classification correlates with outcome but does not guide therapeutic management [46].

Table 30.3 Krouse staging system for inverted papilloma

T_1	Tumor confined to nasal cavity
T_2	Tumor involving the ostiomeatal complex, ethmoid sinuses, and/or medial portion of maxillary sinus ± involvement of nasal cavity
T_3	Tumor involving the lateral, inferior, superior, anterior, or posterior walls of maxillary sinus, the sphenoid sinus, and/or the frontal sinus with or without involvement of the nasal cavity
T_4	All malignant tumors and those tumors with extranasal and extrasinus extension

Management

Surgical resection is key in the management of sinonasal papilloma.

Exophytic Sinonasal Papilloma

Exophytic papilloma lesions should be completely excised, leaving the underlying cartilage exposed. The denuded area of mucosa will normally heal over a period of weeks, but extensive resection may risk fibrosis that may later obstruct the nasal valve.

Inverted Sinonasal Papilloma

Surgery to resect inverted papilloma ranges from limited removal of an intranasal polypoid mass to extensive resection with associated potential risks. The primary aim of surgery should ideally be to achieve complete resection of the tumor to prevent recurrence and eliminate the risk of malignant transformation.

Occasionally, complete resection may not be possible during a single operation. Circumstances include the operative conditions, bleeding, anesthesia, instruments, or equipment failure. However, staged resection is perfectly acceptable in such instances.

Widespread field change within the nasal cavity may cause a dilemma regarding the completeness of clearance. Radical resection of nasal mucosa that creates a large, denuded area within the nose may cause long-term crusting. Inadequate clearance will lead to increased risk of recurrence. Such situations are best managed by considered definitive planned treatment following histological confirmation and further clinical evaluation.

Radiotherapy might be occasionally recommended as an alternative modality for patients with medical conditions that preclude surgical intervention.

Whilst malignant change has been reported in 5–15% of cases of inverted papilloma, these estimates are often from large tertiary referral centers that will attract the more challenging tumors, especially if malignant. Most ENT surgeons will mostly see benign sinonasal papillomata and very little malignancy. A balance must be struck, and whilst patients should not be overly alarmed by quoting a relatively high risk of malignancy, there must be a degree of caution and vigilance.

The clinical features that may suggest an increased risk of malignancy include aggressive tumor behavior, rapid recurrence after resection, bone remodeling and erosion, and invasion beyond the sinuses into adjacent vital structures.

External Surgical Approach Vs. Endoscopic Resection

Prior to the development of endoscopic techniques, lateral rhinotomy and medial maxillectomy became the preferred operation of choice many years ago, enabling complete removal of lesions arising from the lateral nasal wall. Midfacial degloving offered an alternative approach for extensive tumors. Extension to the frontal sinus was typically resected via an osteoplastic flap.

Lateral rhinotomy reduced the high incidence of tumor recurrence compared to previous surgical methods but carried a risk of complications such as epiphora, chronic dacryocystitis, transient diplopia, Eustachian tube dysfunction, facial scars, scar contraction, as well as a longer hospital stay.

However, with the advent of minimally invasive endonasal endoscopic techniques, excellent tumor resection with minimal morbidity and outcomes became feasible. Endoscopic resection is now accepted as the preferred gold standard of care.

Whilst the old concept of radical oncological resection with wide tumor margins is no longer justified for benign sinonasal papilloma, resection must still be complete and performed with precision to decrease the likelihood of later tumor recurrence.

Combined Approach Surgery

Tumors that extend across several sinuses may be best addressed by a combined approach. Selecting the precise approach is at times a difficult surgical judgement and will depend on personal expertise, location and size of the tumor, risk of complications, and medical factors that may influence the type of surgery.

Whilst most inverted papillomas can be removed endoscopically, the endoscope can be combined with external surgery to enhance the exposure and access to the tumor.

Endoscopic surgical images enable a magnified view of the tumor and its attachment, thus facilitating precise resection but minimizing unnecessary removal of healthy tissues (Video 30.1). Endoscopic surgery will also facilitate the early recovery and return of normal mucociliary flow.

Management options must be explained to the patient during the consent process, and patient choice may then determine the type of procedure. Adjuvant therapy should also be considered in difficult situations.

Attachment-Oriented Endoscopic Resection and Frozen Section

The concept of attachment-oriented endoscopic resection for inverted papilloma was described in 2008 [47]. The key surgical steps include:

1. Tumor debulking
2. Precise identification of the tumor's mucosal attachment site
3. Dissection of the subperiosteal attachment site
4. Excision of the tumor attachment site and its surrounding normal mucosa with frozen section control if available and considered necessary
5. Resection or drilling underlying bone at the tumor attachment site

Gentle drilling of the bone surface by a diamond burr with irrigation/suction channel at the tumor attachment site ensures removal of microscopic disease, thus reducing the likelihood of recurrence (Video 30.2). Precise mucosal clearance from the attachment site with small pediatric micro-instruments is most important should the tumor base be inaccessible to accurate drilling. Frozen section should be considered in difficult situations but relies on local availability and services.

Categorization of Tumor and Surgery

Attempts have been made to categorize the tumor and its treatment to standardize management and interpretation of outcomes (Tables 30.4 and 30.5) [48, 49].

Table 30.4 Categorization by tumor characteristics and treatment

Definition of tumor	Description of tumor
Primary tumor	No preceding surgery Diagnosis confirmed by biopsy
Residual tumor	Preceding endoscopic surgery for polyps Histology unexpectedly reported as inverted papilloma
Recurrent tumor	Previous surgery for inverted papilloma Tumor recurrence necessitating revision surgery

Table 30.5 Classification of tumor extent and surgery

	Extent of tumor	Extent of surgery
Type 1: Fig. 30.7a	Confined to middle meatus	Endonasal endoscopic ethmoidectomy Wide maxillary antrostomy Sphenoidotomy
Type 2: Fig. 30.7b	Extends beyond frontal recess	Radical ethmoidectomy Medial maxillectomy Resection of middle turbinate Widening of frontal recess by Draf II–III
Type 3: Fig. 30.7c	Involves alveolar recess mucosa; posterolateral, anterior, or inferior walls of maxillary sinus	Endonasal modified Denker procedure

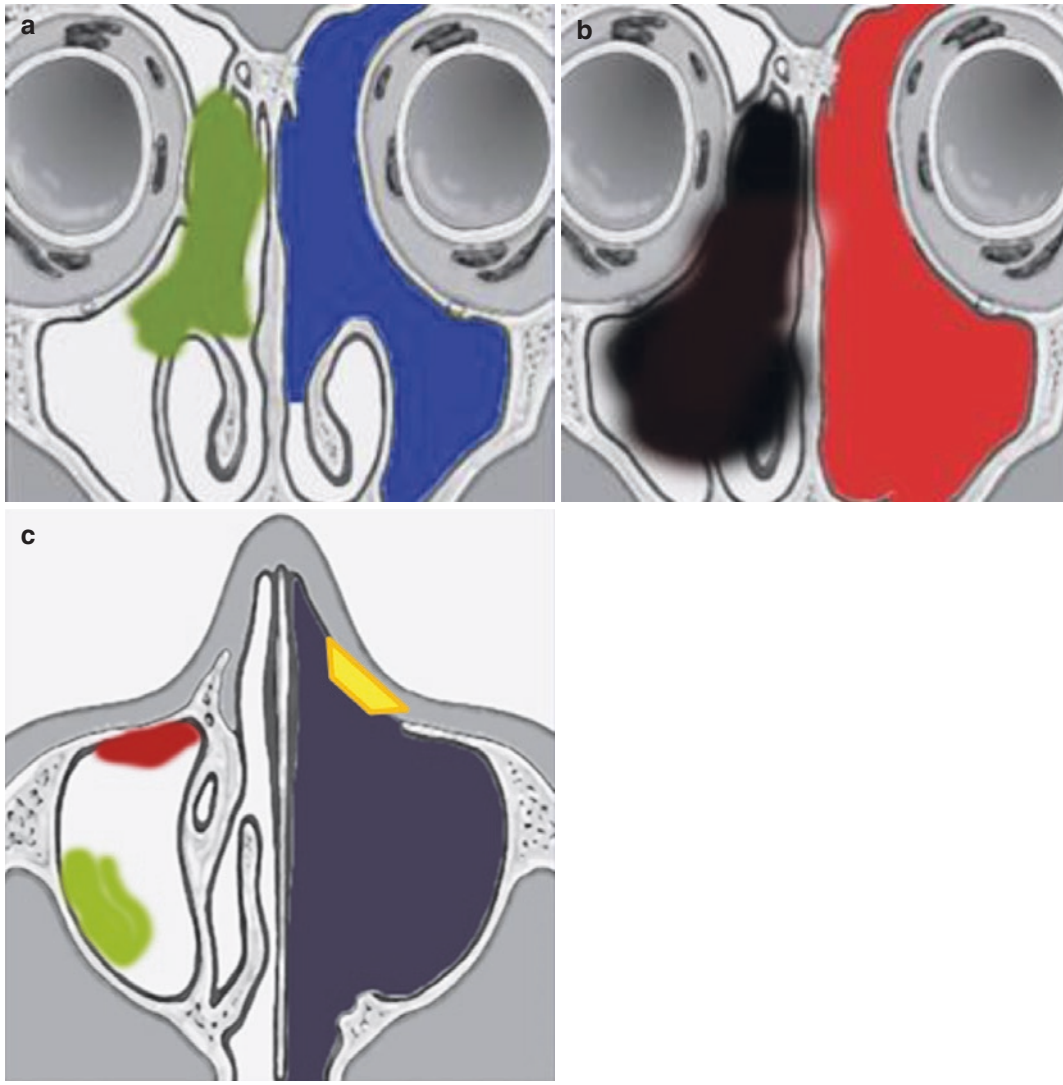

Fig. 30.7 (**a**) Type 1 tumor resection. Extent of inverted papilloma shown in green. Endoscopic ethmoidectomy with wide antrostomy and sphenoidotomy shown in blue. (**b**) Type 2 tumor resection. Extent of inverted papilloma shown in black. Medial maxillectomy with ethmoidectomy and sphenoidotomy for IP partially invading the maxillary sinus shown in red. (**c**) Type 3 tumor resection. Maxillary sinus lesions of lateral and/or anterior wall shown in green/red. Bony window entrance shown in yellow. Extended endoscopic medial maxillectomy, with extension to anterior maxillary wall, shown in blue

Maxillary Sinus Surgery

Inverted papillomas arising from the lateral, inferior, or anterior maxillary sinus wall involvement may require extended endoscopic medial maxillectomy (Video 30.3), transnasal endoscopic partial maxillectomy/modified Denker approach, or endoscopic prelacrimal recess maxillary window [50].

Transnasal Endoscopic Partial Maxillectomy (TEPM): This procedure requires removal of the lateral nasal wall facilitating wide access into the maxillary sinus. The bony resection may extend to include the adjacent piriform aperture and anterior wall of the maxillary sinus but preserving the infraorbital wall (modified Denker procedure: Fig. 30.8; Videos 30.3 and 30.4) [51].

Transection of the nasolacrimal duct may be required, but nasolacrimal drainage normally remains unaffected, and stents are not required.

Combined approaches such as transnasal endoscopic surgery with a Caldwell-Luc procedure offer a good alternative for surgeons who are not trained in advanced endoscopic techniques.

Endoscopic Prelacrimal Recess Approach: A relatively recently described approach is the prelacrimal recess operation, which preserves the integrity of the inferior turbinate and the nasolacrimal duct (Fig. 30.9; Video 30.5). An intranasal mucosal flap is raised on the lateral nasal wall in the anterior nasal cavity. The inferior turbinate concha is sepa-

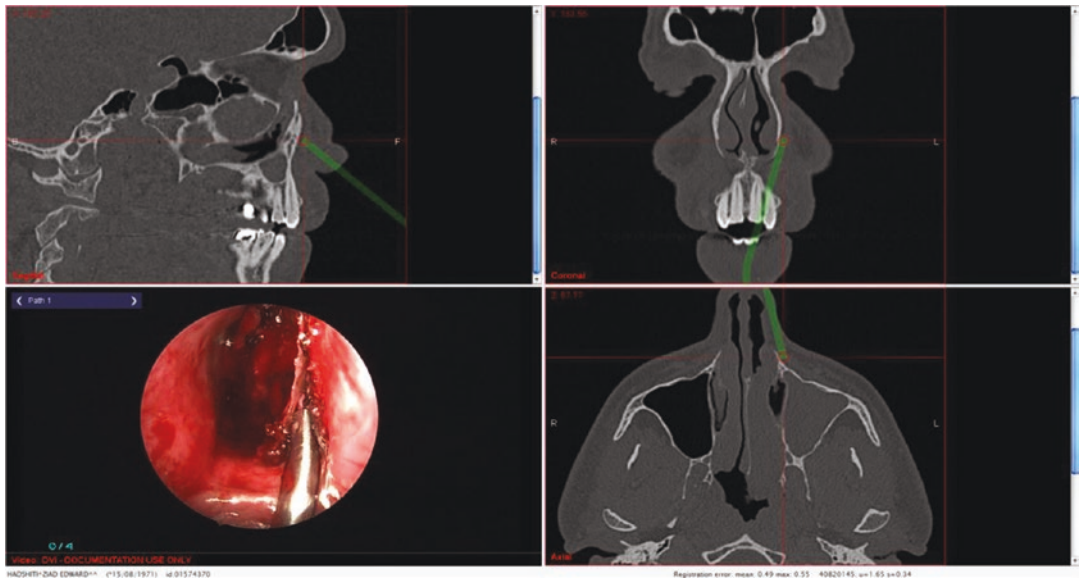

Fig. 30.8 Endoscopic modified Denker procedure. The anterior bony section of the left piriform aperture is removed and extended to include the anterior maxillary sinus wall

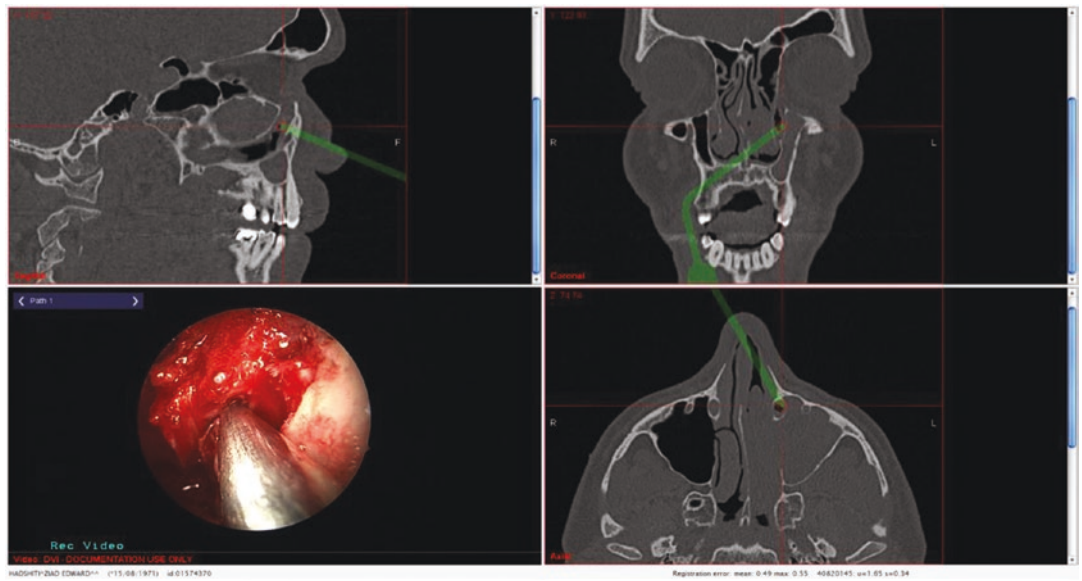

Fig. 30.9 The prelacrimal recess approach to the maxillary sinus. The bony window is created anterior to the nasolacrimal duct

rated from the maxilla, and the anterior bony lateral wall is removed with chisels or a diamond burr, exposing but preserving the nasolacrimal duct. This provides excellent access to remove inverted papilloma from the maxillary sinus. Finally, the anterior mucosal flap is returned to the lateral nasal wall and the posteriorly displaced inferior turbinate is repositioned back to its normal position. It is however advisable to leave an access window into the maxillary sinus for post-operative clinic review should the tumour recur.

Frontal Sinus Surgery

Sinonasal papillomas within the frontal sinus may arise from protrusion of an anterior ethmoid mass that passes through the frontal os. Alternatively, the tumor can arise directly from the mucosa within the frontal sinus. The preoperative evaluation is assisted greatly by a combination of a CT sinus scan as well as an MRI sinus scan.

Resection poses several challenges that are determined by the anatomy and size of the frontal sinus, tumor size and attachment, residual effects from previous surgery, and extension beyond the confines of the frontal sinus.

Large frontal sinus tumors are typically removed by piecemeal resection. The principles of attachment-orientated surgery apply and include identification of the tumor attachment, subperiosteal dissection, and drilling of the underlying bone. Drilling underlying bone in tumors attached to the cribriform plate or the posterior frontal sinus wall may risk a CSF leak. Should a CSF leak occur, repair is best done at the time or soon after the tumor surgery.

Whether a papillomatous dural lesion should be excised and repaired is debatable and may lead to intracranial spread. Bipolar diathermy of the tumor attachment may be a safer effective approach. Frozen section of the mucosal margins may be helpful and should be considered in this situation.

Detailed surgical planning is essential [52]. Key decisions are determined by the local anatomy, pneumatization, extent of tumor attachment, and tumor extension.

Endonasal endoscopic Draf IIa and IIb frontal sinusotomy: Suitable for tumors affecting a small frontal sinus or those limited to the medial aspect of the frontal sinus (Video 30.6).

Endonasal endoscopic Draf III frontal sinusotomy/sinuplasty: Inverted papilloma within an extensively pneumatized frontal sinus.

Extended transorbital-transnasal endoscopic technique: For more extensive tumors as an alternative to an external approach.

Coronal incision and osteoplastic bone flap: Indicated where the tumor attachment within the frontal sinus is extensive; for multifocal disease; in tumors that extend laterally; and for tumor recurrence after a previous Draf type III procedure [53].

External or combined external/endoscopic surgery: Indicated for tumors located in superior or lateral sites within the frontal sinus. External trephination of the frontal sinus should provide a good endoscopic view within the frontal sinus, especially where an obstructed frontal os is being opened.

Radical external or combined external/endoscopic surgery: Indicated for tumors extending beyond the confines of the bony sinus walls into the orbit of intracranial cavity; where there is involvement of the dura; or where malignant transformation has occurred. Craniofacial resection is an option in such tumors [54].

Techniques to avoid: Frontal sinus cranialization, obliteration, or occlusion with bone wax or other resorbable material should be avoided as evaluation for recurrence will be impaired.

Relative contraindications and suggestions with regard to endoscopic frontal sinus surgery are shown in Table 30.6.

Sinonasal papilloma may be an extensive disease that necessitates complex surgery to obtain complete clearance. A series of procedure plans and surgical options is demonstrated in Table 30.7.

Table 30.6 Contraindications to endoscopic frontal sinus surgery

Relative contraindications to endoscopic resection	Mandatory avoidance of endonasal endoscopic surgery
Narrow frontal os (AP diameter <1 cm)	Very narrow or unidentified frontal os
Extension of tumor through the anterior skull base or posterior wall	Massive erosion of the anterior skull base or posterior wall, with intradural invasion
Lateral attachment of tumor, especially in a well-pneumatized frontal sinus	Intraorbital extension (consider transorbital endoscopic surgery)
Extensive scar tissue from previous surgery or post-traumatic bony anatomical anomalies	Massive scar tissue formation after previous frontal sinus surgery
Histological evidence of squamous cell carcinoma (biopsy or frozen section)	Extensive squamous cell carcinoma
Tumor attachment to the anterior or the upper half of the posterior frontal sinus wall	Extensive tumor within a pneumatized frontal sinus

Table 30.7 Summary of surgical plans according to the extent of sinonasal papilloma

Surgical plan	Tumor site	Extent of surgery
Plan 1	Confined to middle meatus, ethmoid complex, sphenoid, frontonasal recess	Endoscopic medial maxillectomy with extended frontal sinusotomy and sphenoidectomy
Plan 2	Involves lateral, inferior, anterior wall of maxillary sinus	Extended endoscopic medial maxillectomy ± intranasal endoscopic prelacrimal recess approach to maxillary sinus or ± modified Denker operation or combined anterior antrostomy and Caldwell-Luc procedure (if endoscopic experience is limited or not available)
Plan 3	Extends to skull base, nasolacrimal region, and orbit	Extended endoscopic medial maxillectomy with resection of inferior turbinate ± preservation or resection of nasolacrimal duct ± endoscopic skull base repair or craniofacial approach
Plan 4	Tumor within frontal sinus with mucosal involvement up to midpoint of orbit	Endoscopic frontal sinusotomy (Draf IIa or IIb) or Draf III procedure or combined with endoscopic frontal trephine approach
Plan 5	Tumor within frontal sinus with mucosal involvement past midpoint of orbit	Endoscopic endonasal orbital transposition technique (120) or endoscopic frontal access via frontal trephine or frontal access via an osteoplastic flap

Sphenoid Sinus Surgery

Sinonasal papilloma is least common in the sphenoid sinus and sphenoethmoid recess. The tumor may be in proximity to vital structures such as the internal carotid artery, the optic nerve, and the pituitary gland, making complete resection much more challenging (Fig. 30.10).

Good exposure is achieved by removing the anterior wall of the sphenoid sinus bilaterally, together with the rostrum and posterior third of the nasal septum. Lateral recess tumors in a pneumatized sphenoid sinus may need a wider extended exposure via a trans-ethmoid-pterygoid sphenoid approach.

Subperiosteal dissection for attachment-orientated surgery may be compromised by the risk to the integrity of the carotid artery and/or injury to the optic nerve.

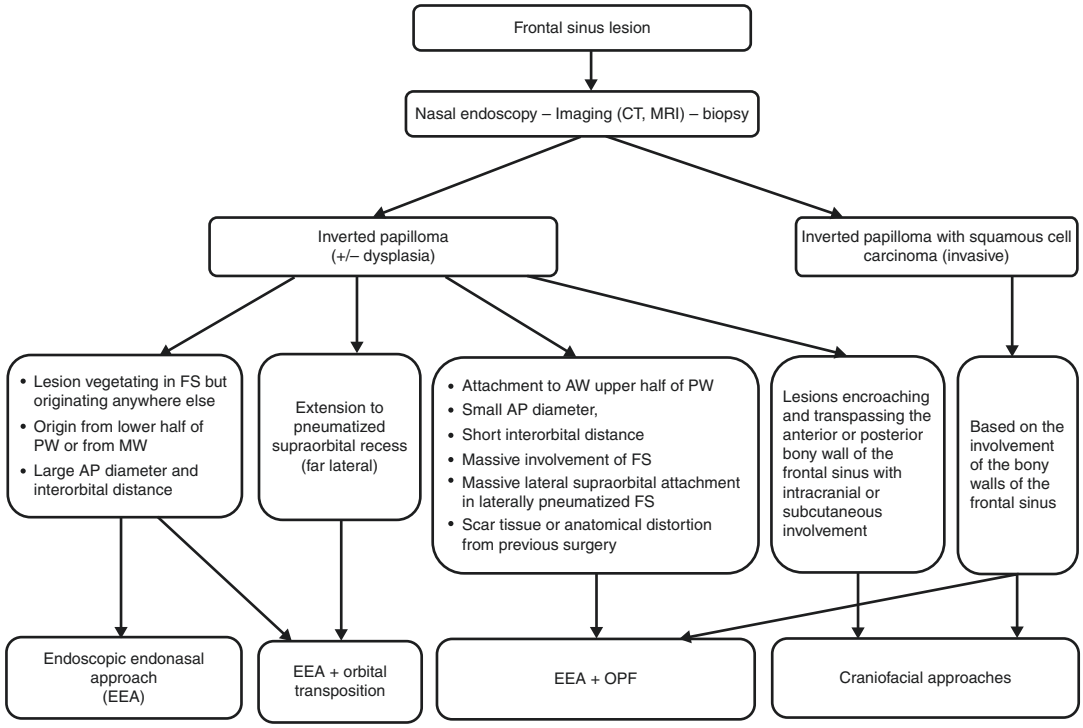

Fig. 30.10 Algorithm for planning surgical resection of frontal sinonasal papilloma. *AP* anteroposterior, *FS* frontal sinus, *PW* posterior wall, *MW* medial wall, *AW* anterior wall, *OPF* osteoplastic flap, *EEA* endoscopic endonasal approach [52]

Surgical Planning

Sinonasal papilloma may be an extensive disease that necessitates complex surgery to obtain complete clearance. An option of surgical options and procedure plans is demonstrated in Table 30.7.

Adjuvant Therapy

Radiotherapy should be considered if the risk of surgery is too high, if recurrence is likely after surgery, or when complete tumor resection is unachievable. Such situations may arise with extensive disease, multifocal tumor seeding, or involvement of challenging sites such as the cavernous sinus and lateral wall of the sphenoid sinus [55]. Radiotherapy should also be considered with features of histological concern such as a high mitotic index, hyperkeratosis, and squamous epithelial hyperplasia [56].

Patients with malignant change should be offered curative radiotherapy or chemoradiotherapy after discussion at a head and neck cancer multidisciplinary team (MDT) meeting.

Interferon has been described for multiple recurrences, advanced disease, or spread to the orbit and skull base. Antiviral therapy against human papillomavirus has also been reported. Both modalities lack a strong evidence base and are considered experimental [57].

Recurrence

Sinonasal inverted papillomas have a reputation for tumor recurrence. Most recurrences of sinonasal inverted papilloma occur within 2 years of surgery [58]. A review period of 3–4 years following comprehensive endoscopic sinus surgery will diagnose >80% of recurrences, but some patients with tumours that display more aggressive unusual behaviour or tumours where residual disease is suspected will require longer follow-up.

External vs. *endoscopic surgery:* A meta-analysis review described recurrence of endoscopically resected inverted papilloma in the frontal sinus as being relatively high (22%) compared to external approach surgery, suggesting that combination surgery would be more effective [59].

Recurrence in the frontal recess and ethmoidal roof is more likely as tumor remnants cannot be easily seen or cleared.

Recurrence after revision surgery: Recurrence rates after revision surgery may range from 15 to 20% according to the individual series and type of surgery performed [60]. The higher rates are explained by limited identification of the attachment site, confusing anatomy, and lack of landmarks [4, 61]. Early recurrence may reflect residual disease rather than suspicious tumor behavior, and this needs to be considered and accepted by the individual surgeon. The differentiation of inflammatory polypoid tissues from tumor may also be unclear (Figs. 30.11 and 30.12).

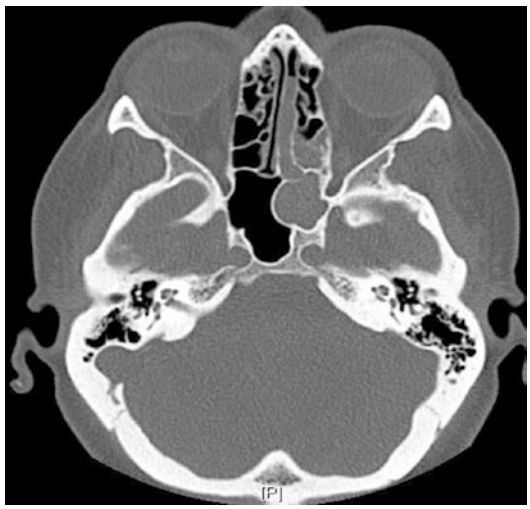

Fig. 30.11 Inverted papilloma of left sphenoid, posterior ethmoid, and olfactory cleft

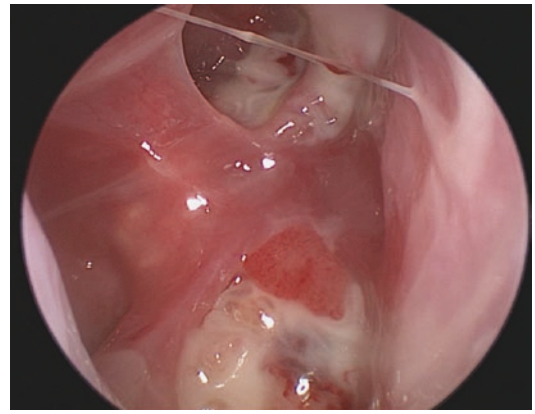

Fig. 30.12 Recurrence of inverted papilloma within sphenoid sinus

Surveillance

The likelihood of recurrence together with the low but potential risk of malignant transformation means that surveillance is necessary. However, sinonasal papilloma lesions are benign, and this leads to an aura of complacency, with many patients being discharged after surgery without subsequent review.

Surveillance in most patients can be relatively infrequent but should include serial endoscopic examination and MRI scans when appropriate. Clinical review of about 3–5 years will identify most recurrences. However, exceptions do occur, and patients with more aggressive tumors should have more frequent review for a longer time period, according to clinical circumstances.

If diagnostic endoscopy is suspicious, intraoperative biopsy should be considered, possibly with frozen section if malignant change is suspected. Patients with rapid recurrence and odd tumor behavior following resection, or those with known subtotal resection, will require closer, more frequent review.

Conclusions

The surgical management for excision of sinonasal papilloma is dependent on the tumor size, histological subtype, location, and expertise of the surgeon.

The greatest most frequent challenge is recurrence after resection of sinonasal inverted papilloma.

Whilst the overall risk of malignant transformation is small, abnormally aggressive unusual behavior should alert the surgeon to possible malignant change.

All removed tissue should be subject to detailed histopathology, and the surgeon and histopathologist should work closely together in this challenging but fascinating condition.

Prolonged review is recommended. The latter depends on clinical acumen as we currently do not have reliable biological markers for recurrence or malignant transformation.

Key Learning Points

- The main types as described by the WHO Classification are based on the histological pattern and exophytic papilloma, oncocytic papilloma, and inverted papilloma.
- The evidence for a clinically significant association of HPV with sinonasal papilloma is variable and weak.
- An inverted papilloma is the most common type and typically appears as an irregular unilateral polyp within the nasal cavity that can be difficult to differentiate from a simple inflammatory polyp.
- The classic characteristics of sinonasal inverted papilloma include tumor recurrence and a risk of malignant transformation.
- Malignant transformation is unusual, but pathology can be challenging. A need for vigilance is therefore essential.
- The ideal management is complete surgical resection that can be achieved endoscopically in most cases.
- Attachment-orientated surgery by subperiosteal dissection and drilling of underlying bone is the optimum technique to prevent tumor recurrence.
- More complex surgery may be necessary for large extensive tumors. Procedures will include surgery to the frontal, sphenoid, or maxillary sinus. Operations may be endoscopic, external, or a combination of the two.
- Regular clinical review over a period of at least 3–5 years is recommended to identify recurrence at an early stage. Longer review is recommended for tumours that display unusual or aggressive features.

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Benign Tumours of the Nose and Sinuses

31

Cem Meco and Hazan Basak

Introduction

Benign tumours of the sinonasal cavity are rare. They encompass a wide variety of histopathological entities with a range of differing management strategies. The unilateral nature of non-specific symptoms should trigger a high level of suspicion that instigates an appropriate diagnostic workup that includes imaging, biopsy or histological analysis of the resected lesion. The optimal management strategy can then be applied to the individual pathology.

Benign and malignant tumours of the sinonasal cavity are rare and present in 1–1.5 per 100,000 population every year. The benign tumours constitute the smallest portion of sinonasal tumours [1, 2].

The sinonasal cavity and its bordering anatomical regions, especially the skull base, not only are an anatomically complex region but also consist of fusion planes of all three embryonic layers, thus hosting an enormous variety of neoplasms derived from a multitude of tissue types. Table 31.1 shows the histopathological classification of benign tumours of the nasal cavity and paranasal sinuses according to the World Health Organization (WHO) [3]. This chapter will review some of the most common and clinically relevant benign tumours of the sinonasal cavity like osteomas and others whilst omitting some like sinonasal papilloma and juvenile angiofibroma (JA), as these are reviewed in dedicated chapters within this book [1].

C. Meco (✉)
Department of Otorhinolaryngology—Head and Neck Surgery, Ankara University, Medical School, Ankara, Turkey

Department of Otorhinolaryngology—Head and Neck Surgery, Salzburg Paracelsus Medical University, Salzburg, Austria

H. Basak
Department of Otorhinolaryngology—Head and Neck Surgery, Ankara University, Medical School, Ankara, Turkey

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Table 31.1 WHO classification [3]

Benign tumours of the nasal cavity and paranasal sinuses	
Benign epithelial tumours	• Sinonasal (Schneiderian) papillomas – Inverted papilloma (Schneiderian papilloma, inverted type) – Oncocytic papilloma (Schneiderian papilloma, oncocytic type) – Exophytic papilloma (Schneiderian papilloma, exophytic type, everted type) • Respiratory epithelial adenomatoid hamartoma • Salivary gland type adenoma – Pleomorphic adenoma – Myoepithelioma – Oncocytoma
Soft tissue tumours	• Myxoma • Leiomyoma • Haemangioma • Schwannoma • Neurofibroma • Meningioma Borderline and low malignant potential tumours of soft tissue • Desmoid-type fibromatosis • Inflammatory myofibroblastic tumour • Glomangiopericytoma • Extrapleural solitary fibrous tumour
Tumours of the bone and cartilage	• Fibrous dysplasia • Ossifying fibroma • Osteoma • Osteoid osteoma • Osteoblastoma • Osteochondroma (exostosis) • Chondroma • Chondroblastoma • Chondromyxoid fibroma • Giant cell lesion • Giant cell tumour of the bone • Ameloblastoma • Nasal chondromesenchymal hamartoma
Haematolymphoid tumours	• Extramedullary plasmacytoma • Langerhans cell histiocytosis • Juvenile xanthogranuloma • Rosai-Dorfman disease
Neuroectodermal tumours	• Heterotopic central nervous system tissue (nasal glioma)
Germ cell tumours	• Dermoid cyst • Mature teratoma Borderline and malignant potential germ cell tumours • Immature teratoma • Sinonasal yolk sac tumour

The Diagnostic Challenge

Regardless of the malignant or benign nature of the tumour, they all present with similar symptoms such as nasal obstruction, nasal discharge, a spectrum of bleeding ranging from bloodstained discharge to epistaxis, headache, facial pain and hyposmia/anosmia. Most symptoms are similar to those triggered by inflammatory sinonasal diseases and may hinder a timely diagnosis. Perhaps the most important concept to emphasise to all physicians, and not just ENT specialists, is to maintain a high level of suspicion and alertness so as not to overlook such sinonasal tumours. It is critical that unilateral sinonasal symptoms, especially nasal obstruction with discharge, should ultimately induce the thought of a sinonasal tumour and lead to further investigations including nasal endoscopy and appropriate imaging.

Due to the non-specific character of symptoms, both patients and primary care physicians could easily overlook these rarely seen pathologies. However, if unilateral symptoms do not resolve after a short-term medical therapy or if orbital or neurological symptoms emerge, no time should be wasted for referral and specialist assessment. Only then, malignancy can be excluded and the optimal management of a benign lesion could be instigated without delay.

Diagnosing benign tumours at an earlier stage may avoid potential complications and minimise the morbidity associated with treatment. Common symptoms and signs of sinonasal tumours according to their location are listed in Table 31.2 [1]. These are mostly related to the nature of pathology, anatomical region and compartments affected by tumour origin and growth and proximity to critical structures.

Table 31.2 Common symptoms and signs of sinonasal tumours according to their location [1]

Primary site	Symptoms
Nasal cavity	Nasal blockage, bleeding, discharge, hyposmia
• Inferiorly into palate	Mass, ulceration, fistula
• Posteriorly into nasopharynx and Eustachian orifice, compression of Eustachian tube	Middle ear effusion/ deafness
• Antero-superiorly into the nasal bone	Glabellar mass
• Externally into the skin	Mass/ulceration
• Superiorly into anterior cranial fossa	Minimal, personality change? Headache, neurological deficit cerebrospinal fluid leak/ meningitis (rarely)
Maxillary sinus	
• Medially into nasal cavity	*As above*
• Anteriorly into the cheek directly or via infraorbital canal	Mass, ulceration of the skin, paraesthesia
• Posteriorly into pterygoid region and infratemporal fossa	Trismus and pain
• Inferiorly into the palate or alveolar ridge	Mass, loosening of the teeth, malignant oro-antral fistula
• Superiorly into orbit	Proptosis, diplopia
Ethmoid sinuses	
• Medially into nasal cavity	*As above*, can cross to contralateral side
• Inferolaterally into maxilla	Mucus retention,
• Medially into orbit	Proptosis, chemosis, diplopia, visual loss, epiphora
• Superiorly into the anterior cranial fossa	Minimal, personality change? Headache, neurological deficit, cerebrospinal fluid leak/meningitis (rarely)
Frontal sinus:	
• Anteriorly	Mass on the forehead or glabella
• Posteriorly into anterior cranial fossa	*As above*
• Inferiorly into nasal cavity, orbit	*As above*
• Medially to contralateral side	Nil of note till breaches confines of sinus

Once a sinonasal tumour is suspected, the ENT examination should focus on the sinonasal region, orbit and cranial nerves and should include an urgent meticulous endoscopy of the nasal cavities and nasopharynx. In most instances nasal endoscopy reveals the lesion straightaway, but in some patients, topical nasal decongestants/anaesthetic spray is required to visualise the middle and superior meati and the olfactory cleft, especially where the access is narrow and limited.

Imaging

Should a sinonasal tumour be seen or further suspected, imaging should be organised. High-resolution computed tomography (CT) and magnetic resonance imaging (MRI) complement each other for precise assessment in axial, coronal and sagittal planes. These imaging modalities establish a radiological diagnosis, reveal the nature and extent of the tumour and delineate which anatomic compartments are involved and which neurovascular critical structures are closely related to the tumour [4]. A CT sinus scan is usually the first examination acquired and provides bony detail that can determine areas of bone erosion or attachment. The information that CT provides for fibro-osseous lesions (FOLS) regarding texture, margins and critical areas is usually adequate to establish the diagnosis and extent of the lesion. However, for most other soft tissue lesions, an MRI scan provides additional essential information and is strongly recommended. Importantly, an MRI scan with gadolinium enhancement will enable differentiation of tumour from adjacent soft tissues and retained mucus. Additionally, it determines involvement of adjacent structures including the periorbita

and orbital contents, as well as nerves, dura, brain and cavernous sinus. MR provides crucial diagnostic key information that directly affects staging and the optimal management modality. Combined findings of CT and MRI alone may be diagnostic for certain lesions.

Tumour Biopsy

Radiological features may help focus the list of differential diagnoses, but a biopsy is usually still be essential to reach a definitive diagnosis especially for soft tissue tumours.

Alternatively, radiological evaluation avoids the risk of unnecessary and potentially dangerous biopsies, either from highly vascular tumours, like JNA, or neural lesions involving the intracranial cavity like meningoencephaloceles.

Unlike soft tissue lesions, bony lesions within the nasal cavity can be diagnosed with reasonable accuracy by nasal endoscopy and CT scan in the absence of histological analysis.

Most biopsies can be performed endoscopically transnasally and generally provide a definitive diagnosis. Nevertheless, it should be borne in mind that tissue samples may not be representative of the tumour. Misleading results could arise from superficial samples or biopsy of overlying inflammatory tissue obscuring the actual pathology. Whenever there is doubt over the histopathological typing failing to reflect the clinical and imaging findings, further biopsies should be taken. Consideration should be given to whether the biopsy can be done safely and adequately in the outpatient clinic, particularly if bleeding is likely to occur, or whether it is more suitable in the operating theatre, and if necessary, under general anaesthesia. Another factor to consider during tissue sampling is to restrict sampling to biopsy needs and avoid disturbing tumour attachment areas; total resection should be reserved for definitive surgery as sinonasal tumours are best treated de novo, rather than treating residual or recurrent disease l [1, 2, 4–6].

Fibro-Osseous Lesions (FOLS)

FOLS of the sinonasal cavity yield a variety of histopathological entities. This chapter will focus on the most common, namely, osteoma, fibrous dysplasia and ossifying fibroma. In common, the normal bone architecture of these proliferative disorders or neoplasms is replaced with varying amounts of collagen, fibroblasts and bone. In general, they may present within the sinonasal cavity from small, asymptomatic findings to massive symptomatic lesions (Fig. 31.1) resulting in

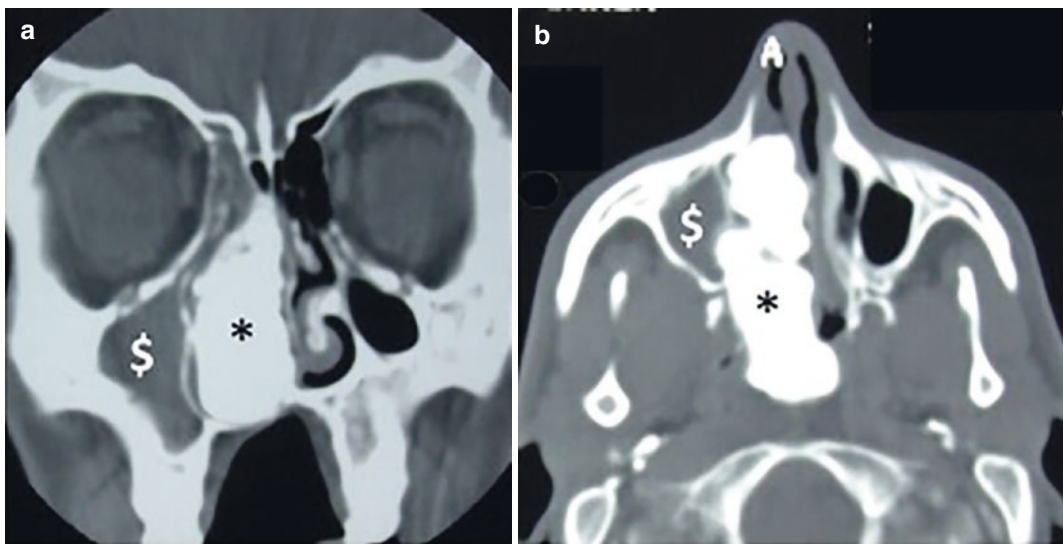

Fig. 31.1 Massive intranasal osteoma (*) causing nasal obstruction and right-sided maxillary mucus retention ($) (**a**) Coronal CT scan, (**b**) axial CT scan

Table 31.3 Main characteristics of fibro-osseous lesions [1, 5]

	Fibrous dysplasia	Ossifying fibroma	Osteoma
Incidence	Not known	Not known	0.43–3%
Most frequent side of origin	Mandible and maxilla	Mandible	Frontal sinus
Histology	Replacement of the bone by fibrous tissue	Fibrous tissue, calcification	Ivory, mature and mixed type
Age of presentation	First to second decades	Second to fourth decades	Third to fourth decades
Male-to-female ratio	1:1	1:5	1.5–3.1:1
Radiology	'Ground-glass' appearance on CT	Expansile mass with sharp demarcation	Homogenous, dense, well circumscribed
Symptoms	Facial asymmetry	Painless swelling, nasal obstruction	Frontal headache
Malignant transformation	0.5% in polyostotic form	Not known	No reports
Treatment	Observation; surgery only in symptomatic cases	Observation; if possible complete surgical resection in extended cases	Observation in asymptomatic cases; surgery in symptomatic patients and complications

CT computed tomography

aesthetic deformities. Their key characteristics are summarised in Table 31.3 [1].

Osteoma

Osteomas are the most common sinonasal cavity benign tumour, in which malignant transformation does not occur [7, 8]. They are present in approximately 3% of all CT scans for sinus symptoms [9]. The frontal sinuses are the most common site of occurrence, followed by the ethmoid, maxillary and rarely the sphenoid sinuses [1, 9, 10]. Even though about half of them do not grow after initial diagnosis, the rest grow slowly from 0.44 to 6.0 mm per year [11–13]. Whilst they can occur at any age, most are diagnosed between the third and fourth decades of life with a slight male predominance (range 1.5 to 3.1 male: 1 female) [10, 14–16].

The aetiology of osteomas is debated with developmental, traumatic and infectious theories. Among them, the developmental theory argues that uncontrolled bone formation is the result of activated embryogenic stem cells that were previously silent earlier in life. On the contrary, traumatic and infectious theories propose an inflammatory process as the initiating factor in bony tumour formation [16–18].

Osteomas have three distinct histological types. Eburnated or ivory osteomas are composed of a lobulated compact dense cortical bone that contains a minimal amount of fibrous tissue without evidence of Haversian ducts. Osteoma spongiosum or the mature osteomas are composed of spongy cancellous bone that are characterised by bony trabeculae divided by conspicuous amount of fibrous tissue, containing fibroblasts in different stages of maturation and a great number of collagen fibres, whilst the connective tissue may often contain distended thin-walled vessels. The third type, the mixed osteomas, contains elements from both ivory and mature types [10, 14, 18–22].

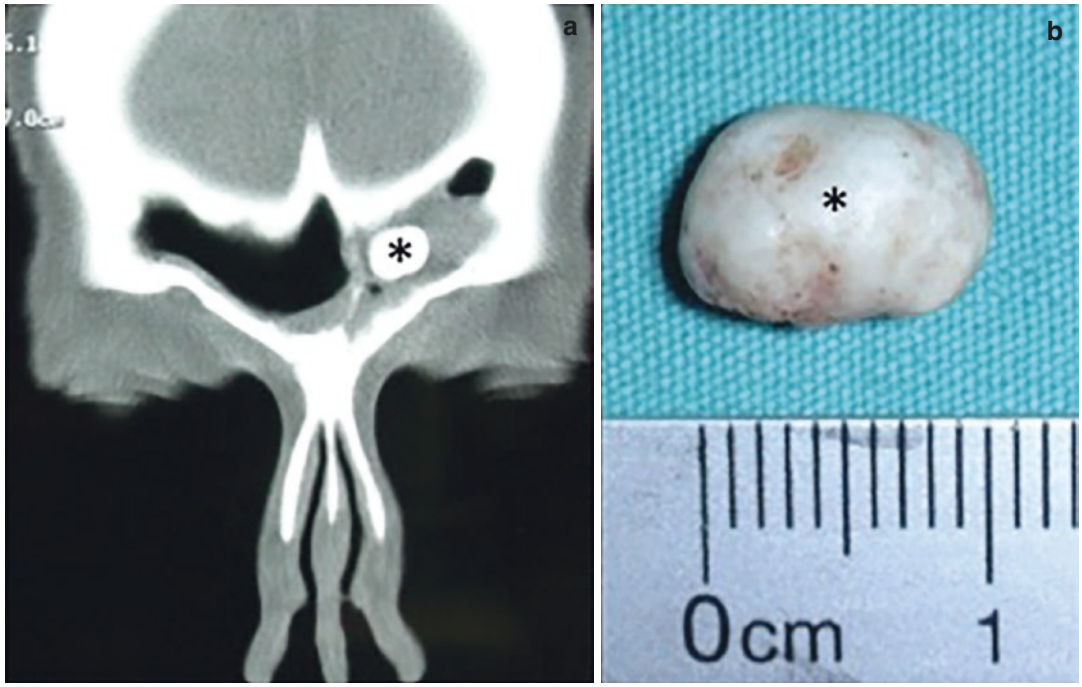

Fig. 31.2 Relatively small frontal osteoma (*) (**a**) Coronal CT showing obstructed left frontal sinus outflow tract by osteoma causing frontal sinusitis, (**b**) resected surgical specimen

Clinical Features

Most osteomas are asymptomatic and diagnosed as incidental radiological findings [23], commonly found in frontal and fronto-ethmoidal sinuses, and frontal headache and facial pain are the most commonly associated clinical symptoms. These symptoms are a consequence of a compromised sinus outflow tract rather than the osteoma causing pain itself. Even though tumours may be small (Fig. 31.2), the drainage obstruction of the sinus triggers inflammation leading to chronic or recurrent acute rhinosinusitis, as well as mucus retention and mucocele formation. Furthermore, symptoms such as facial deformity, exophthalmia, diplopia, epiphora, blindness and intracranial complications are likely to develop with intraorbital or intracranial expansion with encroachment of periorbita or dura. (Fig. 31.3). If the barrier function of dura is involved, serious intracranial complications such as cerebrospinal fluid (CSF) leak, meningitis or brain abscess, as well as an intracranial mucocele or pneumatocele, could occur. The initial presentation of the lesion could, on occasions, be due to the secondary effects of the bony lesion.

If the lesion is visible within the nasal cavity, endoscopy may reveal the firm nasal mass typically covered with normal mucosa. The CT scan appearances may show a well-circumscribed, very dense and homogeneous cortical lesion for the eburnated histological type or a ground-glass pattern with a gradually decreasing density for the mature or spongiose histological type. Thus, the diagnosis can be made without further imaging [24].

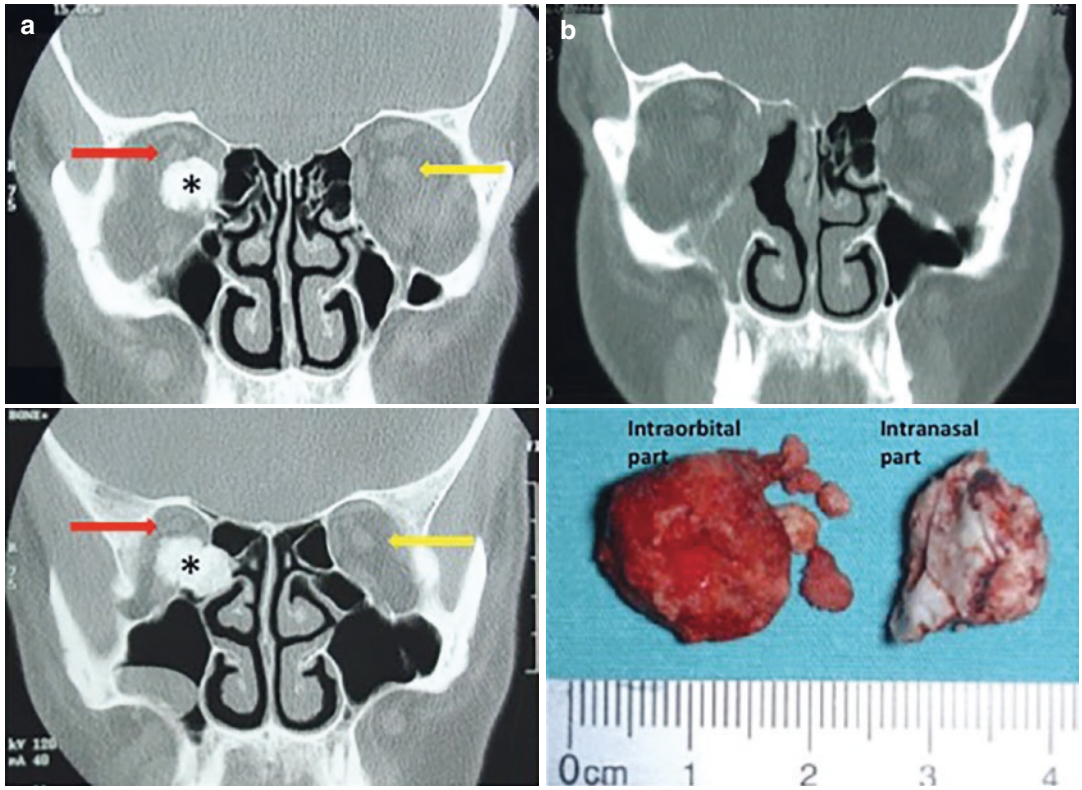

Fig. 31.3 Sinonasal osteoma (*) with intraorbital extension displacing right optic nerve superiorly, (**a**) preoperative coronal CT scans, Red arrow—Right optic nerve, Yellow arrow—Left optic nerve, (**b**) postoperative immediate CT scan and surgical specimen after endonasal endoscopic removal

Should multiple osteomas be present, this could reflect the rare diagnosis of Gardner syndrome. Gardner syndrome is an autosomal dominant disease with benign skin/soft tissue neoplasms and colorectal polyposis that requires timely assessment due to high incidence of malignancy.

Imaging

The origin and attachment sites of an osteoma can normally be seen by reviewing tri-planar CT images. This three-dimensional understanding is essential, especially if surgery is planned; the osteoma should be carefully delineated to evaluate a tailored surgical approach. However, the lobulated nature of some osteomas and invaginations into the contours of the sinuses may mask the exact site of origin. In this situation, MRI imaging is recommended, especially when the osteoma encroaches adjacent periorbita and dura. MRI defines the relationship with critical neurovascular structures and adjacent soft tissues (Fig. 31.4) [1]. MRI is the modality of choice during pregnancy, if proptosis occurs.

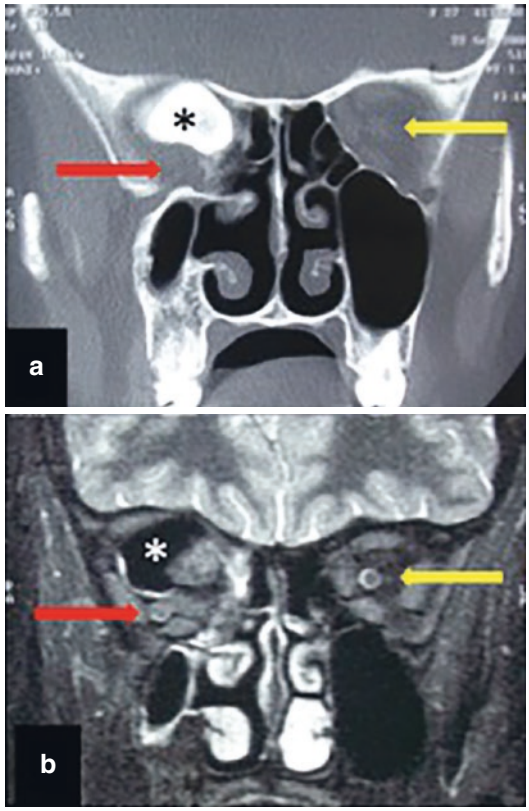

Fig. 31.4 Sinonasal osteoma (*) with intraorbital extension displacing right optic nerve inferiorly, Red arrow—Right optic nerve, Yellow arrow—Left optic nerve, (**a**) coronal CT scan (**b**) coronal T2-weighted MRI scan

It can also reveal subtle findings including heterogenous low-to-intermediate signal intensity, in comparison to the hyper-attenuation detected in CT scans [24].

Management of Osteomas

The management of osteomas is based on presenting symptoms. As most small osteomas are incidental findings and principally slow-growing tumours, current consensus suggests 'watchful waiting' with periodic scans, typically with MRI to reduce radiation exposure [1, 13]. Surgical resection is indicated should there be significant symptoms either at the time of presentation or during follow-up. Other indications for surgery include rapid growth of the tumour (over 1 mm in diameter per year), even though asymptomatic. More definitive indications for surgery include extensive invasion or encroachment upon skull base, orbit or optic nerve, especially if there is risk of intracranial and intraorbital complications.

The Surgical Approach

The surgical aim of complete tumour removal whilst preserving neighbouring neurovascular structures and avoiding possible complications is generally best achieved through an endonasal endoscopic approach (EEA). However, the optimal choice of approach is determined by the localisation, extent and attachment sites of the disease and involved critical structures, as well as the risk of surgical approach. This may include an endoscopic resection (EEA), a traditional external approach, or a combination of the two [1, 25–30]. Additional factors to consider include paranasal sinus anatomical variations, comorbidities that would affect the duration of surgery, the availability of required instrumentation and equipment and the individual surgeon's experience. These are all key issues in case-based decision-making, influenced by the choice and preferences of the patient and the surgeon. Figure 31.5 shows a fronto-orbito-ethmoidal osteoma case with extreme intraorbital extension operated solely through an EEA.

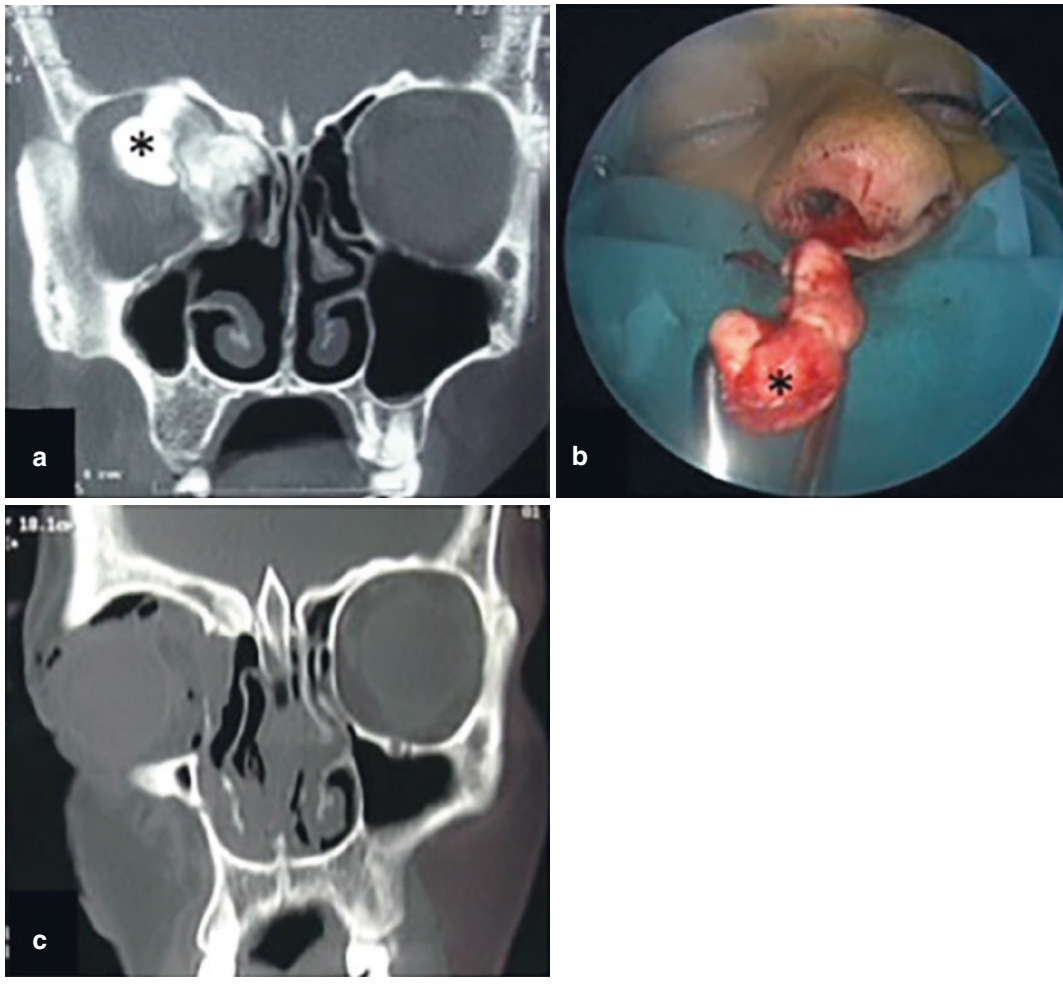

Fig. 31.5 Sinonasal fronto-orbito-ethmoidal osteoma (*) with extreme intraorbital extension, (**a**) preoperative coronal CT scan, (**b**) specimen photo during solely endonasal endoscopic resection, (**c**) postoperative immediate coronal CT scan

The Endoscopic Approach

Endoscopic techniques that implement powered instrumentation and navigation systems have evolved to address most surgical goals for osteoma removal. Nowadays, even large lesions can safely be resected endonasally utilising cavitation techniques that drill the core of the lesion whilst leaving a very thin shell of bone at tumour edges, which can then be delicately dissected and removed from the adjacent structures [28]. The risk of an injury to nearby structures should be evaluated well before surgery and documented during informed consent. Accordingly, the surgeon should be prepared to avoid or efficiently manage all potential risks, such as performing a multilayer duraplasty for a CSF leak should this occur during surgery. However, considering the benign nature of osteoma with almost negligible growth of residual osteoma, it is most important to limit postoperative morbidity. Leaving a thin residual shell of osteoma at critical sites, such as overlying the optic nerve or a thin skull base, could be a very wise option in some cases.

The frontal sinus poses a specific challenge for EEA. Grading systems [31] for this region have been proposed to facilitate recommendations for the optimum approach with regard to endoscopic, external or combined surgical resection [26]. These limitations include osteoma extension lateral to sagittal plane of lamina papyracea, anterior and superior attachment, intracranial and advanced intraorbital extension, narrow (<1 cm) anterior-posterior frontal sinus diameter and over 50% obliteration or total obliteration of the frontal sinus. However, continuously improving instrumentation such as angled drills and navigation systems, as well as developments in endoscopic techniques, e.g. Draf procedures (especially Draf III), has gradually expanded the indications of EEA. In the hands of experienced surgeons and in suitable cases, very large osteomas filling the whole frontal sinus can be removed endonasally. Even far lateral frontal and supraorbital attachments can be managed with further advanced techniques that create an endonasal corridor by suspending the periorbita inferolaterally to temporarily transpose orbital contents away from the surgical approach to the frontal sinus lateral portion [32–35].

Case based decision-making should be made to determine the feasibility of managing intracranial or intraorbital extensions through EEA, as most dural defects can be repaired endoscopically. The major limiting factors reported are extreme superior or lateral extension along the posterior table, beyond the reach of current instrumentation. For lesions located at the far lateral extreme of pneumatised frontal sinuses, EEA can be combined with a frontal trephine or transorbital endoscopic approach if necessary [26, 35–39].

Currently, there are limited areas within the maxillary and frontal sinuses that cannot be effectively reached endoscopically and may require a combined or a solely external approach. Thus, the indications for external approaches have receded. External approaches are still indicated when adequate access to the tumour cannot be achieved by EEA alone, in far lateral disease, where reconstruction of the anterior sinus wall is needed.

External Approach Surgery

Historically, the Caldwell-Luc procedure, midfacial degloving, lateral rhinotomy, external frontoethmoidectomy through a Lynch-Howarth incision and osteoplastic frontal sinus (OFS) approach through coronal incision are classic approaches that were all used routinely [1, 5, 8, 11, 22, 23, 25–31, 35]. Recently, the transorbital endoscopic approach with a near-invisible blepharoplasty incision could additionally offer more than the lateral trephination [38]. When these techniques fall in short, OFS approach is the approach of choice. With this approach the whole frontal sinus, including extreme lateral portion, can be managed perfectly with maxi-

mum exposure. Classically, after removing the tumour, the entire frontal sinus mucosa would be removed, drilling out the sinus walls burred, the frontal outflow tract sealed and the sinus obliterated by abdominal fat. Provided that the outflow pathway is kept intact, fat obliteration may be avoided, thus maintaining a functioning frontal sinus [11, 40]. Traditional external approaches require skin incisions that could increase the morbidity through a visible scar, paraesthesia, pain or mucocele formation. However, this should be balanced by facilitating optimum access to large osteomas and faster tumour resection whilst also enabling obliteration, cranialisation or CSF repair, if required.

Fibrous Dysplasia (FD)

FD is a slowly progressive disease accounting for 5% to 10% of all bone tumours that is characterised by the replacement of medullary bone by abnormal fibrous tissue with different stages of bone metaplasia; thus it rather causes deformation but rarely destruction [1, 41, 42].

It presents in 80% as monostatic (MFD) variant or less commonly as a polyostotic variant. The MFD typically diagnosed within the first three decades of life. The polyostotic variant (PFD) affects the craniofacial bones, and in particular skull base and maxillary involvement, much more commonly (50-to-100% times more common). A subgroup of the PFD variant is known as McCune-Albright syndrome, and additional features include hyper-functional endocrinopathies and skin discolourations.

Whilst PFD tends to present earlier in childhood, disease progression after adolescence is rare and minor [41, 42]. The most common symptom is painless bony enlargement that may lead to facial asymmetry, followed by proptosis, diplopia, exophthalmos, vision impairment, cranial nerve compression, obstructive sinusitis and headache.

CT images show ground-glass appearance on remodelled bones (Fig. 31.6). FD can have <0.5% incidence of malignant transformation [1]. Asymptomatic FD patients are best managed with watchful observation. Patients with encasement of the optic nerve (ON) by FD require regular ophthalmologic assessment and long-term radiological surveillance [41–44]. Current evidence indicates that surgery has no role to pre-emptively decompress ON in asymptomatic patients. However, surgical decompression should be prompt if the patient becomes symptomatic for cranial neuropathies and impaired vision. Surgery is also indicated to relieve pain or address facial disfigurement. The location and extent of the disease and the objective of surgical intervention determine the surgical approach. Nowadays EEA is the option of choice, especially for ON decompression. External approaches still have an important role in correcting facial asymmetry that may include radical excision and reconstruction (Fig. 31.7) [41–45].

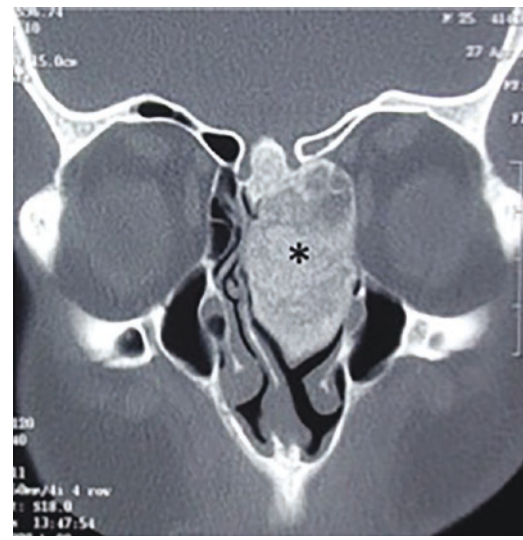

Fig. 31.6 Coronal CT of sinonasal fibrous dysplasia (*) with ground-glass appearance involving crista galli and anterior skull base as well as left lamina papyracea

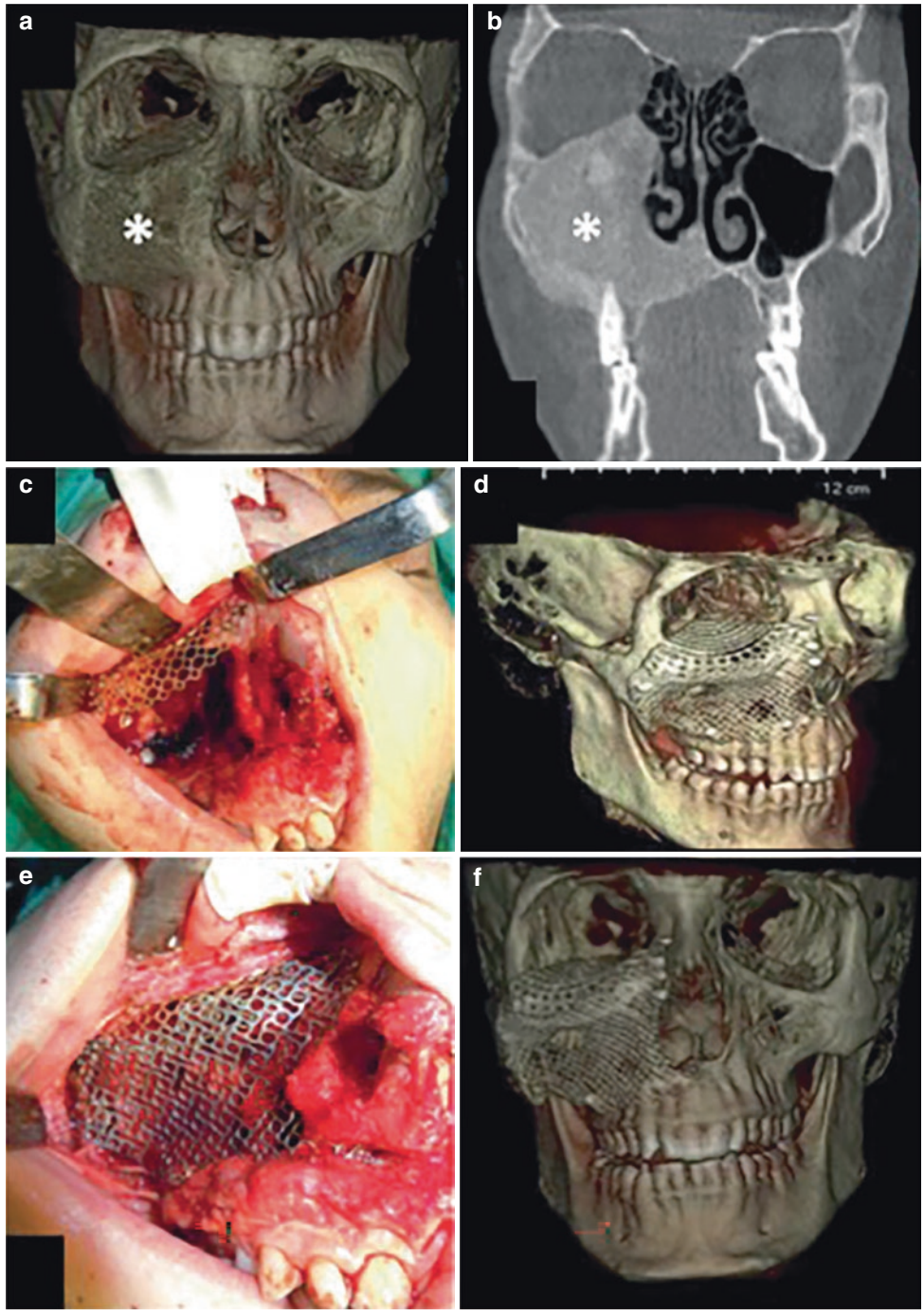

Fig. 31.7 Fibrous dysplasia (*) of the right maxilla causing facial asymmetry (**a**) Three-dimensional (3D) CT reconstruction, (**b**) coronal CT scan, (**c**) midfacial degloving approach, status after resection and orbital floor reconstruction with titanium plate, (**d**) maxilla anterior wall reconstruction with titanium plate, (**e**) postoperative 3D CT reconstruction showing orbit floor reconstruction after tumour resection, (**f**) postoperative 3D CT reconstruction showing anterior maxilla anterior wall reconstruction after tumour resection

Ossifying Fibroma (OF)

OF is another painless expansile fibro-osseous tumour characterised by its aggressive growth, especially in its 'juvenile' histological subtype that cause contour deformity and loss of anatomical shape whilst having a high risk for recurrence after surgical resection.

Juvenile OF is classified into psammomatoid and trabecular lesions. The psammomatoid OF is the most commonly encountered and typically occurs in the sinonasal and orbital bones. The age of onset of OF has a wider range compared to the trabecular OF. The trabecular lesions are usually found in the mandible.

Features include nasal obstruction, ocular symptoms, facial deformity, proptosis, headache and sinonasal disease. Females have 5:1 preponderance [1, 46, 47].

OF is seen as round to oval expansile masses on CT, with multiple loculations and foci of calcifications as well as soft tissues surrounded by thick bony walls. The sharply defined outer margins of OF are a characteristic radiological feature for OF. The differential diagnosis includes fibrous dysplasia (FD) or a malignant tumour, but these have poorly defined margins [47] (Fig. 31.8).

The optimum treatment of OF is based on complete surgical removal, even in the early stage of disease, in order to avoid extensive bone destruction due to the locally invasive behaviour of the tumour. The surgical approach should be tailored to achieve complete resection where possible, according to the location and extend of the OF, with the intent of minimising the risk of recurrence [1, 2, 41–47].

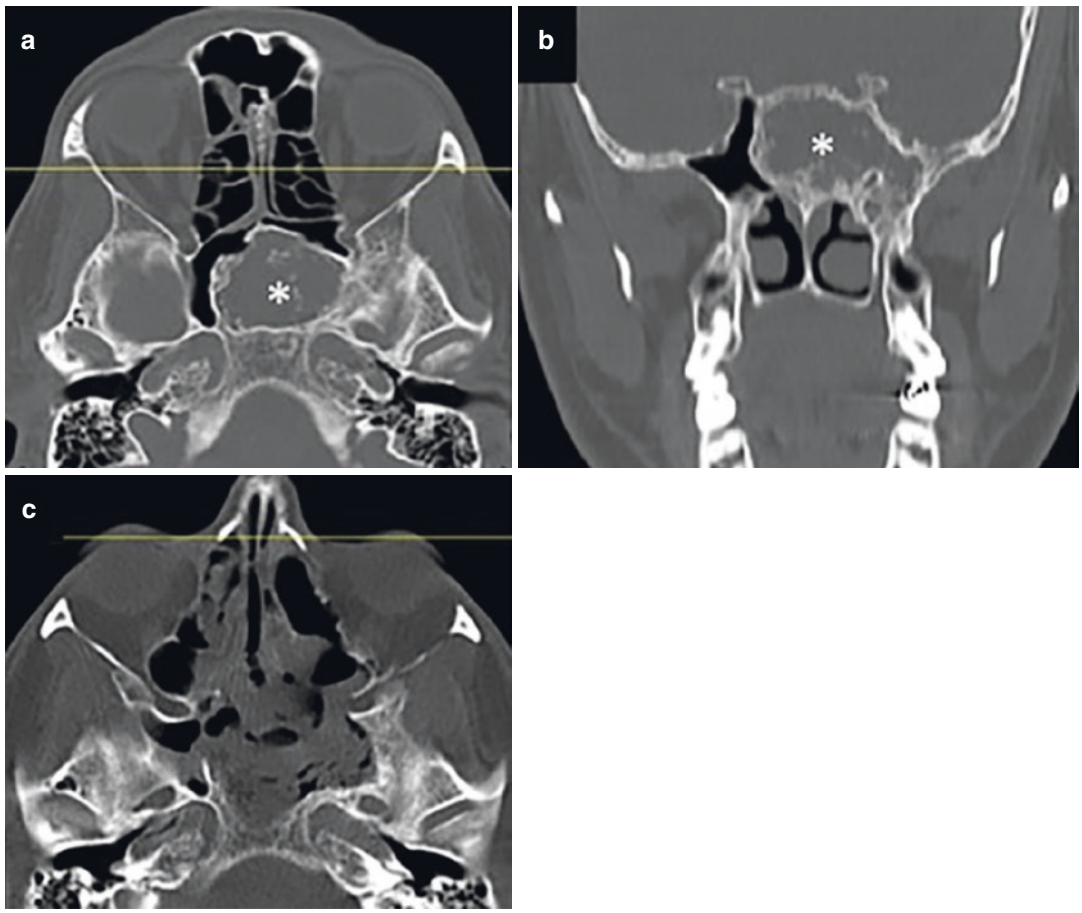

Fig. 31.8 Ossifying fibroma (*) at left sphenoid sinus with sharply defined outside margins, (**a**) Axial CT scan, (**b**) coronal CT scan, (**c**) postoperative immediate axial CT scan after endonasal endoscopic resection

The Antrochoanal Polyp

Antrochoanal polyps (ACPs) are benign, unilateral large polyps originating generally within maxillary sinus and rarely from sphenoid sinus extending through the natural or accessory ostium to the nasal cavity and then choana. They are frequently seen in the paediatric population and young adults with unknown aetiology and pathogenesis with a tendency to recur. According to one widely accepted theory, ACPs arise from maxillary antrum as a cyst due to mucus gland obstruction or ostium obstruction (as a result of an allergic or infectious process). Histologically they show more inflammatory and less eosinophilic cell infiltration.

They clinically present with nasal obstruction, but there are some reports with epistaxis, dysphagia and obstructive sleep apnoea as a presenting symptom. Nasal endoscopic examination reveals a smooth-surfaced polypoid tissue from the middle meatus to the nasal cavity and choana, which can also be demonstrated as soft tissue opacity on imaging studies. Nevertheless, neither the site of origin nor the differential diagnosis from other unilateral sinonasal disease cannot be determined solely by radiological assessment. For proper diagnosis nasal endoscopy with a CT scan of sinuses is crucial (Fig. 31.9).

Treatment of ACP is surgical removal focusing on its attachment site either by cauterising or removing/drilling underlying bone, which can nowadays successfully managed through EEA. Various EEA techniques can be utilised like middle meatal antrostomy, medial maxillectomy and prelacrimal endoscopic or modified Denker's approach. Total removal is curative, but if ACPs are not removed totally at its origin site, recurrence rates are high [48–52].

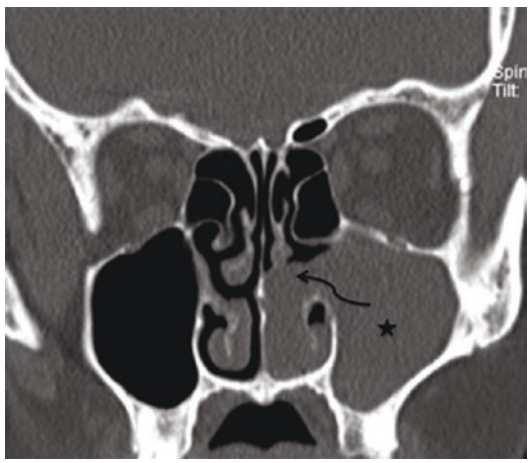

Fig. 31.9 Antrochoanal polyp: computed tomography (CT) of the sinuses shows antrochoanal polyp causing maxillary sinus opacity and extending through natural ostium to the left nasal cavity (black arrow: extension of ACP, (*) left maxillary sinus)

Respiratory Epithelial Adenomatoid Hamartoma (REAH)

REAH is a benign self-limited proliferative glandular lesion containing disorganised mature cells commonly found medial to middle turbinate that is mostly seen in adult and male population and can be associated with nasal polyps in <48% of patients. They present as a soft tissue mass, often seen endoscopically along the olfactory groove. CT and MRI features include widening of the olfactory cleft without bony erosions. Endoscopic biopsy is recommended. The definitive diagnosis is confirmed after excision and histology, although it can cause some histopathological uncertainty and may be confused with inverted papilloma. The aim of treatment is complete endoscopic resection without taking undue risk as this is a benign lesion. The prognosis is excellent [53, 54].

Salivary Gland Tumours

Pleomorphic adenoma (PA), myoepithelioma and oncocytoma are among the benign salivary gland tumours that occur within the sinonasal cavity. They are all rare tumours, but the PA is the most frequent, usually originating from nasal septum, even though secretory glands are mostly located at the lateral nasal wall.

Typical symptoms include nasal obstruction, epistaxis, mucopurulent rhinorrhoea, epiphora and rarely external nasal deformity if the tumour arises in the anterior nasal cavity.

Imaging includes CT and MRI with contrast. Biopsy is necessary to establish precise diagnosis, especially with the risk of malignant transformation, which increases with time (Fig. 31.10).

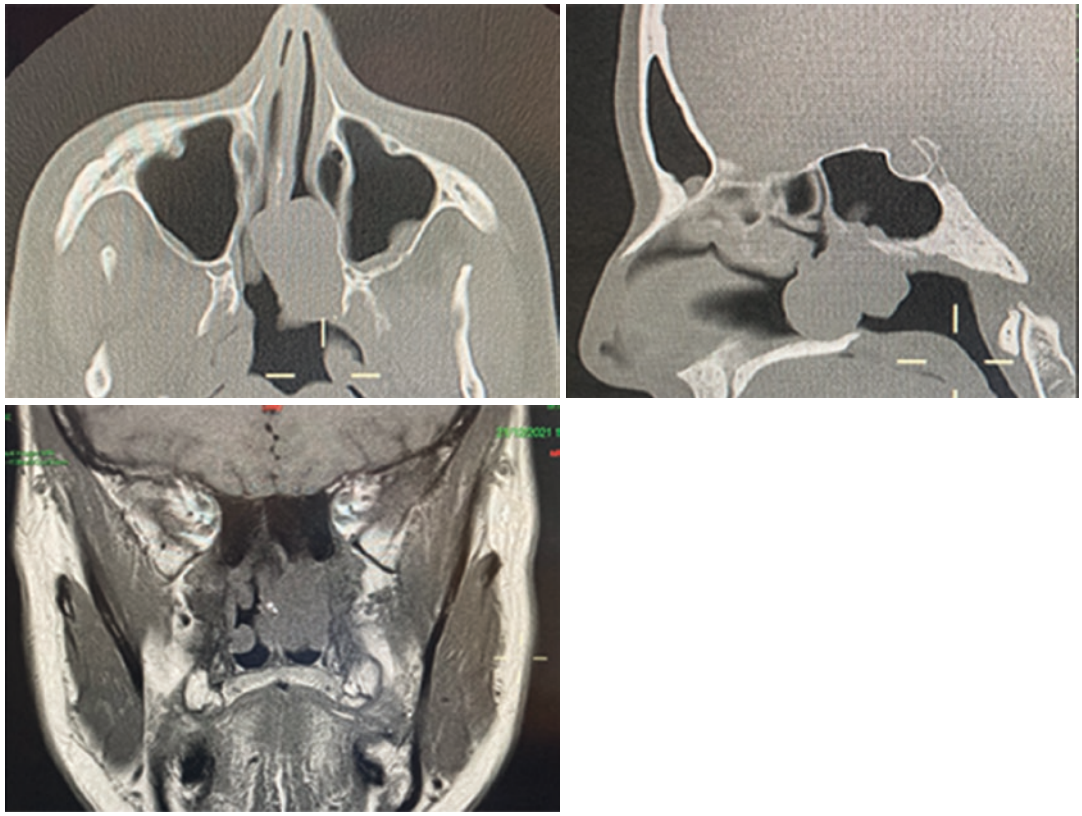

Fig. 31.10 CT and MRI images of adenoid cystic carcinoma of nasal septum. Initial biopsy reported as salivary adenoma. (Courtesy of Andrew Swift)

Clinical acumen and suspicion is particularly important as a benign biopsy may mask underlying malignancy.

Malignant transformation of PA into invasive Carcinoma-Ex-PA is seen approximately 6% of pre-existing PA. Carcinoma-ex-PA can turn into an aggressive tumour [55–57]. Sinonasal oncocytomas are also locally aggressive and have a greater potential of malignant transformation [58]. Likewise, malignant transformation of myoepitheliomas also shows a more aggressive biological course [59].

Given the risk of malignancy, the important principle is that all sinonasal benign salivary gland tumours require total surgical excision with safe margins and histological review. Endoscopic surgery (EEA) is normally possible, but should it fall short of being able to completely manage the site of tumour attachment, a traditional external approach should be utilised to achieve complete removal of the tumour and reduce the risk of recurrence [55–59].

Schwannomas and Neurofibromas

Schwannomas: Sinonasal schwannomas are benign tumours that differentiate from Schwann cells of the sensory and autonomic nerve fibres along the sinonasal cavity. They are uncommon (4% of all schwannomas) and malignant transformation is extremely rare. They present with non-specific nasal symptoms and occasionally have intracranial extension. Although a definitive diagnosis can be established with biopsy, it can also be suggested with a degree of confidence by modern imaging: CT images show a well-demarcated solid mass with remodelling and expansion of bone due to compression; MRI with contrast displays the mass with inhomogeneous uptake and heterogenous enhancement on T1- and T2-weighted images. The main treatment is complete removal, and in most cases, this can be achieved safely by an EEA [60–62] (Fig. 31.11).

Neurofibromas (NF): Neurofibromas are benign peripheral nerve sheath tumours and rarely

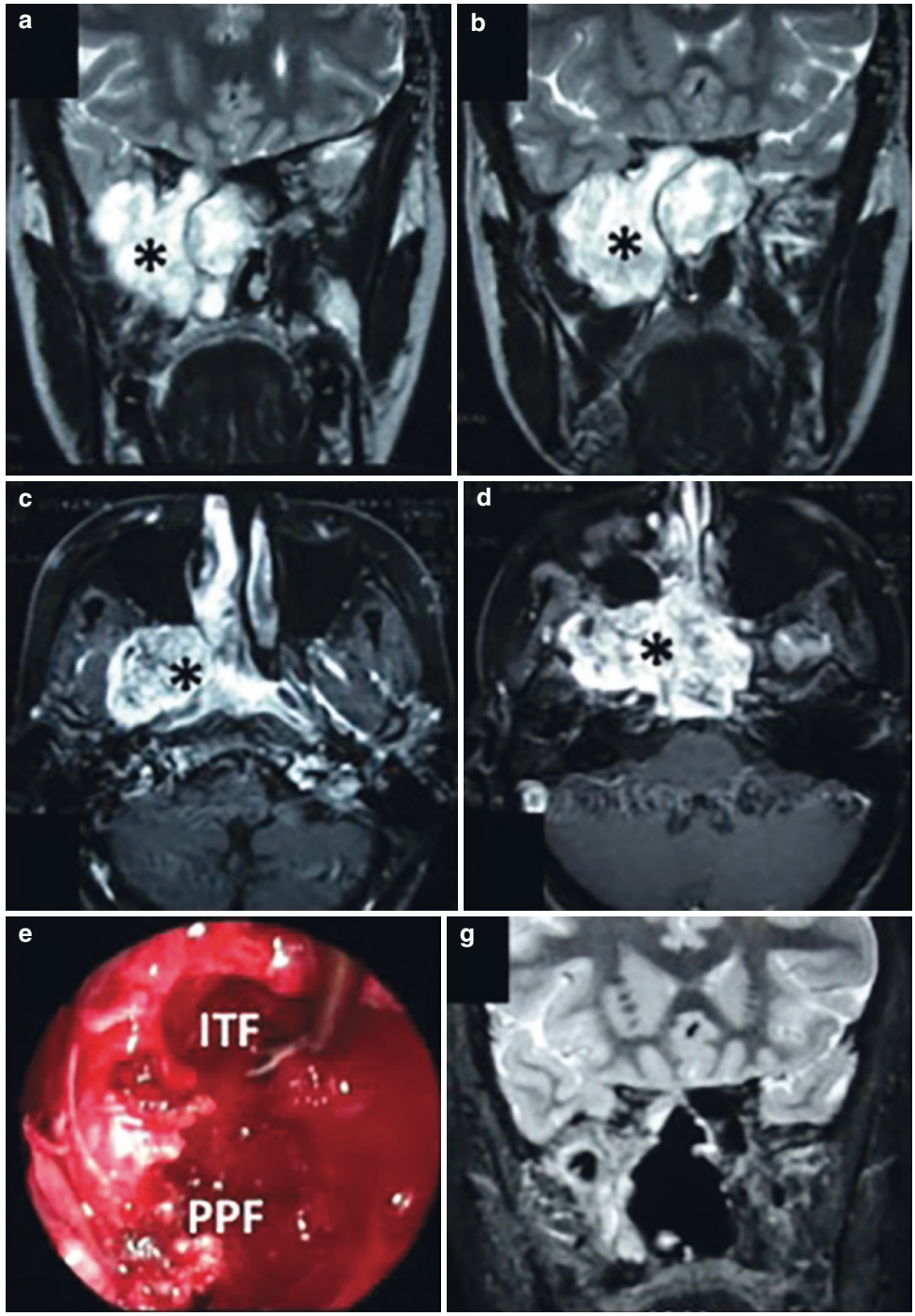

Fig. 31.11 Sinonasal schwannoma (*) involving bilateral sphenoid sinuses, right pterygopalatine fossa (PPF) and right infratemporal fossa (ITF), (**a**) and (**b**) coronal scans of preoperative T2-weighted MRI, (**c**) and (**d**) axial scans of preoperative T1-weighted MRI with gadolinium enhancement, (**e**) intraoperative 45 degree endoscopic view after resection showing right PPF and ITF, (**f**) intraoperative 45 degree endoscopic view after resection showing middle fossa dura (blue arrow), (**g**) coronal and (**h**) axial scans of postoperative MRI after 16 years showing no recurrence of schwannoma after endonasal endoscopic resection

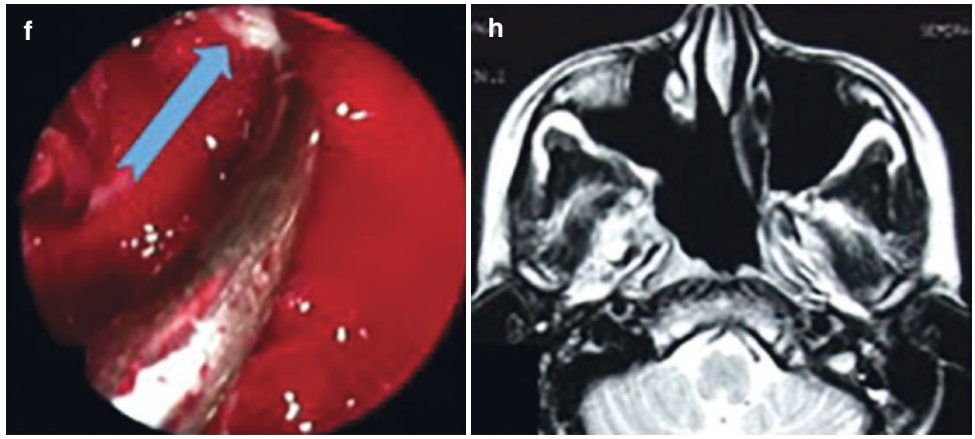

Fig. 31.11 (continued)

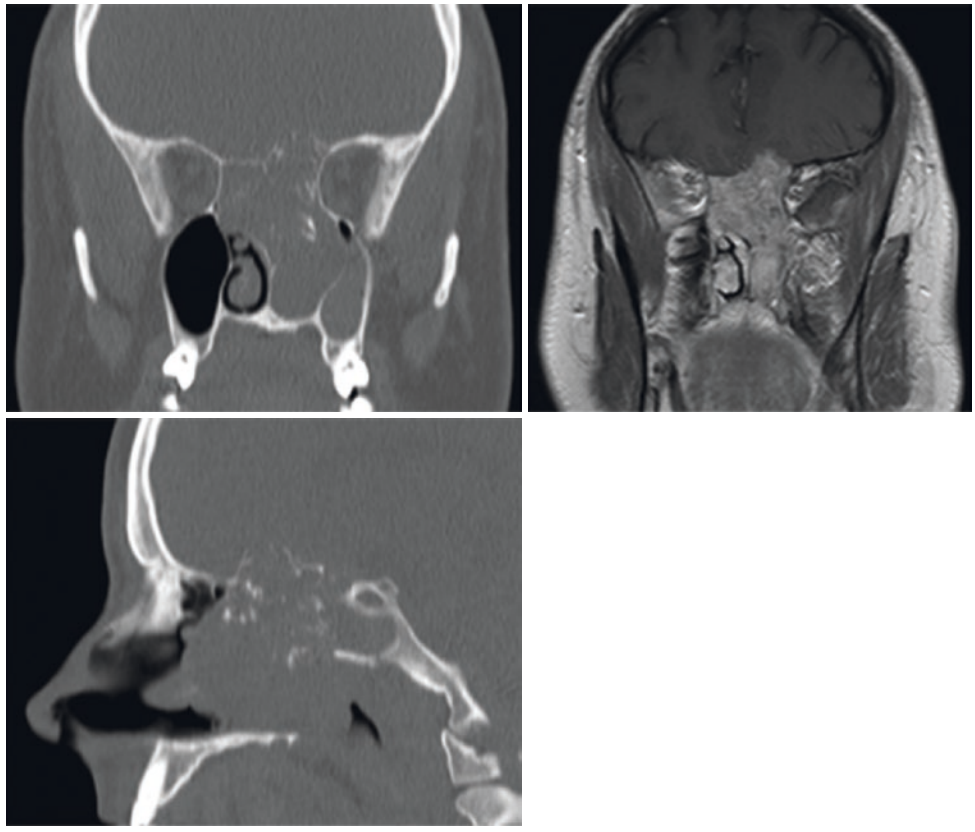

Fig. 31.12 Sinonasal neurofibroma of skull base (courtesy of Andrew Swift)

seen in the sinonasal cavities. NF arise from the endoneurium of peripheral nerve sheaths, and it usually originates within the sinonasal cavity from trigeminal nerve extracranial divisions. They are uncommon and can be solitary or multiple (in patients with neurofibromatosis Types 1 and 2). Sinonasal NF has non-specific symptoms such as nasal obstruction, epistaxis, pain or asymmetry of the face. CT and MRI of the sinuses are helpful to show the extension of the disease, but histopathological examination is essential to establish diagnosis (Fig. 31.12). Nevertheless, it may be difficult

to differentiate NF from other non-epithelial sinonasal tumours. Treatment is total surgical resection; currently for sinonasal NF, EEA is a safe and effective approach. If total removal is achieved, recurrence rates are rare [63–65].

Haemangioma

Haemangiomas are benign vascular tumours commonly seen in the head and neck but rarely in sinonasal cavity. Aetiological factors are uncertain: Suggestions include trauma (multiple nasal packing, digital trauma, nasogastric tube placement), hormonal changes (pregnancy), viral oncogenes, arteriovenous malformations and excess production of angiogenic growth factor.

Subtypes include the lobular capillary haemangioma (LCH) and cavernous haemangioma (CH). The most common type is LCH and characterised by submucosal vascular proliferation and capillary lobules, seen mostly in nasal cavity and septum (Fig. 31.13). CH has larger endothelium lined vascular spaces and mostly seen in sinuses (Fig. 31.14).

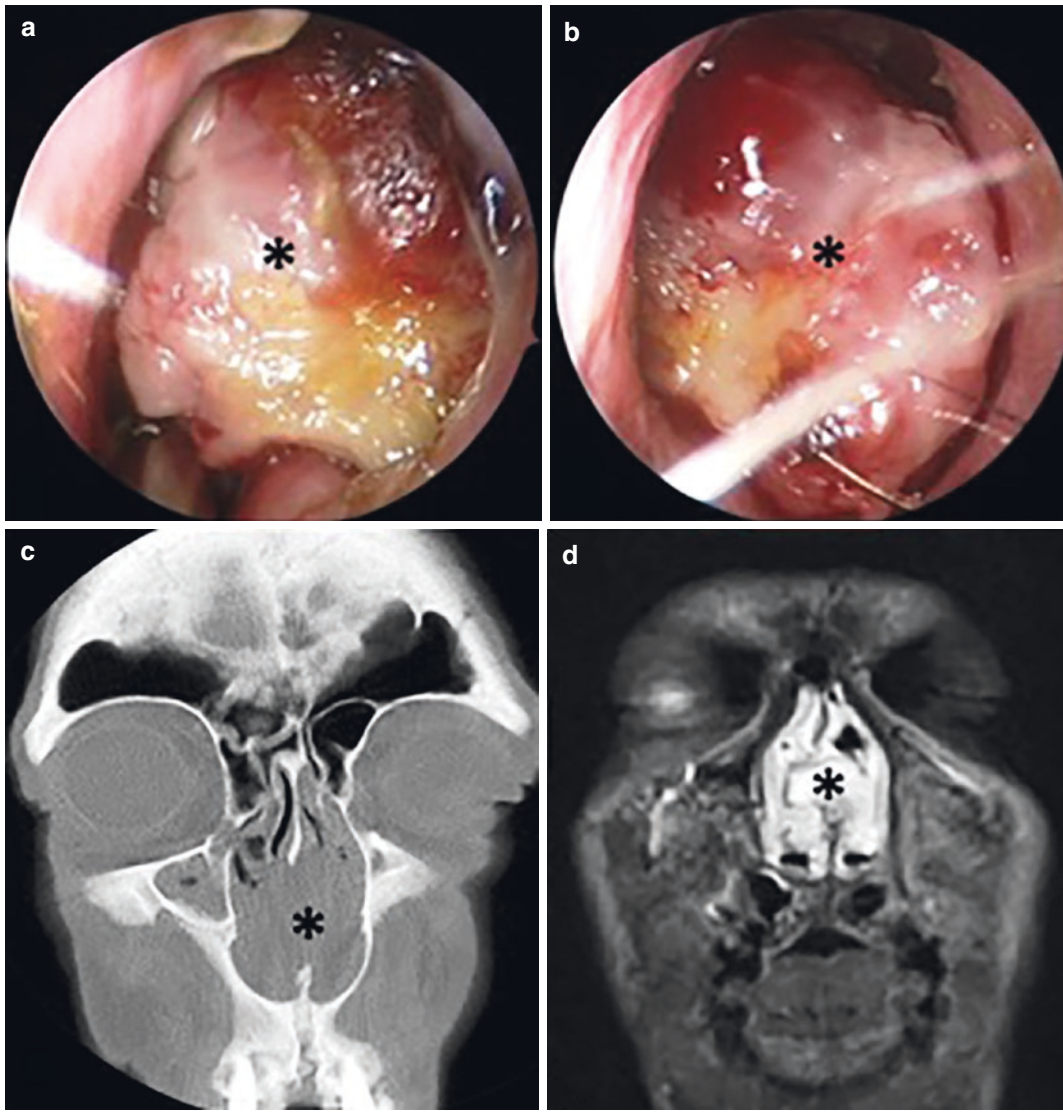

Fig. 31.13 Endoscopic view of lobular capillary haemangioma (LCH), (**a**) right nasal cavity (**b**) left nasal cavity (**c**) coronal scan CT showing anterior nasal cavity mass and septal perforation (**d**) coronal T2-weighted MRI showing hyperintense nasal mass and septal perforation obstructing nasal cavity bilaterally through septal perforation

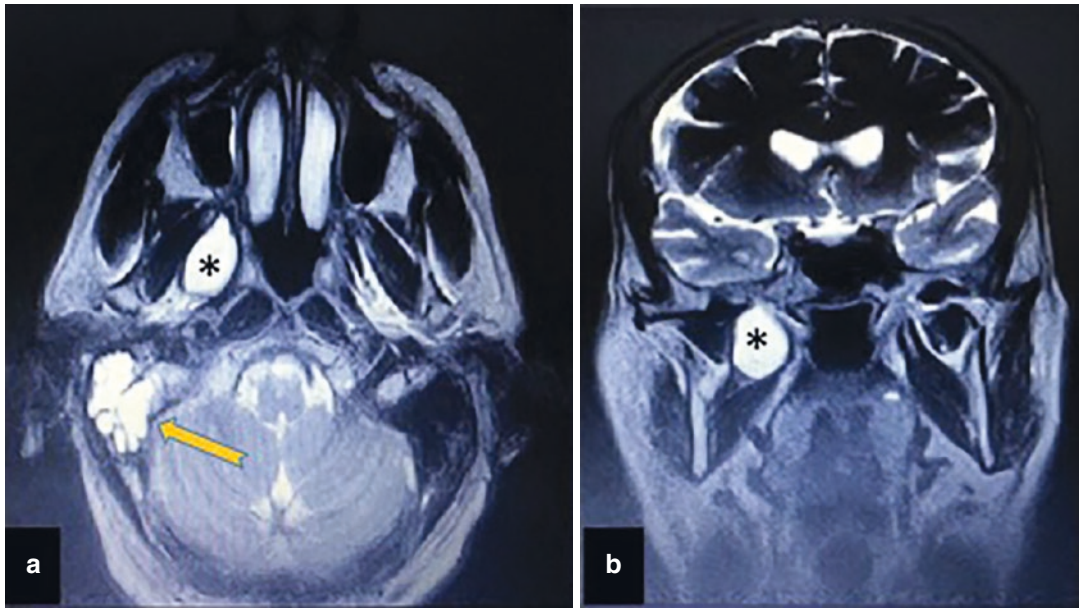

Fig. 31.14 Cavernous haemangioma (CH) (*) of right pterygopalatine fossa (PPF) and infratemporal fossa (ITF) compressing on right Eustachian tube causing persistent otitis media with effusion and mastoiditis (arrow), (**a**) axial and (**b**) coronal scans of T2-weighted MRI

The most common presenting symptoms are epistaxis and nasal obstruction. Contrast-enhanced CT and MRI should differentiate vascular tumours from other neoplasms and may show expansile lesions without bony destruction or erosion and heterogenous high/low signals, respectively.

Biopsy may cause a severe bleed and should be done with caution. Angiography and selective embolisation should be considered in some situations, and the MRI should be discussed with the radiologist, but is not always required as the main vessels are capillary.

Treatment is a surgical resection with curative intent. Endoscopic resection is the preferred choice (EEA) and facilitates precise clearance with removal of the tumour origin/stalk.

Pregnancy-related haemangiomas, known as a pyogenic granuloma, typically present with lesions on the anterior nasal septum. They normally regress postpartum in 1–2 months, but if they bleed excessively, it should be addressed during the pregnancy, according to symptom severity and pregnancy status [66, 67].

Solitary Fibrous Tumour (SFT)

SFT is a very rare neoplasm consisting of vascular branching with spindled fibroblastic cells between the branches. Only 5–27% of all SFTs are located in the head and neck and even more uncommon in sinonasal cavity with non-specific symptoms. Although it is a benign lesion, its aggressive clinical behaviour is unpredictable. Characteristics include local invasion, recurrences and distant metastasis; thus the differential diagnosis from mesenchymal tumours is crucial. Biopsy should confirm the diagnosis; histology should include immunohistochemistry stains for CD34. The optimum treatment method is total surgical excision with safe margins that can be achieved in most cases by EEA. Nevertheless, in cases where complete tumour removal is impossible without morbidity, or aggressive biological behaviour is suspected, multimodal therapy methods (chemotherapy/radiotherapy) can additionally be employed although these are often unnecessary [68, 69].

Glomangiopericytoma

Glomangiopericytomas are borderline and low malignant potential soft tissue tumours of the sinonasal cavity. Occurrence is very rare (<0,1% of all sinonasal tumours). They are described as haemangiopericytoma-like intranasal tumours containing vascular structures but have perivascular myeloid differentiation. The WHO Classification in 2005 renamed the tumour glomangiopericytoma, but the term sinonasal-type haemangiopericytomas are used in the literature and still in widespread use. However, they are very distinct from other haemangiopericytomas in other sites within the body.

Immunohistochemistry staining is helpful in confirming the diagnosis and shows a strong diffuse reactivity to actin, similar to a glomus tumour, but they lack strong diffuse staining for CD34.

Complete surgical resection with negative margins is the best treatment option increasing disease-free survival rates, although recurrence rates are relatively high at around 10%. If total resection is not possible, chemotherapy/radiotherapy could be helpful. Metastatic disease is rare and overall survival rates are high [70, 71].

Inflammatory Myoblastic Tumour

Inflammatory myoblastic tumour (IMT) is an uncommon intermediate soft tissue tumour of unknown aetiology and pathogenesis. In most cases IMTs act as a benign tumours, but may be invasive and recurrent tumours that rarely metastasize. Tumour contains spindle cells with myofibroblastic differentiation, plasma cells and lymphocytes. IMTs are more common in adults and they most commonly occur in the lung and abdomen, but can rarely be seen in the head and neck area. Sinonasal IMTs most frequently affect maxillary sinus followed by nasal cavity, nasal septum, ethmoid and sphenoid sinuses. Clinically the most common symptom is nasal obstruction, but depending to the site of origin, it may cause epistaxis, proptosis, visual changes and numbness. On CT and MRI, a soft tissue mass associated with bony destruction may be seen, but precise diagnosis is possible only with tissue biopsies and histopathology. Treatment is total surgical excision and radiotherapy. Cases with a high risk of malignant transformation (tumours >4 cm, located in maxillary sinus and preoperative neutrophil-to-leucocyte ratio over 1.958, have higher risk of malignant transformation) and recurrent cases can benefit from postoperative radiotherapy. Postoperative long-term follow-ups are necessary [72–74].

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Malignant Tumours

32

Paolo Battaglia, Giorgio Sileo, and Paolo Castelnuovo

Introduction

Sinonasal malignancies are rare tumours, accounting for 0.2–0.8% of all malignancies and 3–5% of head and neck cancers. Their prognosis is extremely variable, being influenced by the local extension of the disease, possible involvement of noble structures such as brain, orbit or internal carotid artery and tumour histology, itself critically influencing the biological aggressiveness [1].

The management of these uncommon diseases is handled by a multidisciplinary oncologic skull base team composed of head and neck surgeons, neurosurgeons, radiologists, radiotherapists, medical oncologists and pathologists.

The spectrum of treatment strategies is wide, from various surgical approaches to multimodal management, and is driven by the tumour histotype and its extension.

Craniofacial resection, firstly described by Ketcham in 1964 [2], has represented the gold standard in the treatment of sinonasal malignant tumours for decades, even though it is burdened by invasive transfacial approaches, significant functional sequelae and a complication and mortality rate of 36.3% and 4.7%, respectively [3].

The endoscopic endonasal approach, which was initially developed in the 1970s for the treatment of inflammatory sinonasal conditions, following progressive refinements in surgical techniques and technologies, has been gradually

P. Battaglia (✉) · P. Castelnuovo
Division of Otorhinolaryngology, Department of Biotechnology and Life Sciences, , University of Insubria-Varese, ASST Sette Laghi, Ospedale di Circolo e Fondazione Macchi, Varese, Italy

Department of Biotechnology and Life Sciences, Head and Neck Surgery and Forensic Dissection Research Center (HNS and FDRc), University of Insubria, Varese, Italy

G. Sileo
Department of Biotechnology and Life Sciences, Head and Neck Surgery and Forensic Dissection Research Center (HNS and FDRc), University of Insubria, Varese, Italy

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applied to selected cases of sinonasal malignancies since 1990 [4], with results comparable to those ones of traditional external approaches.

Epidemiology

In Western countries the incidence varies between 0.8 and 1 per 100,000 people, whereas it is greater in Africa and Eastern countries, where it can reach 2.6 per 100,000 people as reported in Japan [5].

The average age at diagnosis is 60 years; men are more affected than females (58.6%), which is probably due to environmental or occupational exposure. Children can be affected by different histotypes, rhabdomyosarcoma being the most prevalent type [6].

The most common site of origin is the maxillary sinus (50–70%), followed by the nasal cavity (15–30%) and ethmoid sinus (10–20%); frontal and sphenoid sinuses are rarely the primary site, yet they are generally involved by locally advanced tumours with dismal prognosis.

The role of different work-related chemical hazards in determining sinonasal cancers has been widely investigated by epidemiological studies, and the evaluation of the occupational exposure can be very challenging, because of the potential long latency period.

Workers exposed to wood dust, leather, aluminium and other chemicals (such as formaldehyde and solvents) have an increased risk for developing sinonasal malignancies. The strong association between intestinal-type adenocarcinoma (ITAC) and former exposure to wood or leather dust, as demonstrated by Bonzini et al. (87% of patients with ITAC were exposed), is noteworthy [7].

In addition to occupational hazards, other risk factors include previous head and neck irradiation, smoking, genetic alterations and inverted papilloma.

Two thirds of sinonasal malignancies have an epithelial origin and the most common histologies are adenocarcinoma (ADC) in European countries and squamous cell carcinoma (SCC) in North America; other epithelial histotypes include adenoid cystic carcinoma (ACC) and sinonasal undifferentiated carcinoma (SNUC) [8].

Paranasal sinuses may be the site of metastases from other cancers and almost half of all cases is represented by renal cellular carcinoma, followed by breast, prostate, lungs, gastrointestinal tract and thyroid carcinoma [9].

Clinical Features

Sinonasal malignancies commonly present with non-specific signs and symptoms, therefore making the diagnosis difficult and generally delayed. Initial findings can often be misleading because they may mimic more common and benign conditions such as inflammatory diseases.

In our institution, among 565 patients treated in the last 20 years, the most common complaints were respiratory nasal obstruction (71%), epistaxis (51%), olfactory dysfunction (36%), rhinorrhoea (29%), headache (17%), facial pain (13%), epiphora (6%), swelling (4%), visual disturbance (4%) and diplopia (4%).

Symptoms may be an indicator of the local extension of the disease because of the mass effect on surrounding tissues.

Maxillary tumours may present with facial swelling, if extending anteriorly, or palatal swelling and loosening of teeth, in cases with inferior extension; diplopia and proptosis may be the result of orbital invasion, whereas a posterior spread, towards the infratemporal/pterygoid palatine fossa, may cause trismus or facial neuralgia or occasionally altered sensation/numbness because of the involvement of masticatory muscles or maxillary nerve. Ethmoidal malignancies may extend laterally into the orbit, thus causing visual symptoms or proptosis, or intracranially with potential neurological symptoms (Fig. 32.1).

Among this broad spectrum of clinical findings, unilateral persistent symptoms unresponsive to medical treatment must draw clinicians' attention and should prompt a thorough further investigation.

On initial presentation cervical lymph node metastases occur within a range variable from 3 to 30%, whereas distant metastases are less frequent, with an incidence of 1–7% [10].

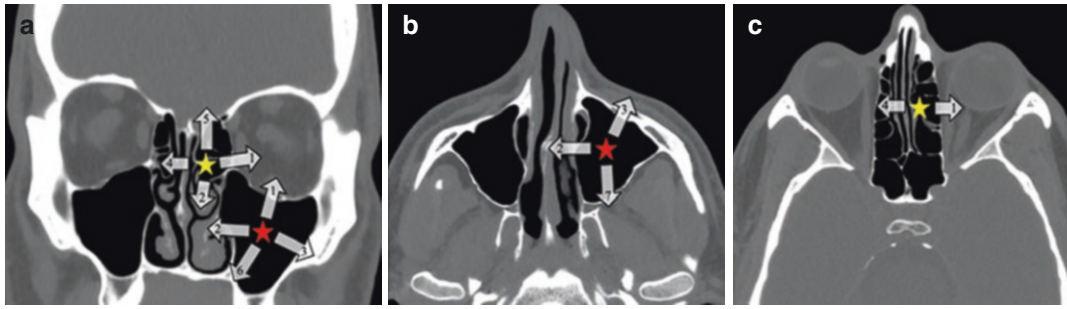

Fig. 32.1 Potential directions of growth of ethmoidal (yellow star) and maxillary (red star) tumours in different CT scan views ((**a**), coronal; (**b**) axial at the level of maxillary sinuses; (**c**) axial at the level of the orbits). Legend: 1 orbital infiltration; 2 nasal cavity extension; 3 anterior/lateral maxillary wall infiltration; 4 contralateral nasal cavity extension; 5 intracranial invasion; 6 extension into the oral cavity; 7 posterior extension into the pterygopalatine or infratemporal fossa

Diagnostic Workup

In cases of suspected sinonasal expansile lesions, the patient must be referred to an otolaryngologist for a complete clinical examination.

Nasal endoscopy, performed with flexible or rigid scopes, is the first diagnostic test of utmost importance since it can detect the lesion, its characteristics (e.g. ulceration, bleeding) and its possible site of origin.

CT Imaging

The second step is computed tomography (CT) imaging, generally done without contrast, to evaluate the sinonasal anatomy and the presence of bony alterations, which can present with different patterns:

- *Bone remodelling*, that is displacement and thinning of bony structures (more frequently observed in benign neoplasms or chronic inflammatory processes)
- *Cortical destruction*, that is interruption in the whole thickness of mineralized bone
- *Intra-diploic growth*, in cases of intra-osseous spread, that is the replacement of spongiosa by solid tissue
- *Permeative invasion*, that is subperiosteal spread with diffuse demineralization (mostly observed in lymphomas and adenoid cystic carcinomas)
- *Sclerosis*, as a result of chronic inflammatory reaction of the spongiosa [11]

The CT scan facilitates the evaluation of the lamina papyracea and skull base, thus providing preliminary details of intraorbital and intracranial extension. Moreover, the enlargement of bony fissures or foramina may be an indicator of perineural spread. Lastly, modern CT scans with three-dimensional reconstruction in axial, coronal and sagittal planes are crucial in surgical planning.

MRI Imaging

The third step consists of magnetic resonance imaging (MRI) scan with contrast (gadolinium), which has the potential to differentiate soft tissue densities and to assess the grade of vascularization. MRI of the head is strongly recommended on occasions where a CT head scan demonstrates unexpected unilateral sinonasal mass in patients with no sinonasal symptoms.

A systematic approach to different MRI sequences is crucial in characterizing the lesion and in evaluating its relationship with adjacent structures. For this purpose, it is useful to compare T2 with plain T1 and contrast-enhanced T1 sequences: The first shows fluid as bright, the second highlights fat as bright, whereas the latter enhances vascularized neoformations, which are

usually hypointense on T2. "Fat-sat" (applicable to both T1 and T2) is another useful sequence that suppresses fat signal, hence helping in delineating the relationship between tumour and fat tissue.

The usefulness of MRI is demonstrated by its ability to assess eventual infiltration of the orbit, anterior cranial fossa and pterygopalatine/infratemporal fossa, which dramatically influences the treatment planning.

Orbital walls appear hypointense on T1 and T2 sequences because of the reduced water content of lamina papyracea and periorbita; thus, neoplastic infiltration is suspected when the hypointense interface is not recognizable.

T2 and contrast-enhanced T1 sequences enable evaluation of different stages of anterior cranial fossa invasion, by looking at its three different layers (cribriform plate, dura and cerebrospinal fluid); indeed, a thickened and enhanced dura suggests skull base invasion.

Posterior extension to the pterygopalatine and infratemporal fossa is demonstrated by maxillary bone erosion, loss of fat signal or altered signal intensity of the pterygoid muscles [12].

However, it is important to appreciate that in almost all cases CT and MRI findings are nonspecific and do not allow to differentiate between different malignant histotypes.

As a general rule, biopsy is best performed after completing imaging studies to minimize the risk of bleeding from vascular tumours (e.g. juvenile angiofibroma, meningoencephalocele). Biopsy is generally performed under local anaesthesia with rigid scopes, but in some cases, general anaesthesia is required.

A pathological second opinion in centres with dedicated expertise is strongly recommended in order to confirm the definitive diagnosis and plan the adequate treatment.

Additional Scanning Protocols

Once a malignant tumour has been confirmed, it is essential to exclude or identify regional and/or distant metastatic disease, according to the policy of the local radiology department. This typically includes ultrasound neck and CT chest and abdomen.

Total body positron emission tomography (PET-CT) scan is preferred in cases of aggressive histotypes (e.g. mucosal melanoma, neuroendocrine carcinoma) or advanced stages.

Staging

Different staging systems have been developed in the past decades to evaluate sinonasal malignancies.

The Union for International Cancer Control/American Joint Committee on Cancer (UICC/AJCC) TNM classification, now in its eighth edition, is the most widely used. In this staging system, the T classification depends on the progressive involvement of adjacent structures; the sinonasal tract is divided into maxillary sinus and nasal cavity/ethmoid sinus. All histotypes are included except for mucosal melanoma, which has its own TNM classification (T3 is the minimum) due to its extremely aggressive behaviour [13].

Different staging systems have been proposed for esthesioneuroblastoma, because of its peculiar biological behaviour: The Kadish classification, which was developed in 1976, is the most commonly used and divides patients into three categories [14]; a fourth new category, for patients with metastases, was introduced by Morita in 1993. In 1992 Dulguerov and Calcaterra developed a new staging system, which was found to be better correlated with survival [15].

The Wang staging system was developed for carcinoma of the nasal vestibule, which is an aggressive cancer with a worse prognosis than other head and neck skin cancers; this staging system is based on the invasion depth and is a better prognostic indicator than the TNM classification [16] (Tables 32.1, 32.2, 32.3, 32.4 and 32.5).

Table 32.1 T staging according to the AJCC eighth edition

		Maxillary sinus	Nasal cavity and ethmoid sinus
T1		Tumour limited to the mucosa (no erosion or destruction of the bone)	Tumour restricted to one subsite[a] of the nasal cavity or ethmoid sinus
T2		Tumour causing bone erosion or destruction (hard palate and/or middle meatus extension is included, whereas extension to posterior maxillary wall and pterygoid plates is excluded)	Tumour involves two subsites in a single site or involves an adjacent sites within the nasoethmoidal complex
T3		Tumour involves any of the following: • Posterior maxillary bony wall • Floor or medial orbital wall • Subcutaneous tissues • Pterygoid fossa • Ethmoid sinuses	Tumour involves any of the following: • Maxillary sinus • Floor or medial orbital wall • Palate • Cribriform plate
T4a		Tumour involves any of the following: • Anterior orbital contents • Skin of the cheek • Pterygoid plates • Sphenoid or frontal sinuses • Cribriform plate • Infratemporal fossa	Tumour involves any of the following: • Anterior orbital contents • Skin of the nose or cheek • Pterygoid plates • Sphenoid or frontal sinuses • Minimal extension to anterior cranial fossa
T4b		Tumour involves any of the following: • Orbital apex • Dura • Brain • Middle cranial fossa • Cranial nerves other than V2 • Nasopharynx or clivus	Tumour involves any of the following: • Orbital apex • Dura • Brain • Middle cranial fossa • Cranial nerves other than V2 • Nasopharynx or clivus

[a] Anatomical site and subsites: nasal cavity (septum, floor, lateral wall, vestibule), maxillary sinus, ethmoid sinus (left, right)

Table 32.2 N staging according to the AJCC eighth edition

Regional lymph nodes	
Nx	Regional lymph nodes cannot be assessed
N0	No regional lymph nodes metastases
N1	Metastasis in a *single* ipsilateral lymph node, ≤3 cm in greatest dimension (no extranodal extension)
N2a	Metastasis in a *single* ipsilateral lymph node, between 3 and 6 cm in greatest dimension (no extranodal extension) or <3 cm with extranodal extension
N2b	Metastasis in *multiple* ipsilateral lymph nodes, ≤6 cm in greatest dimension (no extranodal extension)
N2c	Metastasis in *bilateral or contralateral* lymph nodes, ≤6 cm in greatest dimension (no extranodal extension)
N3a	Metastasis in a lymph node >6 cm in greatest dimension (no extranodal extension)
N3b	Metastasis in a single (>3 cm) or multiple lymph nodes with extranodal extension

Table 32.3 T staging of malignant melanoma of upper airways and digestive tract according to AJCC eighth edition

Malignant melanoma of upper airways and digestive tract	
T3	Tumour is limited to the epithelium and/or submucosa
T4a	Tumour involves the bone, cartilage, deep soft tissue or overlying skin
T4b	Tumour involves any of the following: • Brain • Dura • Skull base • Lower cranial nerves (IX, X, XI, XII) • Masticator space • Carotid artery • Prevertebral space • Mediastinal structures

Table 32.4 Kadish-Morita and Dulguerov-Calcaterra staging system for esthesioneuroblastoma

	Kadish-Morita		Dulguerov-Calcaterra
A	Tumour is limited to the nasal cavity	*T1*	Tumour involves the nasal cavity and/or paranasal sinuses (excluding sphenoid), sparing the most superior ethmoidal cells
B	Tumour involves the nasal cavity and paranasal sinuses	*T2*	Tumour involves the nasal cavity and/or paranasal sinuses (including the sphenoid), with extension to or erosion of cribriform plate
C	Tumour extends beyond the nasal cavity and paranasal sinuses	*T3*	Tumour extends into the orbit or protrudes into the anterior cranial fossa, without dura invasion
D	Regional or distant metastases	*T4*	Tumour involves the brain

Table 32.5 Wang T staging system for carcinoma of the nasal vestibule

Wang T staging system	
T1	Tumour confined to the skin
T2	Tumour invades subcutaneous tissue and cartilage
T3	Tumour invades the bone

Histology-Driven Treatments

In this section the most common histotypes and their multimodal treatment protocols are presented.

Squamous Cell Carcinoma (SCC)

SCC is the most common sinonasal malignancy in the United States: It originates in the maxillary sinus in 60% of cases, less frequently in the nasal cavity or ethmoid. Tumours occur in men twice as much as in women in their 50s and 60s.

It can present with different subtypes: keratinizing (KSCC), non-keratinizing (NKSCC) and other rarer variants.

KSCC is the most common (50% of cases) and is characterized by keratinization; indeed epithelial markers (e.g. citokeratins) are expressed. It is identical to KSCC arising in other sites and it can be found in approximately 5–10% of sinonasal inverted papillomas [17].

NKSCC accounts for 20% of sinonasal SCC and is similar to that one arising in the oropharynx. It is characterized by minimal squamous differentiation and does not have tumour grading. The association with high-risk HPV is found in almost 50% of cases and correlates with a trend towards improved survival [18].

The standard treatment is surgical resection followed by adjuvant radiotherapy; irradiation should include the neck in case of advanced stages (T3–T4), given the high risk of nodal metastases (20%). In case of positive margins or evidence of neural/lymphovascular infiltration, adjuvant chemotherapy can be administered.

Patients with high-grade carcinoma in advanced stages (T3–T4) can be treated with induction chemotherapy regimens followed by surgery and postoperative chemoradiation or definitive chemoradiation; tumour response to induction chemotherapy is associated with better survival and prognosis [19] (Fig. 32.2).

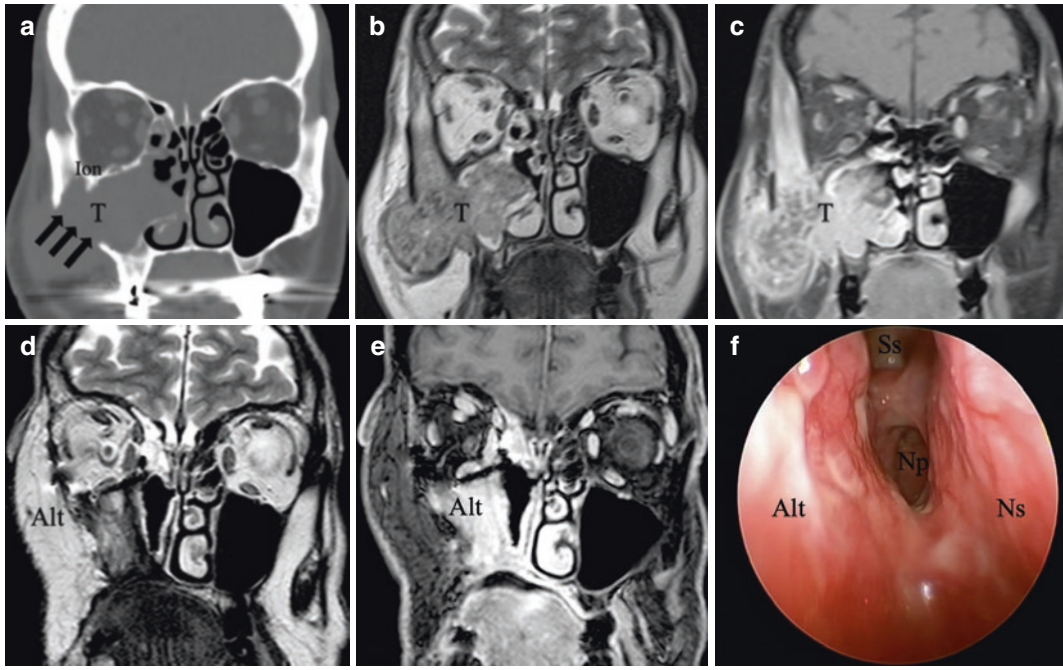

Fig. 32.2 A 54-year-old female affected by right maxillary sinus squamous cell carcinoma G2 extending into the infratemporal fossa, parotid, temporalis muscle and subcutaneous cheek (T4aN0M0). Preoperative CT (**a**) and MRI scans ((**b**) T2W; (**c**) T1W with contrast) in coronal views. The patient underwent craniofacial resection with right selective neck dissection (I–IV), reconstruction with anterolateral thigh free flap and adjuvant radiotherapy (60Gy). MRI scans in coronal views ((**d**) T2W; (**e**) T1W with contrast) and nasal endoscopy (**f**) at 1-year follow-up: the patient is alive without disease. Legend: *Alt* anterolateral thigh free flap, *Ion* infraorbital nerve, *Np* nasopharynx, *Ns* nasal septum, *Ss* sphenoid sinus, *T* tumour, black arrows erosion of the lateral maxillary wall

Adenocarcinoma (ADC)

ADC is the most common sinonasal epithelial malignancy in Europe and it generally originates in the ethmoid (85%), followed by the olfactory cleft (13%).

Intestinal-type adenocarcinoma (ITAC) takes its name from the morphological analogy with intestinal adenocarcinomas and correlates with occupational exposure to leather or wood dust in up to 87% of cases [7]. It affects predominantly men aged between 40 and 70 years.

According to Barnes's classification, different subtypes can be distinguished: papillary (75% of cases), solid, mucinous (e.g. signet-ring cells) and mixed. Solid and mucinous patterns are indicative of poorly differentiated cancers, thus behaving more aggressively [20].

Non-intestinal-type adenocarcinoma (nITAC) represents a diagnosis of exclusion; features of intestinal or salivary gland tumours are absent; positive for markers of seromucinous differentiation (e.g. S100, DOG1) are often demonstrated. As opposed to ITAC, it is not correlated with occupational exposure and patients are generally younger (50s) with a mild female predilection.

Surgical resection is the mainstay of treatment: It is the single effective treatment for low-grade tumours in early stages (T1–T2), but it should be followed by postoperative radiotherapy (PORT) in case of high-grade neoplasms, advanced stages (T3–T4) or infiltrated surgical margins. In case of high-grade lesions with intracranial extension, a prophylactic brain irradiation should also be considered, given the potential risk of leptomeningeal involvement [21] (Fig. 32.3).

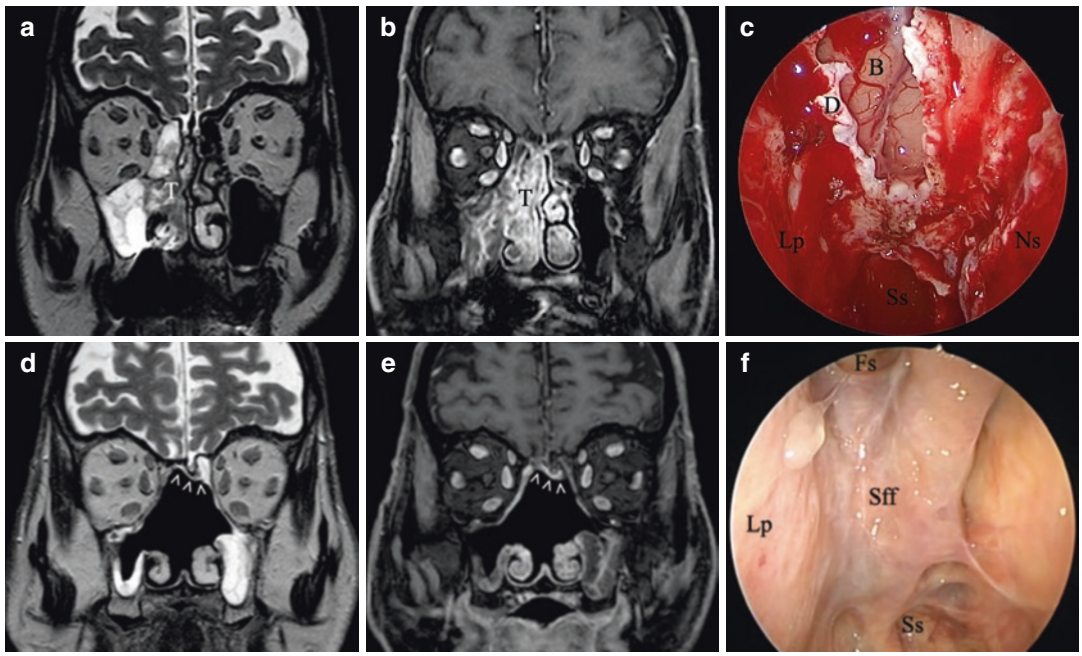

Fig. 32.3 A 78-year-old male, former woodworker, affected by right sinonasal intestinal-type adenocarcinoma G1 (T3N0M0). Preoperative MRI scans in coronal views ((**a**) T2W; (**b**) T1W with contrast). Right endoscopic resection with transnasal craniectomy (ERTC) and skull base reconstruction with fascia lata and septal flip flap was performed ((**c**) right nasal fossa intraoperative view after dura removal), adjuvant radiotherapy followed (66Gy). MRI scans in coronal views ((**d**) T2W; (**e**) T1W with contrast) and nasal endoscopy (**f**) after 5 years demonstrate no evidence of the disease. Legend: *B* brain, *D* dura mater, *Fs* frontal sinus, *Lp* lamina papyracea, *Ns* nasal septum, *Sff* and white arrowheads septal flip flap, *Ss* sphenoid sinus, *T* tumour

The neck is not routinely treated as regional metastases occur in only 7% of patients. Induction chemotherapy has been proposed for advanced-stage (T3–T4) ITAC with functional p53, showing promising results in survival [22].

Adenoid Cystic Carcinoma (ACC)

ACC is a rare salivary gland tumour that involves most frequently the maxillary sinus (60%) and the nasal cavity (30%). It has a slight prevalence in women, with a peak of incidence in the fifth and sixth decades.

Given the strong propensity for perineural and bony spread, intracranial extension (including cavernous sinus) is likely and local recurrence is common (60%). Another important characteristic is distant metastases (lung, bone and brain), often presenting many years after the initial tumour and occurring in approximately 40% of patients [23].

ACC presents in different subtypes: cribriform, tubular and the less differentiated solid. Different grading systems have been proposed to emphasize the importance of histological subtypes; indeed, according to the Perzin/Szanto system, ACC is classified as high grade if the solid component represents more than 30%. In this case the tumour behaves locally more aggressively and tends to develop early distant metastases [24].

ACC is considered a relative radiosensitive tumour; hence the standard treatment is surgical radical resection, whenever feasible, followed by adjuvant radiotherapy to clear positive margins (microscopic or macroscopic) [25].

In cases of locally advanced stages, with involvement of vital structures, function-sparing tumour debulking reduces the target volume, making PORT more selective and efficient.

Heavy particle radiotherapy, with protons or carbon ions, has recently been introduced and demonstrates improved local control, both for postoperative patients and those with unresectable ACC. A significant advantage of this technique is the ability to deliver high tumouricidal doses whilst sparing adjacent normal tissues.

Esthesioneuroblastoma (ENB)

ENB, also named olfactory neuroblastoma, is a malignant neuroectodermal neoplasm that arises from the olfactory neuro-epithelium. It has a slight predominance in male (male-to-female ratio 1.2:1), and although a bimodal distribution in age has been initially reported, it affects patients in the fifth or sixth decade [26].

It is typically located in the superior portion of the nasal vault and involves the cribriform plate. Ectopic location within the paranasal sinuses is extremely rare. It can present with a paraneoplastic syndrome but only in 2% of patients (e.g. syndrome of inappropriate antidiuretic hormone/ADH secretion) [27].

Metastases at presentation are rare; furthermore they develop late in the natural history of the disease, most frequently in cervical lymph nodes. Several staging systems have been proposed, but the Kadish staging system is the most commonly applied.

The Hyams grading system classifies ENB into four grades, from most (grade I) to least differentiated (grade IV), depending on specific histopathological features. Higher grades are associated with more aggressive locoregional disease and worse disease-free survival.

The differential diagnosis is wide, and immunohistochemistry is of utmost importance: neuron-specific enolase, synaptophysin and chromogranin A are typically positive. Review of pathological specimens by expert pathologists is crucial especially when dealing with poorly differentiated ENBs, given that they could easily be confused with other neuroendocrine tumours.

The standard treatment is surgical resection, with removal of the anterior skull base dura and olfactory bulb, followed by adjuvant radiotherapy; irradiation should include the neck in cases of intracranial extension (Kadish C).

The role of chemotherapy is debated; however neoadjuvant regimens (e.g. etoposide/cisplatin) are generally advocated for patients with poorly differentiated ENB in locally advanced stages [28]. Follow-up should be long term, and should metastatic neck disease present at a late stage, neck dissection with possible PORT should be considered (Fig. 32.4).

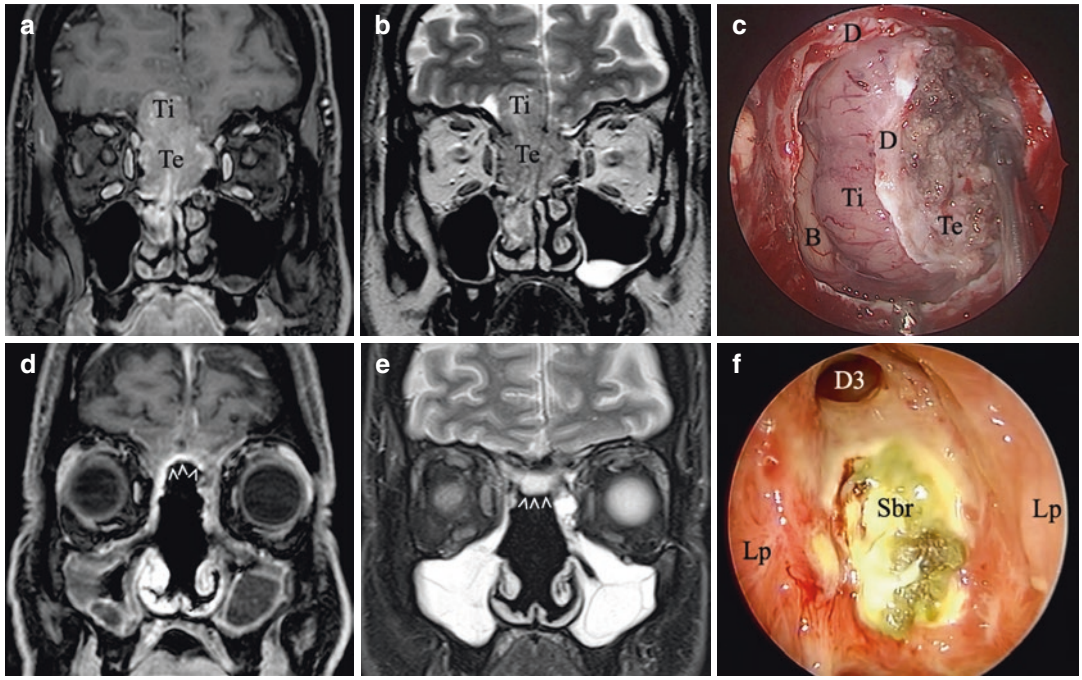

Fig. 32.4 A 58-year-old male affected by right esthesioneuroblastoma Kadish C, Hyams II. The preoperative MRI scans in coronal views ((**a**) T1W with contrast; (**b**) T2W) and intraoperative view (**c**) show the intracranial extension of the disease. The patient underwent bilateral ERTC and skull base reconstruction with fascia lata followed by adjuvant radiotherapy (60/54 Gy on T/N). MRI scans in coronal views ((**d**) T1W with contrast; (**e**) T2W) and nasal endoscopy (**f**) performed at 7-month follow-up demonstrate local control of the disease. Legend: *B* brain, *D* dura mater, *D3* Draf III, *Lp* lamina papyracea, *Sbr and white arrowheads* skull base reconstruction, *Ti* intradural tumour, *Te* extradural tumour

Neuroendocrine Carcinoma (NEC)

Sinonasal tumours with neuroendocrine differentiation is a heterogeneous group of rare neoplasms with neuroectodermal (ENB) or epithelial origin (NEC).

NEC is a high-grade carcinoma with features of neuroendocrine differentiation that accounts for 5% of sinonasal malignancies; it is an aggressive tumour characterized by a dismal prognosis with a high rate of local recurrences and distant metastases (lung, liver and bones). It can be categorized into typical and atypical carcinoids and small cell and large cell NECs.

It has a slight male predominance and a median age at diagnosis of 56 years. The most common site of origin is the ethmoid (64%), followed by the nasal cavity (32%) and the maxillary sinus (14%) [29].

NECs are strongly positive for cytokeratins, epithelial membrane antigen and markers of neuroendocrine differentiation (e.g. synaptophysin); according to a European multicentre study, CK8/18 immunohistochemistry is strongly recommended in order to avoid a misdiagnosis of ENB, due to the negative staining for CKAE1/A3 [28].

Mixed neuroendocrine-nonneuroendocrine neoplasm is a recently described histopathological entity, in which the neuroendocrine component represents at least 30% of the lesion, characterized by an aggressive biological behaviour with frequent recurrences (80%) and poor survival outcomes [30].

The role of neoadjuvant chemotherapy is still debated but promising, due to the frequent distant failures and the chemosensitivity of NEC; the rate of response to induction chemo-

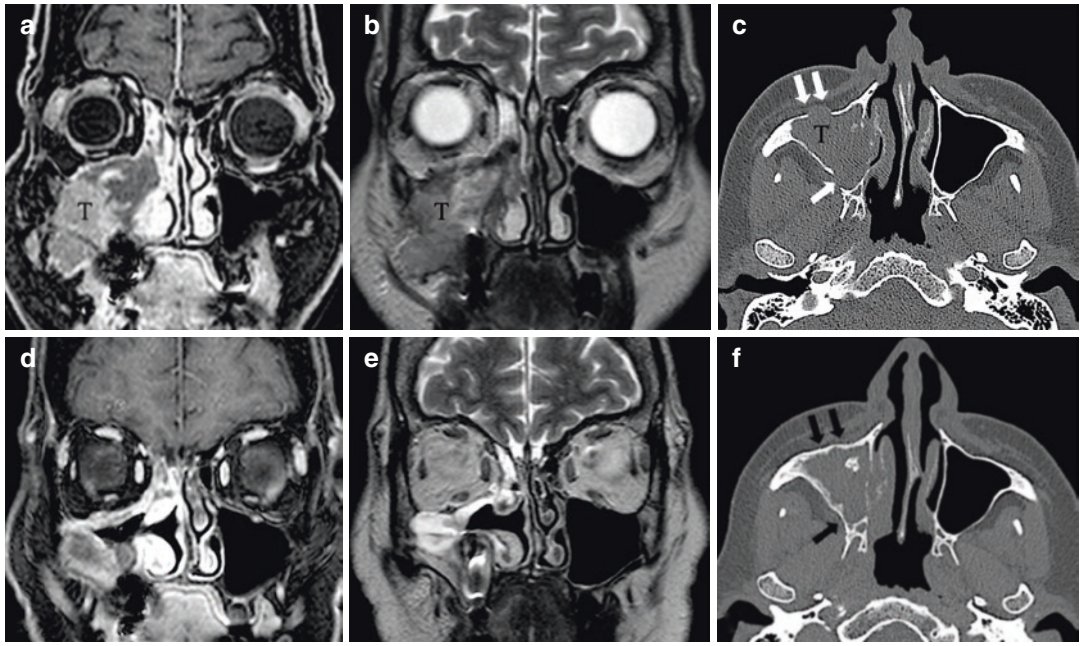

Fig. 32.5 A 52-year-old female affected by right maxillary sinus small cell neuroendocrine carcinoma G3 (T4aN0M0). Pretreatment MRI scans in coronal views ((**a**) T1W with contrast; (**b**) T2W) and (**c**) axial CT scan show focal erosion of the anterior and posterior maxillary walls and extension into the premaxillary soft tissue. Given the good response to induction chemotherapy, the patient underwent exclusive radiochemotherapy. MRI scans in coronal views ((**d**) T1W with contrast; (**e**) T2W) and axial CT scan (**f**) at 8-month follow-up demonstrate local control of disease. Legend: *T* tumour, white arrows focal erosion of the anterior and posterior maxillary walls, black arrows the erosion of the maxillary walls is no more visible

therapy could stratify patients in "responders", eligible for exclusive radiochemotherapy, and "nonresponders", who may benefit from surgery followed by adjuvant radiotherapy or radiochemotherapy [31] (Fig. 32.5).

Sinonasal Undifferentiated Carcinoma (SNUC)

SNUC is a rare, highly aggressive, undifferentiated carcinoma that lacks by definition squamous or glandular differentiation. The average age at diagnosis is 50–60 years, and it shows a male predominance (2–3:1). The most common sites involved are the nasal cavity and ethmoid sinus, and it is usually locally advanced at presentation, frequently showing orbital, skull base and intracranial involvement.

Nodal metastases occur in less than 15% of cases, whereas distant metastases are frequent. The differential diagnosis is broad and includes lymphoma, non-keratinizing SCC, ENB and high-grade NEC; immunohistochemistry demonstrates positivity for cytokeratins and neuron-specific enolase [32].

In 2014 Bishop et al. reported a subset characterized by a lack of SMARCB1 tumour-suppressor gene (also known as INI-1), the presence of rhabdoid features and a more aggressive behaviour with tendency for regional and distant metastases [33].

Gray et al. demonstrated a higher prevalence of HPV in SNUC (64.3%) than previously reported, thus suggesting a role in the carcinogenic process with a trend towards improved survival [34].

SNUC is a chemosensitive tumour, which generally presents in local advanced stages (almost 70% of cases are T4) and may benefit from aggressive multimodality treatment: Induction chemotherapy followed by either

chemoradiation or surgery with postoperative irradiation provides the best survival outcomes.

Different studies have demonstrated the feasibility and effectiveness of induction chemotherapy, which may reduce the incidence of distant metastases; the most frequently employed regimen is cyclophosphamide, doxorubicin and vincristine.

Mucosal Melanoma (MM)

MM is an aggressive malignant neoplasm, accounting for 1% of all melanomas, characterized by a high tendency for recurrence and systemic spread. It does not show gender predominance and the incidence peak is in the seventh decade.

Mucosal and cutaneous melanomas are biologically distinct; indeed, MM is characterized by a complex array of abnormalities with high rates of KIT mutations (20–40%), followed by NRAS (15%) and rare BRAF mutations (0–3%) [35].

In the sinonasal tract, the most common site of origin is the nasal cavity and tumours originating in the paranasal sinuses are associated with worse survival [36].

In 50% of cases, MM is amelanotic, therefore contributing to a diagnostic delay and a broader differential diagnosis (that includes ENB, SNUC and NEC). According to the seventh edition of the AJCC cancer staging, all MMs are considered T3–T4 and associated with extremely poor prognosis (5 years overall survival <30%).

The treatment of choice is surgery and minimally invasive endoscopic approaches should be preferred to external aggressive surgeries, which may be associated with impaired immune balance, hence a higher risk of local recurrence or systemic dissemination [37].

Adjuvant radiotherapy is generally delivered in cases of positive surgical margins, although MM is known to be radioresistant. According to a large multicentre retrospective study, carbon-ion irradiation achieves superior local control and notable survival benefit compared to conventional radiotherapy [38].

Recently, novel targeted therapies such as tyrosine kinase inhibitors (given the high prevalence of KIT gene mutations) and immunotherapy have shown encouraging results; moreover the combination of radiation, in particular carbon-ion radiotherapy, with concurrent immunotherapy might synergistically promote tumour response and prolong survival [39] (Fig. 32.6).

Long-term follow-up and endoscopic review is essential. Interval MRI surveillance scans are recommended to detect hidden recurrence in inaccessible areas such as the infratemporal fossa.

Key Learning Points

- Malignant tumours of the paranasal sinuses are rare and account for less than 5% of head and neck cancers.
- The diagnosis is generally delayed and tumours present in advanced stages because of non-specific clinical features.
- Unilateral signs and symptoms (e.g. nasal obstruction, rhinorrhoea, epistaxis, swelling) unresponsive to medical treatments must raise suspicion; particular attention must be paid in patients with occupational exposure to leather or wood dust.
- A thorough diagnostic workup requires clinical examination with nasal endoscopy, imaging (CT scan, MRI scan with contrast, total body CT scan) and biopsy; because of the wide spectrum of histological entities, a pathological second opinion should be considered to confirm the diagnosis.
- Multidisciplinary management is of utmost importance in the management of sinonasal malignancies.
- A correct histological diagnosis is mandatory in order to plan appropriately among different multimodal treatment protocols.

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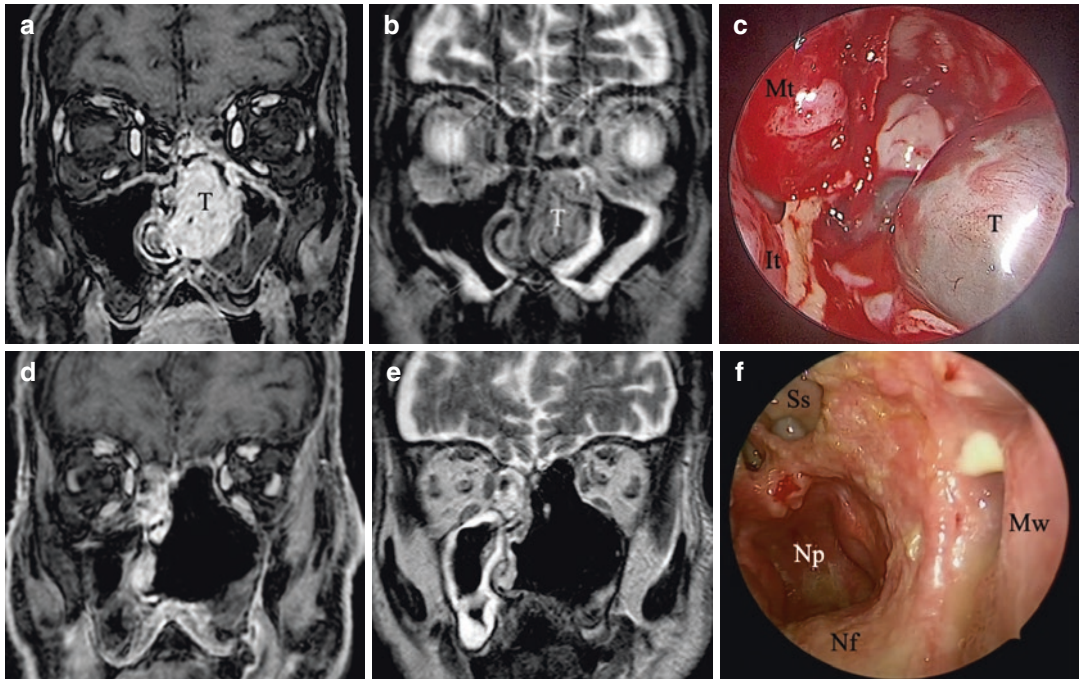

Fig. 32.6 A 71-year-old male affected by left nasal fossa mucosal melanoma T3N0M0. Preoperative MRI scans in coronal views ((**a**) T1W with contrast; (**b**) T2W) show the tumour occluding the left nasal fossa and infiltrating the nasal septum. The patient underwent a left transnasal endoscopic medial maxillectomy type IIIb with removal of the nasal septum and drilling of the hard palate. Intraoperative view (**c**) shows the tumour in the left nasal fossa after removal of the infiltrated nasal septum. Adjuvant carbon-ion radiotherapy was delivered (65.6 Gy). Postoperative MRI scans in coronal views ((**d**) T1W with contrast; (**e**) T2W) and nasal endoscopy (**f**) at 8-month follow-up confirm local control of disease. Legend: *It* inferior turbinate, *Mt* middle turbinate, *Mw* lateral maxillary wall, *Nf* nasal floor, *Np* nasopharynx, *Ss* sphenoid sinus, *T* tumour

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Juvenile Angiofibroma

33

Haissan Iftikhar, Ann-Louise McDermott, and Shahzada Ahmed

Natural History of the Disease

Juvenile angiofibroma is histologically classified as a benign lesion, although it commonly demonstrates aggressive behaviour with rapid growth and bony erosion of the sphenoid sinus floor, clivus and pterygoid plates.

Angiofibroma has been referred to as Juvenile nasopharyngeal angiofibroma (JNA) for many years but this is strictly no longer correct as the tumour does not arise from the nasopharynx. The term 'juvenile' reflects the predilection for its occurrence in adolescent boys but it can sometimes present in young adult men.

The predilection of angiofibroma for adolescent males suggests a hormonally influenced tumour. Studies of steroid receptors have had variable results, generally finding the tumours to be positive for androgen receptors whose hormone has physiological peaks around puberty. This also explains why Angiofibromas are almost never seen in girls, and when the tumour is seen in older men, it is likely to have originated in adolescence.

The exact anatomical site of origin of an angiofibroma is not completely clear: It is initially thought to have its origins from the upper margin of the sphenopalatine foramen at the junction of the sphenoidal process of the palatine bone and the pterygoid process or alternatively from the pterygoid canal.

The tumour can then expand in many directions:

1. It may extend into the sphenoid sinus without infiltrating the mucosa.
2. It may spread beyond the sphenoid sinus to affect the central skull base and its foramina.
3. Occasionally, the cavernous sinus is affected and in advanced cases, intracranial spread may occur.
4. The tumour may pass through the sphenopalatine foramen, expanding laterally to the pterygopalatine fossa, with anterior bowing of the posterior maxillary sinus wall demonstrated on axial CT imaging, known as the Holman-Miller sign [1].
5. Anterolateral spread through the inferior orbital fissure leads directly to the orbit.
6. Rarely, it can travel through the superior orbital fissure to the intracranial cavity. However, the tumour typically stays in the extradural space and rarely infiltrates the dura and brain (Fig. 33.1).

H. Iftikhar · S. Ahmed (✉)
University Hospitals Birmingham NHS Trust, Birmingham, UK
e-mail: shahz.ahmed@nhs.net

A.-L. McDermott
Department of Otolaryngology, Birmingham Childrens Hospital, Birmingham Womens and Childrens Hospital NHS Foundation Trust, Birmingham, UK

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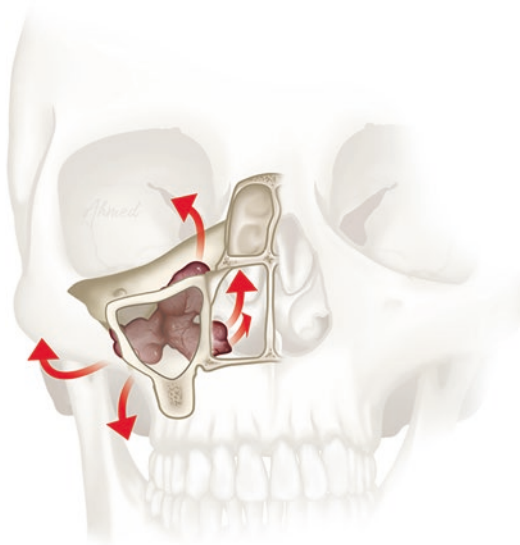

Fig. 33.1 Routes of spread of angiofibroma

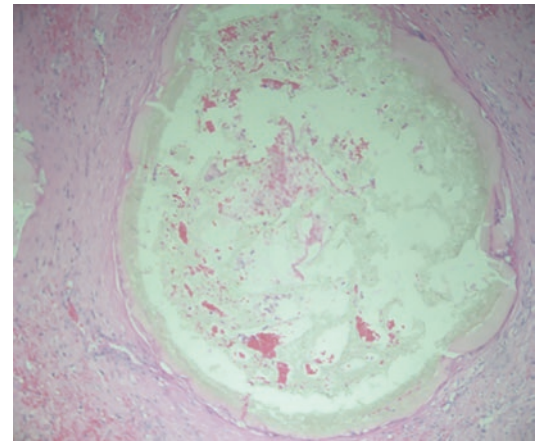

Fig. 33.2 Haematoxylin and eosin for tumour cells embedded in a delicate vascular stroma

Theory and Growth

Juvenile angiofibroma is thought to arise from incomplete regression of the first branchial arch artery. This theory helps explain a number of key points:

- The first branchial arch artery recedes close to the sphenopalatine foramen and the pterygoid base (which is the region it arises). The remnant of this artery forms part of the maxillary artery whose terminal branch is the sphenopalatine artery. The predominant blood supply to an angiofibroma is from the internal maxillary artery and its branches including the sphenopalatine artery. This supports the 'branchial arch artery theory'.
- The connection of the first arch artery to cavernous segment of the internal carotid artery (ICA) also explains how the vascular supply of Angiofibromas is derived from both external and internal carotid arteries [2].

Pathology

Juvenile angiofibroma consists of fibrovascular tissue (Fig. 33.2).

The tissue density varies across the cross-sectional area of the tumour as does the range of vascularity between individual patients. The centre of the tumour is often more fibrous with fewer vessels compared to the higher vessel density near the surface of the pseudocapsule [3]. This pushes the surgical dissection plane more superficially following the surface of the pseudocapsule to minimize the risk of massive haemorrhage.

The cross-section of the vessel walls shows incomplete irregular tissue architecture with a deficient tunica media. As a consequence, the vessels do not contract after injury and can lead to profuse haemorrhage. The lack of tunica media and associated vessel contraction can also lead to profuse bleeding.

Clinical Features

Symptoms and signs: The most common presenting features are progressive unilateral nasal obstruction and/or profuse spontaneous epistaxis, which may or may not be life threatening.

Orbital extension will cause proptosis and possible visual disturbance, especially if the optic nerve is compressed.

Lateral growth to the infratemporal fossa or masseteric space will cause unilateral facial swelling. Headache and neurological deficits can

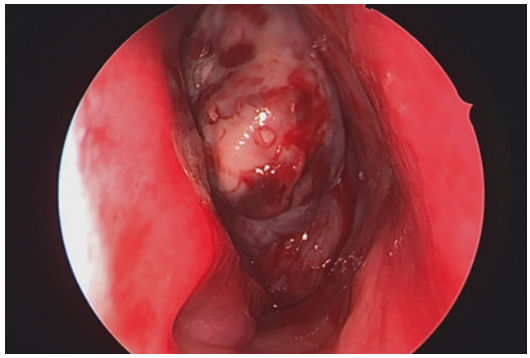

Fig. 33.3 Nasal endoscopy (right nostril) demonstrating angiofibroma occupying the nasal cavity

be encountered in rare instances with intracranial extension of angiofibroma.

Clinical examination: Anterior rhinoscopy typically reveals a smooth well-defined mass in the nose (see Fig. 33.3).

Nasal endoscopy is essential to delineate the tumour extent that may occupy the nasopharynx and obstruct the contralateral choanae. Eustachian tube obstruction and a unilateral middle ear effusion are commonly identified in such cases.

Radiology

MRI imaging is the modality of choice that facilitates an accurate diagnosis and differentiation from other tumours, whilst computed tomography (CT) provides information on bone erosion and bony surgical landmarks.

The typical CT scan findings demonstrate the angiofibroma as an enhancing expansile mass in the pterygopalatine fossa that produces the typical radiological Holman-Miller sign [1] with anterior bowing of the posterior maxillary sinus wall demonstrated on axial computed tomography (CT) imaging (Fig. 33.4).

Magnetic resonance imaging (MRI) is necessary to demonstrate the anatomical extent and involvement of structures surrounding the angiofibroma. MRI with gadolinium typically depicts a high-signal lesion with characteristic feeding vessels throughout the tumour that appear as 'flow voids' (salt and pepper appearance) best appreciated on T1, T2 and unenhanced MRI (Fig. 33.5).

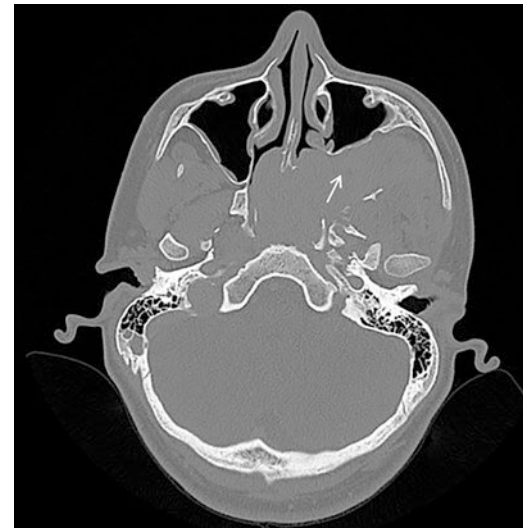

Fig. 33.4 CT scan (axial cut) demonstrates angiofibroma in the left pterygopalatine fossa extending laterally into the infratemporal fossa, medially extending into the nose and nasopharynx and producing the typical radiological Holman-Miller sign [1] with anterior bowing of the posterior maxillary sinus wall (arrow)

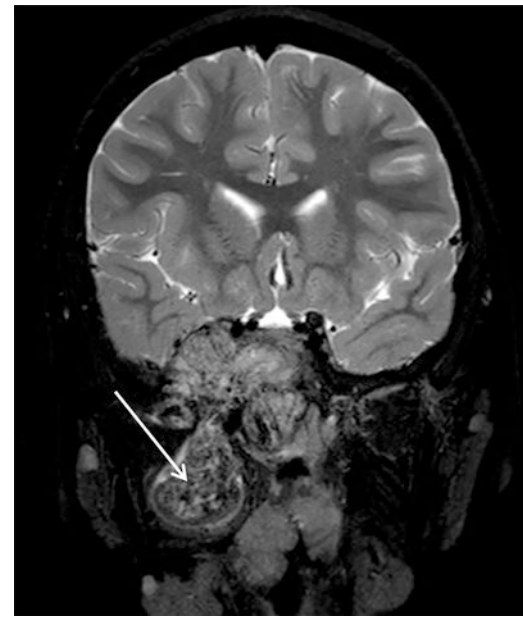

Fig. 33.5 MRI demonstrating flow voids (salt and pepper appearance) of angiofibroma on the right side

The overall vascularity of individual tumours however is variable, with a spectrum, some more fibrous and some predominantly vascular.

Finally, CT angiography is imperative for surgical planning to identify the feeding vessels supplying the angiofibroma. These vessels may be branches of both the external and internal carotid artery systems, and some of these branches may then be embolized to substantially reduce blood flow to the angiofibroma in readiness for surgery (Fig. 33.6).

The combination of characteristic MRI findings of signal voids representing major intralesional vessels, 'finger-like' projections of angiofibroma tumour extension into the surrounding soft tissues and submucosal invasion of the basisphenoid strongly support the diagnosis of angiofibroma.

These characteristic signs have not been reported in any other nasal lesions [3]. Biopsy is contraindicated due to the highly vascularized nature of the tumour.

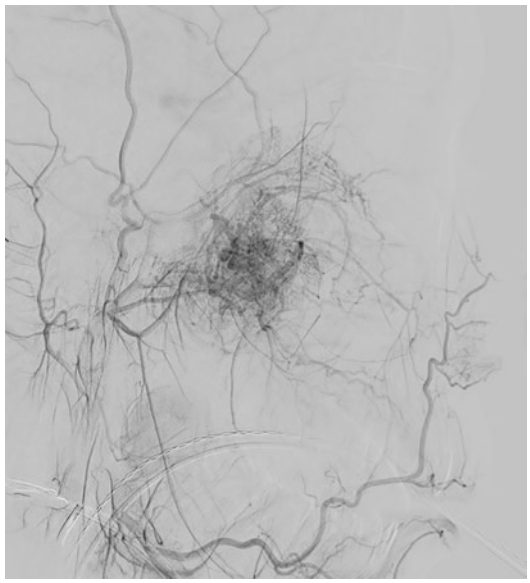

Fig. 33.6 Angiography demonstrating vascular blush attributed to the highly vascular nature of angiofibroma

Biopsy

Biopsy carries a serious risk of catastrophic haemorrhage and is definitely contraindicated in the outpatient setting. In most cases, the diagnosis is obvious and biopsy is not recommended. In the rare event that a biopsy is thought necessary, it should only be done in theatre with adequate planning and precautions.

Staging

Staging the tumour is now an integral part of tumour assessment during the preoperative workup and helps plan surgical intervention.

Several angiofibroma staging systems have been proposed according to tumour location and extension to involve the infratemporal fossa, orbit and cranial cavity. Sessions et al. [3] proposed the first staging system in 1981. Since then, there have been many others including Andrews et al. [4] based on tumour growth and spread. Radkowski [5] proposed a classification mostly based on the size and extent of the angiofibroma, and Onerci [6] revised this classification based on whether the tumour was amenable for endoscopic excision or would require a combined approach. In 2016 a new staging system was described by Snyderman et al. [7] that reflected the changes in surgical techniques of recent years, encompassing the endonasal endoscopic techniques. It included the vascularity and routes of cranial base extension providing better prediction of immediate morbidity and tumour recurrence [7, 8] (Table 33.1).

Table 33.1 Endoscopic staging system for angiofibroma described by Snyderman et al. (2016) [7]

Stage	Description
I	No significant extension beyond site of origin and remaining medial to the midpoint of the pterygopalatine fossa
II	Extension to the paranasal sinuses and lateral to the midpoint of the pterygopalatine fossa
III	Locally advanced with skull base erosion or extension to additional extracranial spaces, including orbit and infratemporal fossa, no residual vascularity following embolization
IV	Skull base erosion, orbit and infratemporal fossa residual vascularity
V	Intracranial extension, residual vascularity M, medial extension; L, lateral extension

Preoperative Embolization

The tendency of an angiofibroma to bleed leads many surgeons (including our group) to consider preoperative embolization in the majority of cases. This requires an experienced interventional neuroradiologist and is ideally undertaken at a maximum of 48 h before surgery. Any delay in surgery (>48 h) has the potential to reopen collateral vessels and increase the risk of significant intraoperative haemorrhage. Depending on the experience and preference of the neuroradiologist, embolization may be either under general anaesthetic or local anaesthetic. The aim is to occlude the feeding vessels, thereby reducing haemorrhage intraoperatively. This can be done either by trans-arterial embolization (TAE) or rarely by direct intra-tumoural embolization (DIE). The latter is usually undertaken via a direct endonasal route in theatre, and this requires both surgical and interventional neuroradiology teams to be working together simultaneously. Many surgeons however do not use any embolization and rely on intraoperative identification of the main arterial feeders before tumour resection.

Trans-arterial embolization (TAE): TAE utilizes particles such as polyvinyl alcohol or microspheres [9]. Similarly, coils, glue and ethylene vinyl alcohol copolymer can also be used. These materials are precisely injected to embolize the feeding vasculature arising predominantly from external carotid artery branches. These include maxillary artery, sphenopalatine artery, ascending pharyngeal and descending palatine artery. Embolizing the supply from branches of internal carotid artery such as that by the vidian artery, ophthalmic artery and meningohypophyseal trunks carries the risk of stroke and blindness by accidental dislodgement of the particles into the brain.

Limitations of TAE are small tortuous vessels, multiple small collaterals, ligation of external carotid artery secondary to previous surgery and anastomoses between the extracranial and intracranial circulation.

Intra-tumoural embolization involves direct intraparenchymal injection *(DIE)* of the embolic material. This bypasses the limitations of TAE but requires the interventional radiologist to attend theatre at the time of definitive resection. Depending upon the anatomy of the tumour and the preference of the interventional neuroradiologist and surgeon, DIE may be done under fluoroscopic guidance to prevent reflux into the internal carotid artery vasculature.

It is the lead author's practice to request navigation protocol CT imaging immediately post embolization, thereby allowing surgeons to navigate to the embolization coils and feeding vessels intraoperatively using their surgical image guidance system. This facilitates better control of bleeding and more proximal tumour resection [10].

Preoperative Workup Considerations

In young patients or those who refuse blood transfusion, a cell saver should be considered. A group and save sample should be taken from all patients with blood cross-matched in selected cases.

Surgery

Surgery should only be performed in centres with surgeons experienced in the management of angiofibroma particularly those cases with extension beyond the sinuses.

Endoscopic Endonasal Approach

The key to a successful resection is to establish the true extent of the angiofibroma preoperatively and to create wide surgical corridors to allow controlled and safe resection under endoscopic visualization.

Bleeding can be minimized by tumour dissection in a submucosal plane. Very large tumours are sometimes disassembled using a coblation dissection wand to allow segmental removal. Extensive Angiofibromas may occasionally bleed

so much that surgery has to be staged due to blood loss. In this situation the patient is stabilized ± transfused and angiography repeated to embolize any feeder vessels from the external carotid artery that are still patent. The timing of repeat surgery should ideally be within 1 or 2 weeks as additional collateral vessels from the internal carotid artery start to supply the tumour that are more challenging to control. The use of warm irrigation at 49°C has been shown to be effective in reducing diffuse bleeding from sinonasal mucosa [11]. Haemostatic agents such as FLOSEAL (Baxter) and Surgiflow® Hemostatic Matrix (Ethicon) can aid in the management of venous bleeding from the cavernous sinus, pterygoid and the basilar plexuses, but intra-arterial injection should be avoided.

Wide exposure to visualize the extent of tumour invasion and growth is of paramount importance. This can be achieved in a number of ways:

(a) At the outset, a wide ipsilateral medial maxillectomy with modified Denker's approach, also known as Sturman-Canfield approach [12], with complete removal of ethmoidal air cells, and a bilateral sphenoidotomy, is performed. This is augmented by a posterior septectomy that assists in accessing the sphenoid sinus and can also be utilized for a '4 hand 2 nostril' (two surgeon) approach. The medial wall of the maxillary sinus should be drilled up to the nasolacrimal sac, and then the nasolacrimal duct is cut obliquely with sharp scissors or a scalpel to give wide access to the posterior maxillary wall.
(b) Tumour involvement of the pterygopalatine and infratemporal fossae can be approached by removing the entire posterior wall of the maxillary sinus as far as its attachment to the anterolateral wall. Care must be taken to avoid injury to the infraorbital nerve and maxillary nerve in the pterygopalatine fossa. The maxillary periosteum on the external surface of the maxilla should be distinguished from the surface of angiofibroma for identification of a clear dissection plane. Early surgical clip placement on the internal maxillary artery will avoid inadvertent damage and bleeding during surgery. Complete tumour removal, by drilling out the basisphenoid and the vidian canal, is paramount as microscopic nests at these regions can lead to tumour recurrence. The vidian canal often bleeds as it receives blood from the second genu of the internal carotid artery. This is controlled with bone wax (Fig. 33.7).

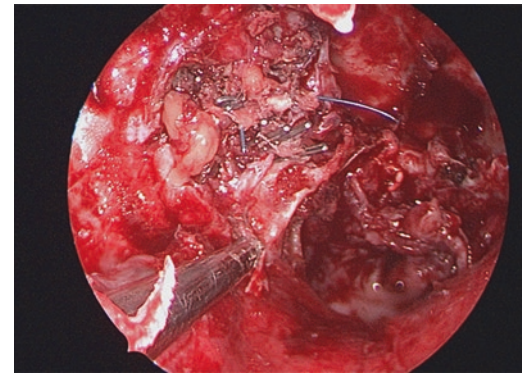

Fig. 33.7 Intraoperative view of angiofibroma being resected, embolization coils can be seen whilst dissecting angiofibroma

In those cases where an angiofibroma extends into the cavernous sinus or transgresses the foramen rotundum, the authors undertake removal of this portion in the final operative steps. Angiofibromas usually have a tough pseudocapsule and the tumour can often be safely teased out from these structures as the pseudocapsule is loosely adherent to surround structures. Care should be taken to avoid direct pressure on the internal carotid artery, which could compromise blood supply to the brain.

External Approaches

Historically Angiofibromas were resected utilizing open approaches, typically a lateral rhinotomy, midfacial degloving or infratemporal fossa type C approach. With advances in the understanding of endoscopic skull base anatomy and enhanced magnified endoscopic visualization, there has been a paradigm shift to transnasal

endoscopic angiofibroma resection. Open or combined endonasal and open approaches are reserved for Angiofibromas with significant orbital invasion or where there is massive intracranial extension and an external approach with neurosurgical assistance is warranted. A recent systematic review has highlighted lower recurrence rates and lower blood loss with extended endoscopic techniques [13].

When tumours are situated in high-risk locations, for instance, those with intracranial extension completely encompassing the internal carotid artery, a small residuum may be intentionally left behind and followed up with serial MRI.

Outcomes

Residual and Recurrent Angiofibroma

Small areas of residual tumour that remain following surgery can be followed up with serial MRI. In many instances, these remnants do not grow and, in some cases, have been reported to regress once they have been embolized and are devoid of a blood supply [6, 13]. Recurrent angiofibroma grows from microscopic rests that are not visible on initial imaging. The first postoperative MRI scan should not be before 6 weeks to properly assess for residuum after the initial postoperative swelling has resolved. Postoperative MRI surveillance should then be every 6 months for 3 years [9].

Role of Radiation Therapy

Radiation therapy has been reported in both the primary setting and after surgery. Local control rates of 80–85% have been reported in most series, but involution may take up to 3 years [9]. The use of radiation therapy, particularly in adolescence, raises concerns about the development of secondary malignancy and as such is not routine practice. Other reported long-term effects include malignant transformation to fibrosarcoma, growth impairment and encephalopathy [14].

Cytotoxic Drugs and Hormonal Therapy

There have been few reports of the use of cytotoxic drugs in the management of Angiofibromas, but evidence of clinical effectiveness remains limited. Furthermore, the growth of angiofibroma is highly influenced by hormonal levels, as a result of testosterone and dihydrotestosterone receptors. Flutamide, a non-steroidal androgen antagonist, effectively blocks androgen receptors without the known side effects of oestrogen analogues. A number of studies have suggested that a 6-week course of flutamide may be effective in managing recurrent angiofibroma in post-pubertal males [14].

Controversies

Embolization

Preoperative embolization of feeding vessels arising from branches of the external carotid artery leads to significant reduction of bleeding intraoperatively. However, the cost of embolization is not insignificant, and some surgeons prefer the residual tumour to bleed, thus assisting intraoperative localization and facilitating such lesions to be removed more completely. In the United Kingdom, the general consensus is to embolize patients 24–48 h prior to surgery.

Key Learning Points

General

- Angiofibroma typically affects adolescent males.
- Ten to twenty per cent of advanced lesions have intracranial extension.
- The diagnosis is based on clinical history and characteristic MRI and CT findings.
- Biopsy is contraindicated because of the risk of profuse bleeding.

Tumour Facts

- Growth occurs through the natural foramina and fissures along paths of least resistance.
- The blood supply is predominantly from the sphenopalatine and the ipsilateral internal

maxillary artery in the early stages of the disease.
- The blood supply in advanced disease includes branches of the contralateral internal maxillary artery and internal carotid artery.

Surgical Facts
- If preoperative embolization is undertaken, it should be carried out 24–48 h prior to surgery.
- Pterygoid base and clival tumour clearance is essential to reduce residual/recurrent tumour.
- Tumour dissection is best performed adjacent to the pseudocapsule to reduce haemorrhage.
- Advances in instrumentation, navigation systems and improvements in understanding of endoscopic skull base anatomy have allowed endoscopic excision to be the preferred option in most cases.

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Section VI

Surgery of the Sinuses and Anterior Skull Base

Complications of Endoscopic Sinus Surgery

34

Juan Carlos Ceballos Cantu, Isam Alobid Alobid, and Manuel Bernal-Sprekelsen

Introduction

Despite constant advances in surgical technique and instrumentation, the risk of serious complications during endoscopic sinus surgery (ESS) is always present due to close proximity with critical structures. The surgeon is responsible in minimizing the risks by a meticulous preoperative preparation, a careful operative technique and a correct postoperative care.

Complications following endoscopic sinus and skull base surgery are uncommon, but both trainee and experienced surgeons must maintain good awareness and understanding of them. Such knowledge should minimize the risk associated with surgery and also ensure that such unfortunate events are managed correctly to minimize their effect.

An integral component with surgery is the consent process, but for surgeons to do this effectively, they need to have a clear systematic way of classifying complications so that these can be explained both logically and in perspective to the patient.

Classification of Complications

Complications can be classified in several ways, such as by the anatomical system location, the severity or time related to surgery.

Anatomical classification: Complications can be described according to anatomical systems and location, such as vascular, neurologic, ophthalmic, wound healing or packing-related complications (Table 34.1).

J. C. C. Cantu (✉) · I. A. Alobid · M. Bernal-Sprekelsen
Department of ORL-HNS, Hospital Clinic, Barcelona, Spain
e-mail: jcceballos@clinic.cat

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Table 34.1 Classification of complications

Vascular complications. Injury to the anterior or posterior ethmoidal arteries sphenopalatine arteries or internal carotid artery (ICA): Consider major if the resulting of the damage affects cerebral circulation and in rare cases causing a significant drop in haemoglobin that may require transfusion
Neurological complications. Cerebrospinal fluid (CFS) leak, tension pneumocephalus, meningitis, abscess, intracranial hemorrhage, direct brain injury or encephalocele formation
Ophthalmological complications. Medial rectus injury, optic nerve injury, orbital haematoma and nasolacrimal duct injury that may result in double vision, loss of vision and epiphora
Other complications (wound healing and toxic shock syndrome)

Severity

Complications can be considered as major and minor. Major complications are those that might put the patient's life at risk; require urgent surgical intervention, blood transfusion or transfer to ICU; and cause significant risk of severe and/or long-lasting or permanent sequelae. Fortunately, complications are rare, occurring in 0.36–3.1%, but they still need to be explained and documented in the preoperative consent process, as well as a formal consent form, particularly with the ever-increasing risk of potential medicolegal claims [1].

Whilst minor complications are more common, they do not produce persistent significant adverse outcomes. These may include periorbital emphysema and ecchymosis, herniation of fat through the lamina papyracea, minor bleeds not requiring blood transfusion, facial swelling, hyposmia, facial hypoesthesia due to inflammation of the infraorbital nerve, synechia formation or atrophic rhinitis.

Time Related to Surgery

Complications may also be classified as intraoperative, early postoperative or late postoperative. One example is CSF leak, which, when recognized during surgery, can be fixed intraoperatively, thus minimizing the risk of an ascending bacterial meningitis or of an intracranial abscess.

Early postoperative complications, like hemorrhage or intranasal adhesions, may occur at any time right after surgery or up to a few weeks after the surgical procedure.

Late complications, such as a mucocele formation, may present many years after surgery. Whilst these categories are used for a more academic discussion and comprehensive overview, what is most important is recognizing and managing them appropriately in the clinical and surgical scenario.

The risk of some complications is increased and may be more severe according to surgical site and the individual sinus. Therefore, each particular sinus and its anatomical surroundings need to be fully addressed in every single patient in order to provide a safe and clean endoscopic approach.

Vascular Complications

Bleeding as a result of ESS may occur during or after the procedure. Most intraoperative bleeds are easily managed, as suction and coagulation devices should be easily accessible. Bleeding is therefore rarely registered as a complication.

Most epistaxes occur in the early postoperative course but is only considered as a major complication if the hemorrhage is severe enough to require nasal packing, surgical exploration to find the source or a blood transfusion. Postoperative hemorrhage is the most frequent of all major complications, accounting for 23–39% [2], but the need for blood transfusion is rare, being estimated at only 0.76% of patients in one large review [3].

Preoperative Scenario

Various risk factors may increase the risk of surgical bleeding. Such risk factors include pre-existing infection (sinusitis) or a range of systemic comorbidities such as hypertension, peripheral vascular disease, liver or renal diseases, chronic alcohol abuse and vitamin deficiencies that may need to be addressed and optimized both before and during surgery. Bleeding disorders such as haemophilia and von Willebrand disease will require clotting factor replacement or specialized pharmacotherapy that must be planned and managed in accordance with specialized haematological assistance.

Some medications, such as non-steroidal anti-inflammatory drugs, aspirin, warfarin, antiplatelet agents or other anticoagulants, will increase the risk of bleeding and must be managed appropriately before surgery. Aspirin and NSAIDS should be stopped at least 5–7 days before surgery, and warfarin doses need to be reduced and monitored by a daily INR level. However, should there be a risk to a patient having a period without anticoagulation, the need for surgery should be reassessed, or the operation may be covered by low-molecular-weight heparin.

Many patients are now taking anticoagulant therapy from a new group of medications known as direct oral anticoagulants, some of which are not reversible. These should be stopped 5–7 days prior to surgery, and if there is any element of doubt, haematological advice is sought.

Some herbal and alternative drugs may also severely affect coagulation pathways, such as ginseng, gingko and fish oil, and all herbal additives must be discontinued at least 7 days before surgery [4, 5].

Tips

Ensure that all medications and herbal additives that may alter coagulation have been identified before surgery and managed appropriately in the week before surgery.

Substitute anticoagulation treatment by subcutaneous heparin 5 days before surgery and monitor coagulation parameters prior to surgery.

Operative Scenario

It is really important to optimize the visual field in ESS surgery by minimizing bleeding. Important measures that help to achieve a blood-free field are as shown in Table 34.2.

Table 34.2 Recommended measures for minimizing bleeding

Minimizing bleeding	
Preoperative systemic steroids	Oral steroids reduce not only the size of polyps but also inflammation and the vascularity of polyps and sinus mucosa, thus reducing capillary bleeding
Preoperative antibiotics	Preoperative antibiotics may reduce infection in some patients (benefits in need of further research to clarify optimal dose and length of treatment [6])
Patient positioning	Reverse Trendelenburg and elevation of the head and thorax has a major impact on reducing bleeding during surgery [7, 8]
Topical and local vasoconstriction	Oxymetazoline reduces about 59% nasal mucosal blood flow and acts over 6 h [9]. Cocaine solution (in Moffet's solution) is a highly effective vasoconstrictor, but medical cocaine is not allowed in many countries
Arterial pressure and heart rate	A mean arterial pressure between 60 and 75 mmHg and an ideal heart rate at less than 60 beats/min [10]
Recommended anaesthesia	Total intravenous anaesthesia seems to reduce intraoperative bleeding (TIVA) [11]

Tips

At the end of the procedure, it is important to have the patient's blood pressure restored before extubation to best verify haemostasis. With a suction monopolar or bipolar instrument at hand, proceed to examine areas of common postoperative arterial bleeding after ESS (e.g. the region supplied by branches of the sphenopalatine and ethmoidal arteries; the posterior rim of an enlarged maxillary sinus in the middle meatus; the area of the sphenopalatine foramen, especially after a partial middle turbinate resection; the anterior face of an enlarged sphenoid sinus ostium supplied by the posterior nasal-septal branch and the skull base must be carefully inspected. Finally, the nasopharynx must be suctioned again and inspected for pooling of fresh blood, as the last manoeuvre performed in any endoscopic sinus procedure [2].

Nasal packing is usually not necessary after ESS when proper haemostasis is achieved. Some studies have provided evidence that, in terms of postoperative haemorrhage, the safety of the electrocauterization and no-packing technique after ESS is comparable with that of nasal packing [12].

If in doubt, a small fragmentable nasal dressing can be inserted in the middle meatus or areas where bleeding may be anticipated.

Postoperative Scenario

Severe haemorrhage may require intensive proactive interventional management, beginning with the patient's ABCs (Airway, Breathing and Circulation). However, patient airway intervention is exceedingly rare.

Nasal packs are ideally avoided as they induce discomfort and stress, additional bleeding when withdrawn, occasional septal perforation or rarely toxic shock syndrome. However, inserting nasal packing postoperatively risks additional trauma to fragile healing tissues and should be avoided whenever possible.

Should a severe epistaxis occur in an unpacked patient, a soft inflatable haemostatic device such as Rapid Rhino™ or a soft non-absorbable pack can be attempted until endoscopically controlled coagulation or clipping can be undertaken.

Tips

Severe bleeding typically arises from the sphenopalatine artery or its branches or the septal branches of the anterior ethmoidal artery.

Special attention must be paid to the posterior septal artery, a branch from the sphenopalatine artery, typically exposed and possibly traumatized during sphenoidotomy whilst enlarging the ostium inferiorly [13].

Management of Specific Arteries

Anterior Ethmoidal Artery Injury

The anterior ethmoidal artery (AEA), a terminal branch of the ophthalmic artery arising from the internal carotid artery, may cause significant haemorrhage during surgery, and a complete transection may result in retraction of the proximal (lateral) end into the orbit causing a rapidly expanding orbital haematoma. The position of the AEA on the CT sinus scan should be noted preoperatively from the coronal sections. It is typically seen as a pinch or "nipple" between the medial rectus and superior oblique muscles. The AEA runs in a mesentery in about one third of cases and tends to be associated with a longer lateral lamella of the olfactory fossa and steeper skull base at the ethmoidal level [14].

Tips

The best way of preventing damage to the AEA is either to avoid exposure by keeping dissection in front of the anterior wall of the bulla or by early endoscopic identification of the AEA at the insertion of the anterior wall of the bulla with the skull base or right behind it.

When using the microdebrider at this level, it is important to avoid movements in a posterior to anterior fashion. Instead, a perpendicular plane to the skull base is recommended as a safer alternative. A partial transection injury to the artery can be easily managed with a suction bipolar forceps. The management of a complete transection

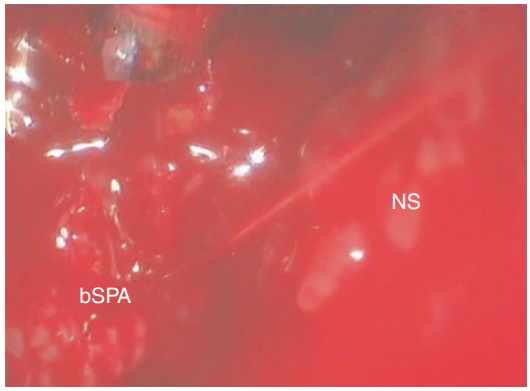

Fig. 34.1 Intraoperative arterial bleeding of a branch of the sphenopalatine artery middle turbinate resection. NS nasal septum, bSPAb branch of the Sphenopalatine artery

with retraction of the lateral end into the orbit will be discussed below.

Sphenopalatine Artery Injury

The sphenopalatine artery, with its many branches, provides the main vascular supply of the nasal cavity and can be a common source of arterial bleeding during surgery, particularly when performing surgery on the turbinates or a sphenoidotomy (Fig. 34.1).

Tips

Dissect the mucoperiosteum off the anterior wall of the sphenoid sinus and push it downwards before enlarging the natural ostium inferiorly with a 90° Kerrison punch. Should the posterior nasal artery be transected, the bleeding may cease spontaneously by vascular retraction and vasospasm, but coagulation of the arterial ends is recommended to bleeding from relaxation of vasospasm in the early postoperative phase with increasing blood pressure.

Internal Carotid Artery (ICA) Injury

The ICA is at risk even during standard ESS, especially when the intersphenoidal septum is oblique and attached to the thin bone overlying the carotid artery. The carotid can be dehiscent in around 10% of patients [15], and it is important to appreciate that the bone covering the carotid artery is only about 1 mm thick. The risk to carotid artery injury is much higher during extended skull base surgery, especially in tumours that directly involve the carotid artery or in pituitary macroadenomas that extend into the cavernous sinus.

Tips

Powered instrumentation inside the sphenoid sinus should be strictly avoided. An oblique intersphenoidal septum should only be removed by drilling and never by twisting and fracturing. Also, a paraseptal approach to the sphenoid sinus is much safer for beginners than a transethmoidal approach, as this ensures that the surgeon is medial to the ICA.

Management of ICA Lesions

The best approach is careful preoperative planning with a detailed review of the preoperative CT scan and prevention of damage to the internal carotid artery.

Should the risk be foreseen, as in tumours surrounding the cavernous portion of the ICA or along its horizontal or intrapetrous aspect, then preoperative stenting can be considered and planned, thus avoiding a medical catastrophe. As always, the best recommendation is to have a "plan of action" beforehand, just in case.

Once the carotid artery is bleeding, the surgical team will experience significant stress, and this can lead to delayed or even wrong decision-making. If the risk of a carotid arterial bleed is likely, there should be a clear agreed protocol about the actions to be taken, including who shall be holding which instrument, the role of the individual team members and the order that things will happen. There are several training courses worldwide where surgeons can learn how to deal with such a massive bleeding. The courses also demonstrate that the reaction time is reduced when the exercise is repeated.

Fortunately, ICA lesions are isolated events. Therefore, there are no (prospective) studies about the ideal management, but only case reports. What makes sense is to firstly block blood loss by the fastest way possible to prevent hypovolemic shock. Current international con-

sensus recommends to then harvest a piece of muscle (from the thigh or sternocleidomastoid) of at least 1.5 x1.5 cm that is used to plug the hole in the ICA. This repair may be reinforced with any type of fibrin glue available. Needless to say, this procedure requires four hands, two good-working suction devices and the anaesthesiology team keeping the systolic pressure at a reasonable level to maintain cerebral perfusion.

Once bleeding is controlled, a pedicled septal flap can be rotated into the sphenoid to cover the muscle patch, and the sphenoid is then packed with Gelfoam.

Once control is achieved, an emergency angiogram should be obtained. The images will then facilitate a decision as to whether endovascular intervention is required and whether the ICA should be stented or coiled. The nasal pack can be then removed after 5–7 days, but in a controlled theatre environment under general anaesthesia.

Tips

Do not try to coagulate or clip the ICA. It will not work.

Keep the muscle patch in place for 10 min with a mild compression.

Do not send the patient to neuroradiology before making sure that the bleeding is under control.

It is recommended to consult with a neurosurgeon/neurologist not only because of the risk of intracranial lesions but also for medicolegal reasons. ICA bleedings with intact dura will not track endocranially; however, with an open dura, the risk of intracranial bleeding and its consequences is very high.

The angiogram should be repeated at 6 weeks and 3 months later to exclude the development of a pseudo-aneurysm.

Neurological Complications

Cerebrospinal Fluid (CSF) Leak

Although a constant concern during surgery, most series report a rate between 0.17 and 0.8% [16]. Usually recognized by a clear washout of fluid, it can also look like a sudden onset of brisk venous bleeding. A high index of suspicion for CSF leak must be kept in unilateral watery rhinorrhoea, especially when surgery has been performed close to the skull base. The risks on an unrecognized or untreated postoperative dural defect including pneumocephalus, tension pneumocephalus, meningitis, encephalitis and epidural or subdural abscess may occur [1, 17].

Preoperative Scenario

A detailed preoperative assessment of the CT sinus scan images to identify any variations of skull base anatomy is key to preventing skull base lesions and intracranial complications [18]. Check the CT scan for any potential dehiscence, especially in revision cases or when the disease reaches the skull base. Classically, the Keros classification has been used to assess the depth of the olfactory fossa and subsequently the length of the lateral lamella. In types III or in an asymmetric skull base, one has to be more careful. A new classification system, based on the angle formed between the lateral lamella of the cribriform plate and the continuation of an horizontal plane passing through the cribriform plate, has shown to be more sensitive to anatomical variations associated with CSF leak than the Keros classification [19].

Operative Scenario

Frequent locations for iatrogenic CSF leak are along the anterior vertical lamella at the *fovea ethmoidalis* constituting the lateral wall of the olfactory fossa (Fig. 34.2). Here, the thickness of the lateral lamella can measure as little as 0.1 mm being the thinnest area of the skull base. It is perforated by the anterior ethmoidal artery (AEA). Cautery of the AEA close to the vertical lamella may produce adjacent thermal injury causing a CSF leak, this risk being even greater when using monopolar coagulation [15].

Another high-risk area is the frontal sinus during a frontal drill-out procedure (Draf III, modified Lothrop) when drilling the bone close to the first olfactory fibres to create the “frontal T”.

Also, enlarging the natural sphenoidal ostium superiorly during sphenoidotomy carries a risk of

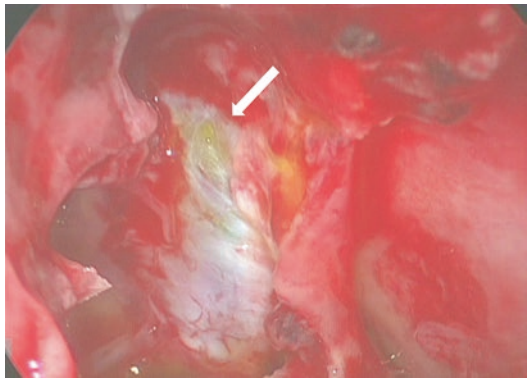

Fig. 34.2 Endoscopic view of a CSF fistula at the lateral wall of the olfactory recess (white arrow). Identification and repair during surgery enables a normal postoperative recovery

perforating the posterior ethmoidal roof as the natural ostium is close to the skull base.

Small skull base injuries that usually display a low-flow CSF leakage can generally be repaired with small grafts of fat, fascia or nasal mucosa. Larger skull base defects may require larger grafts of fascia lata and high-flow CSF leaks a pedicled flap.

Tips

Perform dissection along the skull preferably from posteriorly to anteriorly avoiding to apply any force towards the skull base.

Postoperative Scenario

An intraoperative but unnoticed CSF leak will display as a clear unilateral watery rhinorrhoea with a salty taste, especially when leaning forward or with the increase of intracranial and abdominal pressure (e.g. a Valsalva manoeuvre). Confirmation must be done by analysing a small sample of fluid for beta 2-transferrin assay or a beta-trace testing (faster and cheaper).

Intrathecal infiltration of 0.5–1 mL of 5% fluorescein can be applied around 30–60 min to better localize the dural defect, visualize the CSF flow and confirm that the reconstruction of the defect is watertight.

After reconstructing a large defect in expanded endoscopic skull base surgery, often supported by pedicled flaps, bed rest, head and chest elevation and stool softeners are recommended to prevent a recurrent leak during the healing phase and to facilitate and promote healing.

Lumbar drainage is recommended to decrease intracranial pressure for the initial 36–48 h after surgery on occasions where a high-flow CSF leak has been repaired. Persistence of CSF leak warrants further surgical exploration.

Prophylactic antibiotics after skull base reconstruction is still a matter of debate. In our patients, we routinely place one preoperative shot of an antibiotic with a good CSF penetration, such as first- or second-generation cephalosporin.

Associated Complications

Tension Pneumocephalus

Tension pneumocephalus is characterized by a steady increase of retained intracranial air through a dural defect that acts as a one-way valve. This process is hastened when a lumbar drain is placed. Rising air volume increases intracranial pressure, compromises cerebral perfusion and, in severe cases, results in brain herniation through the tentorium. Symptoms such as headache, lethargy or a decreased level of consciousness within a few hours after surgery should raise suspicion. An emergency CT scan is mandatory for definitive assessment. The "Mount Fuji sign" indicates an advanced and dangerous stage.

Management depends on the severity of the symptoms. Initial conservative management may include administration of 100% oxygen inhalation (most of the gas within the pneumocephalus is nitrogen). A lumbar drain, if present, should be clamped. Once the emergency situation has been resolved, the skull base defect needs to be localized and repaired.

Meningitis

Bacterial ascending meningitis or abscess formation may occur after resection of lesions of the skull base, with or without CSF leak, even years after the initial event. In some cases, an initial CSF leak may have gone unnoticed or conservative management measures were adopted. Responsible bacteria are those usually located in

the nasal cavity and nasopharynx, such as S*treptococcus pneumonia, Haemophilus influenzae* and, occasionally, *Moraxella catarrhalis* [20]. Symptoms include fever, headache, photophobia, neck stiffness and lethargy. Classically, physical examination may display positive Kernig or Brudzinski signs indicating the presence of meningeal irritation. The clinical workup includes a lumbar puncture, CSF culture and sensitivities, a contrast CT scan of the head with contrast to rule out an abscess and high-resolution HRCT of the skull base that may demonstrate a skull base defect. A dural defect that has caused intracranial infection should be repaired as soon as the patient is stable enough to undergo general anaesthesia.

Ophthalmic and Orbital Complications

Orbital complications from endoscopic sinus surgery (ESS) are fortunately uncommon, with analyses offering varying rates from 0.07 to 0.23% [1, 3].

Preoperative Scenario

Appreciation of anatomical variations on the CT scan is paramount. The preoperative assessment of the CT sinus scan should include a detailed review of the integrity of the lamina papyracea, orbital fat protrusion or an excessively medialized position of the lamina papyracea that may facilitate intraorbital injury. The position of the uncinate process in relation to the proximity to the medial orbital wall should be noted. The presence of sphenoethmoidal (Onodi) cells and the trajectory of the optic nerve within such cells should be noted.

Operative Scenario

Optic Nerve Injury

The optic nerve canal can usually be identified during ESS in the absence of excessive mucosal disease. The thickness of the bone covering this nerve is variable and may be dehiscent. When the inferior clinoid process is highly pneumatized (Fig. 34.3), the optic canal may run through a mesentery within the sphenoid and the potential for injury to the optic nerve increases (Fig. 34.4). A sphenoethmoidal air cell (previously known as an Onodi cell – a posterolateral ethmoid cell that extends posteriorly and above the true sphenoid sinus) is an anatomical variant that places the optic nerve at increased risk of injury.

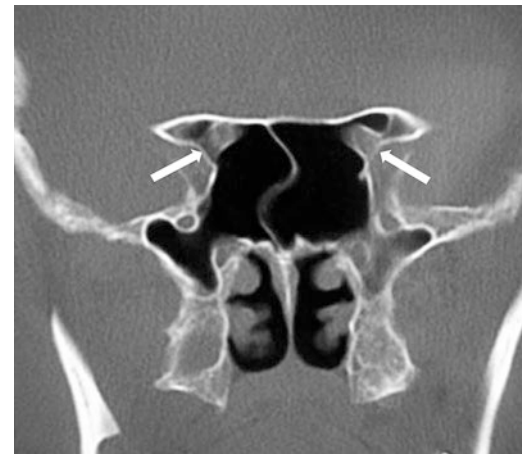

Fig. 34.3 Inferior clinoid process is highly pneumatized

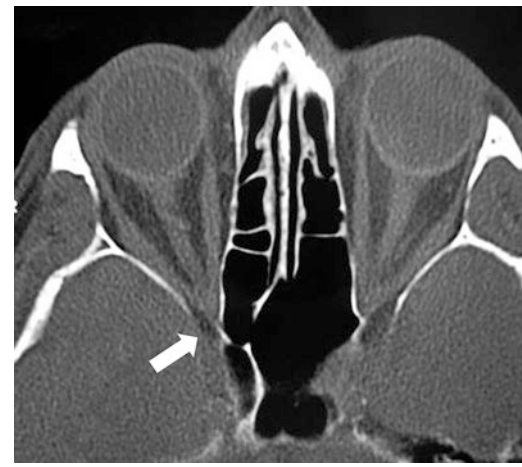

Fig. 34.4 Accidental transection of a bone splinter through the optic nerve (arrow)

Injury of the optic nerve will induce an immediate decrease or loss of vision and a pupillary defect may be found.

In such a situation, immediate ophthalmological consultation is recommended, and nasal packing, if present, should be removed. High dose of intravenous steroids are commenced providing that there are no contraindications. In collaboration with an ophthalmologist, the patient should be taken back to the theatre for exploration and optic nerve decompression. Although there is no definitive proof that neither steroid therapy nor surgical decompression is superior to observation alone [21], we believe that, from a medicolegal point of view, a surgical revision is advised, unless the nerve has been transected.

Tips

Optic nerve injury can also occur from vasoconstriction. Avoid using cottonoids soaked in such drugs in the sphenoid sinus or close to the vicinity of the optic nerve.

An MRI may provide a good study of anatomical integrity of the optic nerve.

Infraorbital Nerve Injury

Injury to this terminal branch of the trigeminal nerve innervating the skin of the cheek may result in transient or permanent anaesthesia or paraesthesia. In a routine ESS, it is a rare event. However, infraorbital nerve becomes susceptible to surgical trauma when running within a mesentery, during assessment or clearance of the roof of the maxillary sinus and during removal the posterior maxillary wall to gain access to the infratemporal fossa. Prevention is achieved by identifying a low-set or exposed nerve in a preoperative CT scan and by minimizing instrumentation along the roof of the sinus.

Management is conservative, even if it is completely transected. Should the nerve stay anatomically intact, the patient should expect a slow return of sensitivity over several months, although paraesthesia may be permanent.

Orbital Injury

Orbital injury can be divided grossly into the extraconal compartment, containing mostly fat, and the intraconal compartment, which contains muscles, the optic nerve and the ocular globe.

Orbital injury is fortunately uncommon, but the risk is increased should the surgeon be disorientated and confused by excessive bleeding, scarring from previous surgery or anatomical abnormalities caused by intraorbital pathology. It is a surgical field where it is so important to maintain good orientation and vision and far better to abandon surgery if this principle cannot be maintained. The usual mechanisms of orbital injury include direct penetration, thermal injury or the use of powered instruments, which have the greatest potential for causing severe, long-lasting sequelae [22].

An ophthalmological assessment is essential in the immediate postoperative scenario, and it is important to instruct the patient not to blow the nose for about 2 weeks following surgery.

Tips

Avoid dissecting with instruments or probes pointing towards the orbit and do not apply pressure on the lamina papyracea. Always keep the tip of the instruments in the visual field. The use of the microdebrider is discouraged during removal of the vertical portion of the uncinate process if located too close to the lamina papyracea.

In the advent of a mild injury without any evidence of damage to the orbital contents, we recommend leaving the area alone and avoiding further exploration of the injury. The surgeon should avoid suction of exposed orbital fat, to avoid trying to replace fat back into the orbit and to avoid the use of coagulation forceps or power instrumentation in the vicinity of the orbital breach.

If in doubt of a perforation of the lamina papyracea, ask the scrub nurse to gently push the eye whilst looking for potential movements of the orbital contents with the endoscope.

Extraocular Muscle Injury

The incidence of extraocular muscle injury is extremely low. The medial rectus muscle is the most common one involved, followed by the inferior rectus muscle.

Prevention is best achieved by a meticulous scrutiny of the CT imaging where a potential dehiscence of the medial orbital wall can be detected, especially in cases with a history of previous surgery. Additional risk factors include facial trauma, sinonasal neoplasm or expansive inflammatory processes.

The immediate management consists of excluding the possibility of severe but reversible complications that could threaten the patient's vision.

Magnetic resonance helps to determine the possible site, extent and pattern of the injury. Re-anastomosis of the muscle, grafting or sutures may be attempted in a second stage.

Orbital Haematoma

The collection of blood inside the orbital space is mainly due to bleeding from the anterior ethmoid artery (Fig. 34.5). Blindness can occur due to a multitude of causes that included increased orbital pressure, stretching of the optic nerve, optic nerve ischaemia, compression of the central retinal artery and other retinal vessels.

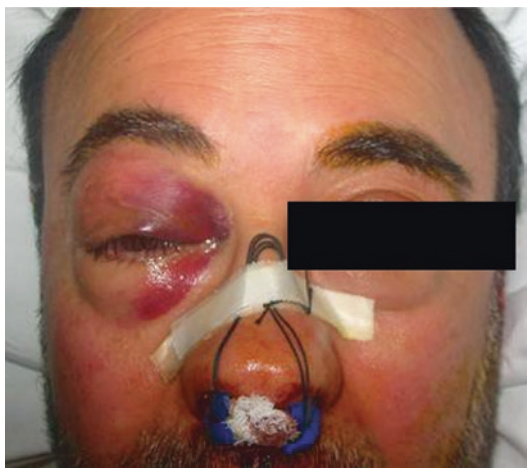

Fig. 34.5 Orbital hematoma due to bleeding from the anterior ethmoid artery. Tip: remove packing

It is suggested that to prevent blindness, an orbital haematoma must be treated within 90 min, but this is derived from historical data following animal research that is no longer valid or relevant. In reality, ischaemic damage to the retina is likely to occur within 10 min, but the circumstances and blood supply are so variable that this cannot be standardized. The important message is to act quickly, but not to concede or give up if delay happens, as recovery can still sometimes occur after a significant delay of several hours before surgical decompression.

Clinically, one may observe proptosis, oedema, conjunctival haemorrhage and an afferent pupillary defect. Additional features include orbital pain, diplopia, loss of colour vision (the red colour being the first) and eventually blindness.

Management includes ophthalmological consultation, immediate removal of nasal packing, orbital massage to decrease intraorbital pressure (*caveat: orbital massage is contraindicated in patients with elevated intraocular pressure > 21 mmHG*) and intravenous Mannitol.

Should the orbit feel tense, it is best to perform an immediate lateral canthotomy and cantholysis, ideally under general anaesthesia or local if necessary. This releases the periorbital fascia and allows the orbital contents to protrude anteriorly, thus reducing the intraorbital pressure immediately (Fig. 34.6). This rapidly provides excellent decompression of 14 to 30 mmHg. The procedure is much more effective than endoscopic orbital decompression that requires clearance of the lamina papyracea followed by exposure and incision of the periorbita, allowing orbital fat to herniate into the nasal cavity [23]. However, if there is a significant threat to vision, lateral canthotomy and cantholysis can be combined with medial decompression. Incising the periorbita and releasing orbital fat may optimise the outcome in the event of recurrent bleeding or increasing soft tissue swelling, but is not considered mandatory.

Urgent ophthalmological consultation should be obtained. Tonometry and fundoscopy are helpful in assessing the perfusion to the optic nerve.

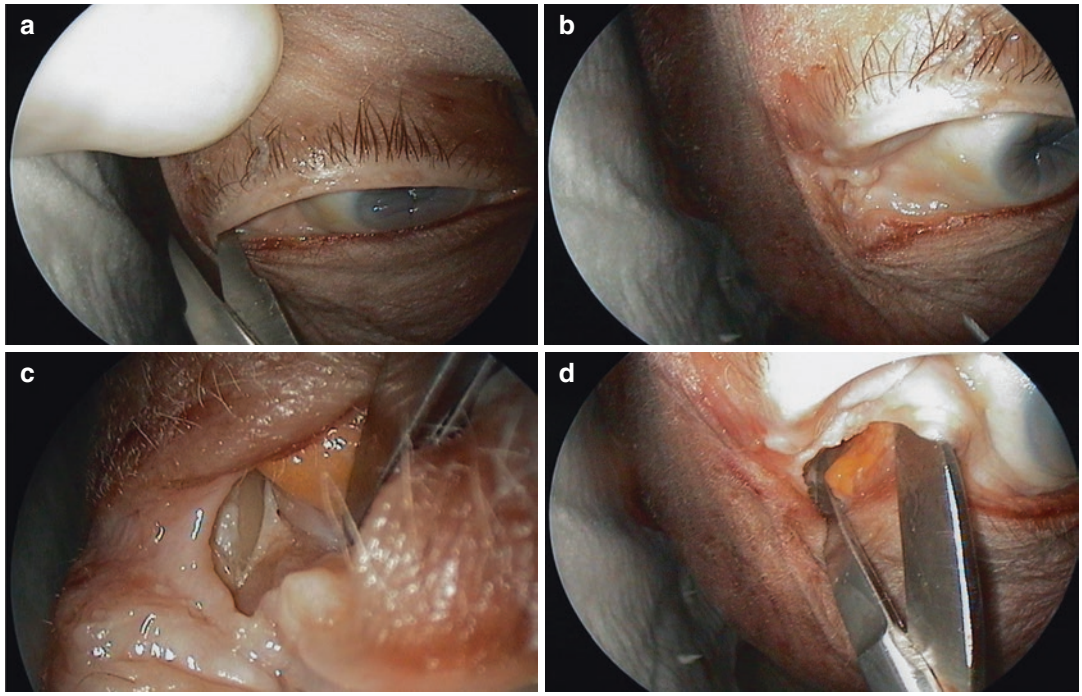

Fig. 34.6 Canthotomy and inferior cantholysis. (**a**) The cornea must always be protected, (**b**) horizontal incision of lateral canthal ligament to the bone, (**c**) incise the periosteum on the lateral orbital rim (cygomatic), (**d**) scissors or Freer are used to allow the fat to protrude and lower the pressure on the orbit

Tips

Regular examination of the eyes during ESS is recommended, and thus, the eyes should not be hidden or covered in the surgical field.

Nasolacrimal Duct Injury

Injury to the nasolacrimal duct and subsequent scarring may result in partial or complete obstruction between the nasolacrimal sac or duct and the inferior meatus. Some published reports found injury to the lacrimal duct from 0.62% to 15% depending on the surgical technique [24]. Injury usually occurs when removing the vertical portion of the uncinate process with the backbiter. When injured, the duct should be cut sharply allowing it to heal in a patent configuration. Epiphora as a sequela is rare as the duct tends to heal spontaneously creating a patent drainage system. When detected in the postoperative scenario, a wait-and-see policy is recommended as epiphora is usually temporarily and will resolve. Should it persist, then endoscopic dacryocystorhinostomy is indicated.

Key Learning Points

- The risk of complications is significantly reduced by good preoperative planning, detailed review of imaging at the time of surgery, gentle good technique and attention to anatomy and anatomical variations.
- Most complications are relatively minor and their effects can be minimized by attention to good management.
- Serious complications are fortunately uncommon, but always possible. Should the surgeon inadvertently cause such a complication, they should calmly assess the situation and ensure that they do not make matters worse.
- Causing a serious complication is a stressful experience for a surgeon, and contacting an

experienced colleague to discuss the patient management is strongly recommended.

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Open Approaches to the Paranasal Sinuses

35

Stephen Hayes and Sean Carrie

Maxillary Sinus

The majority of maxillary sinus pathology can be managed successfully with endoscopic sinus surgery. Increasingly, endoscopic techniques are allowing access to even the most anterolateral aspects of the sinus. However, having the knowledge and ability to perform transantral approaches to the orbit and skull base is important.

Maxillary Antral Puncture/Washout

History

Puncturing the maxillary sinus via the inferior meatus was first described by Lichtwitz in the nineteenth century to help treat rising levels of infected maxillary sinusitis. Lichtwitz designed and gave his name to the 'Lichtwitz' trocar and cannula still used today. Although advances in endoscopic techniques have made the antral washout largely obsolete, in some cases this simple-to-perform and cost-effective procedure can be very useful in obtaining a diagnostic aspirate.

Procedure

Performed under local or general anaesthetic, the inferior meatus is prepared with pledgets soaked in topical anaesthetic and adrenaline (such as 4% Xylocaine in 1:10,000 adrenaline). If under general anaesthetic, the ipsilateral eye must remain uncovered during the procedure. The trocar is placed under the attachment of the inferior turbinate and aimed towards the ipsilateral pinna. The surgeon must place their index finger one third up from the trocar point, to act as a safety buffer. The trocar is firmly turned and a 'give' is felt as the lateral nasal wall is penetrated. The trocar is removed leaving the cannula in place within the sinus. Using a syringe, the sinus is aspirated and pus sent for microbiology. If required, the sinus can be flushed with warm saline. If the patient is awake, they should be instructed to keep their mouth open and a kidney dish is placed under their jaw to catch the flushed sinus contents.

S. Hayes (✉)
Rhinology and Facial Plastics, Portsmouth Hospitals University NHS Trust, Queen Alexandra Hospital, Portsmouth, UK
e-mail: drhayes@doctors.net.uk

S. Carrie
Rhinology and Skull Base Surgery, Newcastle upon Tyne Hospitals NHS Foundation Trust, Newcastle upon Tyne, UK

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Caldwell Luc Procedure (Anterior Antrostomy)

The definitive open-approach procedure to the maxillary sinus is the Caldwell Luc anterior antrostomy. Although once commonly performed, the Caldwell Luc procedure is now reserved for cases where the surgeon's instrumentation does not allow adequate access to the whole maxillary sinus. This may be required rarely in cases where pathology occupies the most anterolateral limits of the maxillary sinus, such as in fungal mycetomas, inverted papillomas, antrochoanal polyps and neoplastic masses [1]. Other reported indications include removal of foreign bodies, orbital decompression, revision odontogenic sinusitis [2], chronic rhinosinusitis following failed endoscopic surgery [3] and excision of pterygopalatine tumours, such as juvenile angiofibroma [4]. This maxillary sinus approach was used historically to access pathology of the ethmoid and sphenoid sinuses (please see 'Ethmoid sinuses' below).

History

At the latter end of the nineteenth century, two surgeons in two separate continents independently described approaching the paranasal sinuses through the anterior maxillary wall via the canine fossae [5]. In 1893, George Caldwell, an American surgeon working in New York City, first described performing an 'anterior antrostomy' combined with an inferior meatal antrostomy and demonstrated that 'counter-drainage' significantly improved surgical outcomes [5]. Four years later in 1897, a Parisian otorhinolaryngologist called Henry Luc, who was often described as the 'Father of French rhinology', published the same technique but combined with a middle meatal antrostomy [5].

Complications

Within the literature, the commonest short-term complications reported were facial swelling (61.9–79%), followed by facial pain and numbness (46.0%), dental pain and numbness (30.9%), bleeding (0.4%), oroantral fistulae (0.4%), epiphora (0.4%) and dental discolouration (0.4%) [6, 7]. Long-term reported complications include facial asymmetry, dacryocystitis and devitalised teeth [8].

Technique

Nowadays the Caldwell Luc approach is generally performed in combination with endoscopic sinus surgery. A middle meatal antrostomy is performed first to establish an intranasal drainage pathway. This facilitates maxillary sinus drainage preventing postoperative fistulation. A Caldwell Luc procedure is usually performed under general anaesthetic but is possible under local anaesthetic using pterygopalatine and posterosuperior alveolar nerve blocks. The canine fossa is identified as a shallow depression superolateral to the root of the canine tooth (Fig. 35.1). The canine fossa and buccogingival sulcus are infiltrated with 2% Lidocaine in 1:80,000 adrenaline. With the lip retracted, a 3.5–4 cm horizonal incision is made 3 mm above the buccogingival sulcus, running from the canine ridge to the maxillary buttress parallel to the dental line [9] (Fig. 35.2a). After dissection down to the bone, the periosteal elevator is used to expose the anterior maxillary wall superiorly up to, but not including, the infraorbital foramen [10] (Fig. 35.2b). To reduce the chances of damaging the anterior superior alveolar nerve when performing the canine fossa punch, an osteotome or 4 mm trocar should be used at the point where the mid-pupillary line intersects with a horizonal line from the floor of the nasal vestibule [11, 12] (Fig. 35.2c). Once through the anterior wall, the antrostomy is enlarged with a 3 mm Kerrison Rongeur, completing the anterior antrostomy [9] (Fig. 35.2d). At the end of the case, the incision is closed in layers, avoiding gaps to prevent fistulation [9]. Depending on the requirement, the maxillary sinus may or may not be packed with either a dissolvable pack or ribbon gauze instilled with bismuth iodoform paraffin paste. On waking, the patient is nursed at 30° and ice packs may be applied to the face to reduce facial swelling and pain.

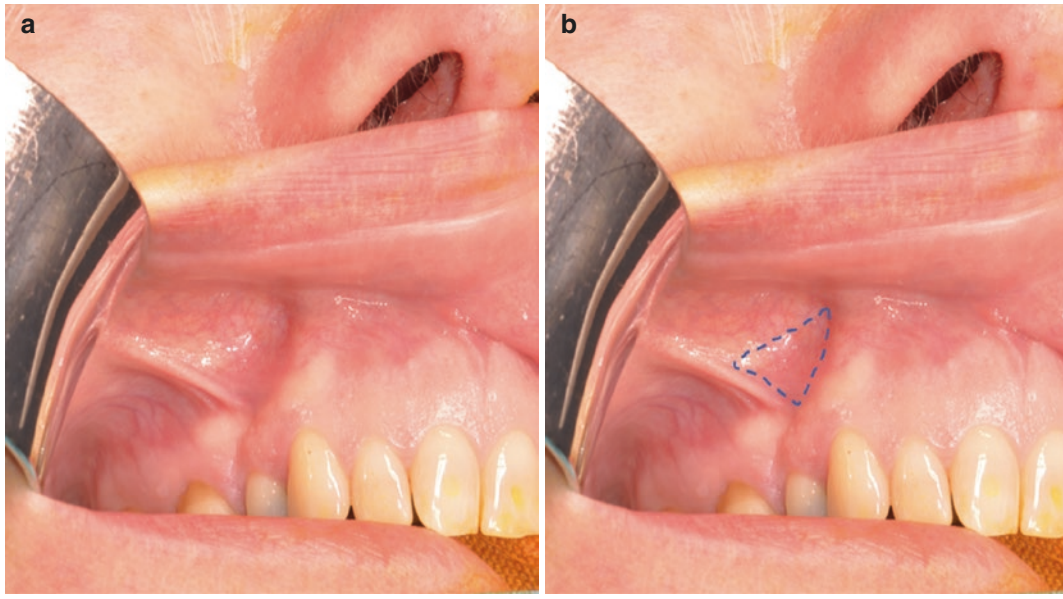

Fig. 35.1 (**a**) A right-sided canine fossa can be seen here as a shallow depression superolateral to the canine root. (**b**) Canine fossa marked with a dotted line. Photographs courtesy of Mr Gerald McGarry

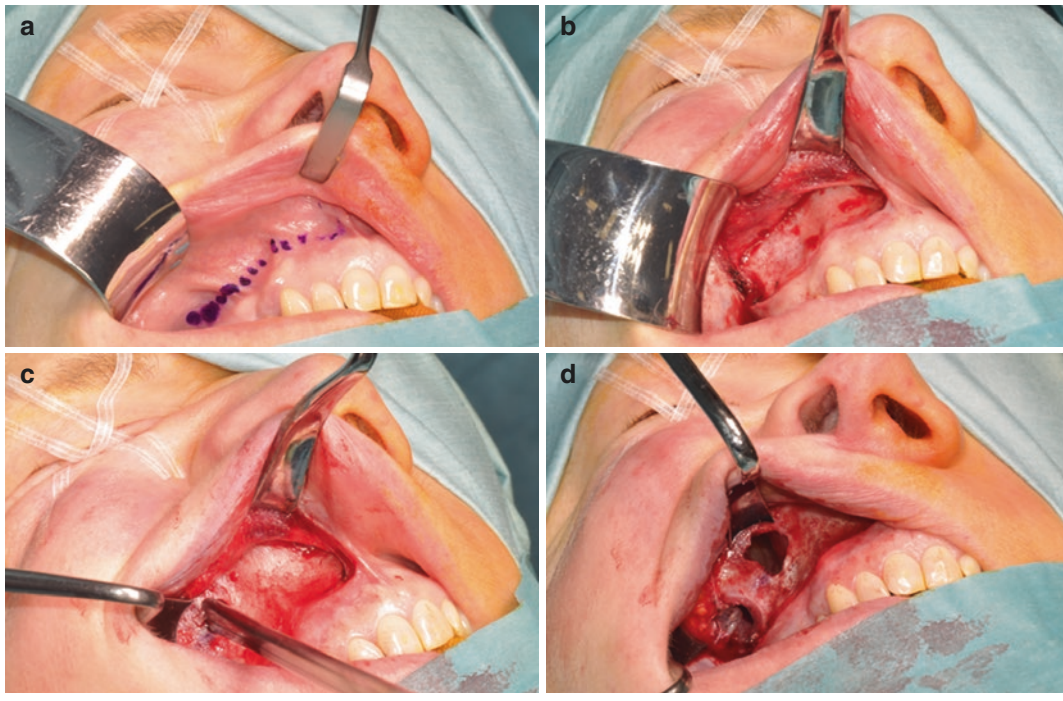

Fig. 35.2 (**a–d**) A right-sided Caldwell-Luc technique. (**a**) With the lip retracted, the buccogingival margin is exposed and marked. (**b**) A 3.5–4 cm horizontal incision is made and the periosteum elevated to expose the anterior maxillary wall. (**c**) A canine fossa punch is made with an osteotome. (**d**) The antrostomy is enlarged to complete the Caldwell-Luc procedure. Photographs courtesy of Mr Gerald McGarry

Ethmoid Sinuses

Over the last 30 years, ethmoidal sinus disease has been almost exclusively managed endoscopically. An open-approach ethmoidectomy is rarely performed and reserved only for cases where clearance of disease endoscopically is not possible or due to resource limitations [13]. Such cases include removal of large osteomas or excision of tumours extending into the anterior cranial fossa [13]. However, the transcutaneous approach to the ethmoid sinuses is still regularly performed in the emergency setting, to ligate an anterior ethmoidal artery in traumatic epistaxis, to drain a periorbital abscess or to repair an orbital fracture [13].

History

The first open-approach ethmoidectomy was described by Jensen in Germany in 1897, as part of an external frontoethmoidectomy. In 1921, Lynch and Howarth modified this technique and gave their names to the incision (Lynch-Howarth incision) (Fig. 35.3a). The Lynch-Howarth incision allowed access to the medial orbital wall, the ethmoid cavity and the frontal sinus. An alternative technique of historical interest is the transantral ethmoidectomy via a Caldwell-Luc maxillary sinus approach. In the days before endoscopic sinus surgery, the transantral technique allowed removal of most ethmoid pathology, with the exception of the anterior ethmoid cells, and could be extended to include the sphenoid sinus

Complications

Reported complications include scar, webbing and ectropion (avoided if a medial orbital transconjunctival approach is used), haemorrhage, corneal abrasions, periorbital swelling and bruising, diplopia (damage to the medial rectus muscle), telecanthus, epiphora, numbness (supraorbital, supratrochlear and infratrochlear nerve distribution), blindness (retro-orbital hae-

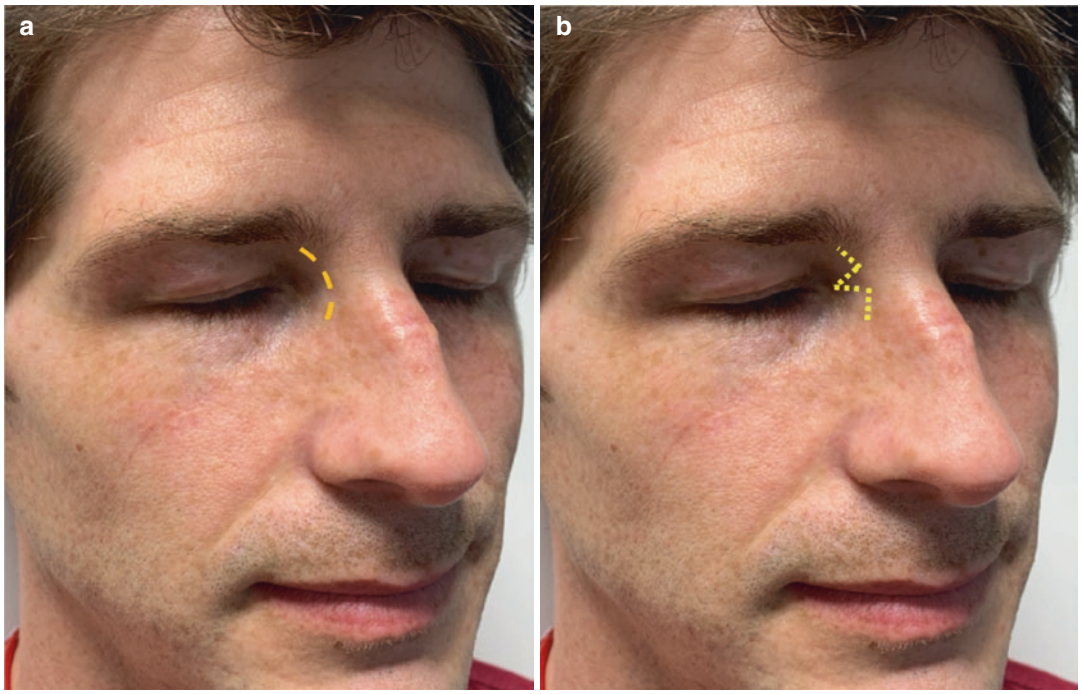

Fig. 35.3 (**a, b**) Photographs demonstrating the (**a**) Lynch-Howarth and (**b**) gull-wing incision. With permission from Mr Jonathan Bird

matoma or direct optic nerve damage) and cerebrospinal fluid leak (skull base injury in external ethmoidectomy) [10]. Also, postoperative iatrogenic scarring of the frontal recess can lead to a chronic frontal sinus outflow obstruction.

Transcutaneous Approach

The transcutaneous approach can be performed under local or general anaesthetic depending on the planned procedure. An ipsilateral temporary tarsorrhaphy is performed to protect the eye. After infiltration with 2% Lidocaine in 1:80,000 adrenaline, the Lynch-Howarth incision is made halfway between the medial canthus and the nasal dorsum, one third above the medial canthus and two thirds below. Soft tissue is dissected down to the bone and the periosteum is excised. A subperiosteal dissection is developed laterally and superiorly along the medial orbital wall. Once a significant flap is raised, a zero-degree endoscope can be used to aid the dissection.

One disadvantage of the Lynch-Howarth incision is the postoperative scarring and webbing. Alternative incisions, such as the gull-wing-shaped incision (Fig. 35.3b), have been described to help address these issues. However, despite reducing the webbing and contractures, they still leave a visible scar on the face, which may be undesirable particularly in children and patients suffering with keloid or hypertrophic scarring.

Increasingly, approaches to the ethmoidal sinuses and medial orbital wall are being replaced with transconjunctival approaches, such as the transcaruncular approach, which avoids an external scar [14, 15]. Described originally for the repair of orbital fractures and decompression of the orbital apex, the transcaruncular approach provides good access to the medial orbital wall and ethmoidal sinuses through the lacrimal caruncle, avoiding a skin incision [14, 15]. This is performed through a 12 mm vertical incision through the lateral third of the caruncle, posterior to the lacrimal sac [14]. Dissection is made through the fascial layer deep to the caruncle between the medial orbital septum and the posterior fibres of the pretarsal orbicularis oculi muscle (Horner's muscle). Within this plane, Horner's muscle acts as a buffer, keeping the lacrimal sac safe. Once through this natural bloodless plane, the medial orbital wall is exposed [14].

Drainage of an Orbital Subperiosteal Abscess

Drainage of an orbital subperiosteal abscess is performed to prevent complications of blindness and ophthalmoplegia. Surgical interventions include either endoscopic orbital decompression or external drainage. Due to severe sinus inflammation and mucosal friability, an open approach is commonly performed in these cases. This can be performed through either a transcutaneous or transcaruncular approach, as described above. Preoperative measurement of the depth of the collection on the computer tomography (CT) scan is useful to help guide the surgeon and limit excessive subperiosteal dissection along the medial orbital wall. Once the cavity is opened, a pus swab is taken for microbiology, the cavity is gently irrigated with saline and a Yeates (or similar) drain is left in situ for 24–72 h. Endoscopic drainage of the affected sinuses can be performed at the same time to remove the source of the infection.

Anterior Ethmoid Artery Ligation

The anterior ethmoid artery can be accessed through either a transcutaneous or transcaruncular approach (Fig. 35.4a). Using a periosteal elevator to expose the medial orbital wall (Fig. 35.4b), the anterior ethmoidal artery is located along the frontoethmoidal suture 24 mm from the anterior lacrimal crest (Fig. 35.4c). The posterior ethmoidal artery is located a further 12 mm from the anterior ethmoidal artery along the frontoethmoidal suture, and the optic nerve is found a further 6 mm from the posterior ethmoidal artery. Extreme care must be taken behind the level of the posterior ethmoidal artery to avoid trauma to the optic nerve or a retro-orbital haemorrhage, both of which could result in blindness [10]. The anterior ethmoidal artery is either ligated with clips or cauterised with bipolar diathermy (Fig. 35.4d).

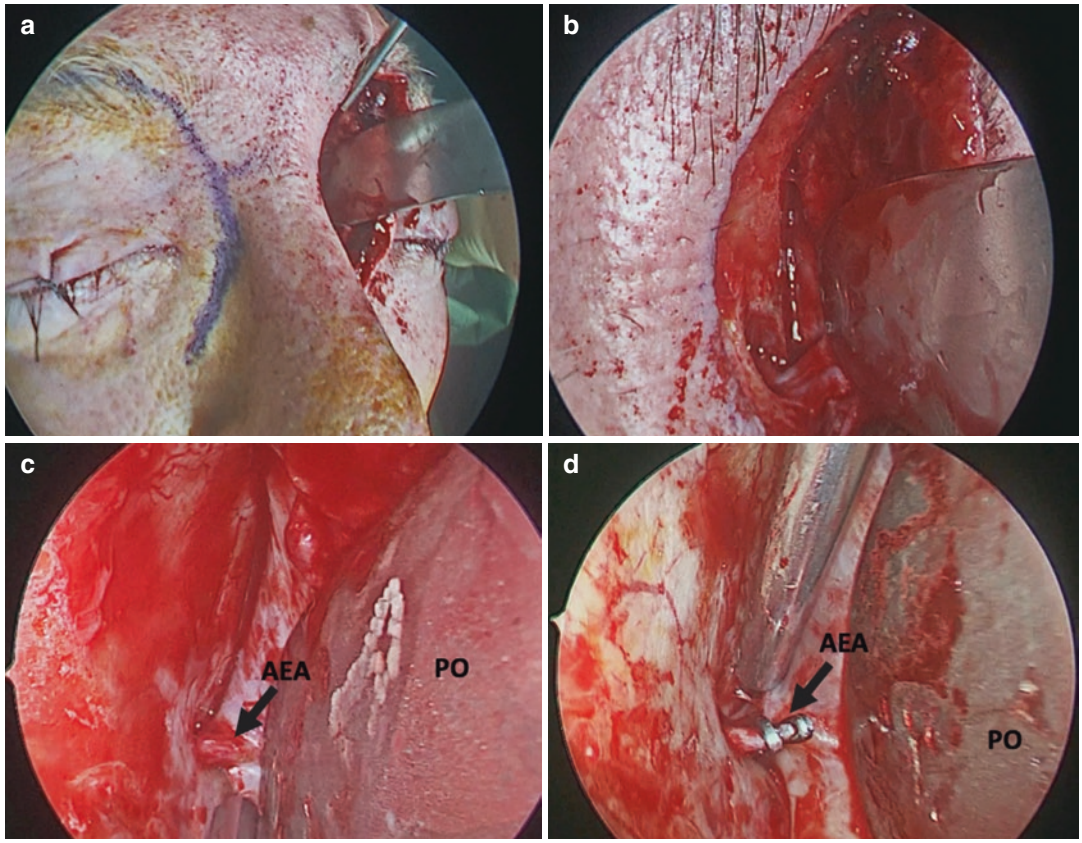

Fig. 35.4 (**a–d**) Endoscopic images demonstrating a left-sided anterior ethmoid artery (AEA) ligation. (**a**) A left-sided Lynch-Howarth incision is performed followed by a (**b**) subperiosteal dissection along the medial orbital wall. (**c**) The periorbita (PO) lateralised exposing the AEA 24 mm from the anterior lacrimal crest along the fronto-ethmoidal suture. (**d**) The AEA is ligated with clips. Photographs courtesy of Mr Gerald McGarry

Open-Approach Ethmoidectomy

Although rarely performed in recent times, it is important for the endoscopic surgeon to appreciate this technique when faced with an older patient, who may have undergone this procedure in the past.

In the very rare situation where an open-approach ethmoidectomy is required, the approach of choice would be via a transcutaneous incision, as described earlier. The frontal process of the maxilla, lacrimal bone and lamina papyracea are all exposed with a periosteal elevator [10]. Bipolar haemostasis of the inferior distal branches of the angular vessels may be required at this point [10]. Using a malleable retractor, the orbital contents are gently lateralised and the anterior ethmoidal artery is ligated [10]. Entry into the ethmoidal sinuses is made through the anterior two thirds of the lamina papyracea [13]. The ethmoidal mucosa is resected. Medially, the middle turbinate can be excised for greater access

[13]. Dissection can proceed posteriorly into sphenoid sinus [13, 16]. Once the ethmoidectomy is complete, the incision is closed in layers with careful reattachment of the medial canthus to the underlying periosteum [13, 16].

Tip

- *The frontoethmoidal suture and anterior ethmoidal artery are accurate landmarks for the fovea ethmoidalis and anterior cranial fossa (at the junction of the frontal bone and lamina papyracea), and as such dissection should not proceed superiorly to these landmarks* [17].

Frontal Sinus

Endoscopic approaches are the procedure of choice in the management of most frontal sinus pathologies. However, there are specific anatomical and pathological instances when an external approach may be required [18]. In addition to the anatomical complexity, excessive instrumentation of the frontal recess can lead to restenosis, resulting in surgical failure despite repeated endoscopic surgeries. The two commonest open approaches used today include frontal trephination and the frontal osteoplastic flap.

Frontal Trephination

Frontal trephination is the most common and least invasive open approach to the frontal sinus. First described by Runge in 1750 for draining pus in acute frontal sinusitis, it remains a useful procedure predominantly for this pathology [19]. Using a trephine to drain, decompress and obtain a microbiological sample in a symptomatic or intracranially complicated acute frontal sinusitis may be preferrable to endoscopically accessing a severely inflamed anatomically complex and friable frontal recess. A conventional frontal trephine is usually performed in this setting due to the flexibility of burr size, allowing for removal of thick pus and/or placement of a drain or catheter.

Risk and Complications

Frontal trephination is a safe and effective adjunct in the management of complex frontal sinus surgery with a reported complication rate of <10% [20, 21]. However, due to the close vicinity of critically important anatomical structures, complications can be severe when they happen. Within the literature, reported complications include infection at trephine site; external scar; numbness of the forehead, upper eyelid and nasal bridge (supraorbital and supratrochlear nerves); bleeding and haematoma (supraorbital and supratrochlear arteries and veins); cerebrospinal fluid leak (transgression of the anterior skull base); and damage to the orbital contents [10, 20].

Pre-procedural CT Scan Assessment

To minimise the risk of complications, preoperative evaluation of the CT scan is essential to assess frontal sinus depth, the position of the sinus septum and the relationship of the frontal sinus to the orbit and skull base.

Conventional Frontal Trephination Technique

Although most commonly performed under a general anaesthetic, a frontal trephine can be performed under a local anaesthetic, if required. The transcutaneous approach is usually performed with a medial brow incision. A 0.5–1 cm incision is made between the midline and the supraorbital foramen, being careful to avoid both the supratrochlear and supraorbital neurovascular bundles [10]. Dissection is made down to the frontal bone and the periosteum is elevated to expose the thin inferior wall of the frontal sinus [10]. A trephine is made using a 3 mm cutting burr (Fig. 35.5a). Correct placement of the trephine can be confirmed by suctioning with a 20 mL syringe (partially filled with saline) or, if possible, by direct inspection through the trephine with an endoscope [22]. Pus is sent for microbiological analysis and the sinus is irrigated with normal saline.

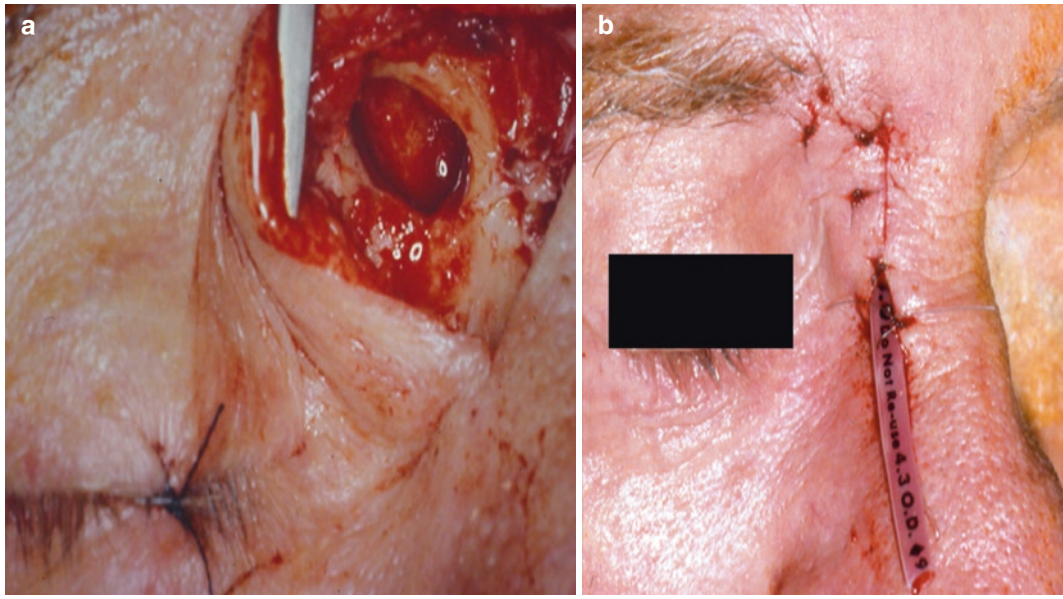

Fig. 35.5 (**a, b**) Clinical photograph showing a (**a**) right-sided conventional frontal sinus trephine. (**b**) Closure of the Lynch-Howarth incision with drain in situ. Photographs courtesy of Mr Gerald McGarry

Either a drain or a catheter (for flushing) is placed into the sinus and secured to the skin. Excessive incision margins are closed around the drain/catheter (Fig. 35.5a).

Frontal Trephination Technique Using a Mini-trephination Set

The Medtronic mini-trephination set (Medtronic ENT, Jacksonville, FL) has become popular in recent years as it contains all instruments (Fig. 35.6a) required to perform a quick and safe frontal trephination with a good postoperative cosmetic result. The mini-trephine is usually performed electively in combination with endoscopic sinus surgery to help confirm the correct opening of the frontal recess in patients with severe oedema or with a narrowed recess complicated by additional frontoethmoidal cells (particularly Type 3 or Type 4 cells) [20]. The mini-trephine also facilitates flushing of fungal debris, mucus and eosinophilic mucin from the lateral limits of the frontal sinus [20].

The optimum external entry point is reported as 10 mm from the midline within the medial aspect of the eyebrow [19]. Care must be taken to avoid the supraorbital bundle located along the supraorbital rim approximately 22–24 mm from the facial midline and 26–28 mm from the temporal crest of the frontal bone [23]. An anterior-posterior depth of at least 7 mm is essential to avoid transgression into the anterior cranial fossa [19]. Infiltration is performed with 2% Lidocaine in 1:80,000 adrenaline and a full-thickness stab incision is made down to the bone (scalpel with size 15 blade). Iris scissors can be used to divide tissue layers to help facilitate placement of the drill guide directly onto the bone. The drill is placed within the drill guide (Fig. 35.6b, c), and using irrigation, the anterior table is carefully drilled using short pulses until the frontal sinus is breached [20]. Replacing the drill with the guidewire, the frontal cannula is fed over the wire into the trephine and secured with careful rotations until flush with the skin (Fig. 35.6d, e). Using a 5–10 mL syringe, partially filled with saline, correct placement of the trephine is confirmed with aspiration of either air bubbles, pus or blood (Fig. 35.6f). Aspiration of clear fluid may indicate CSF and possible transgression of the posterior table [20]. To help confirm the true frontal drain-

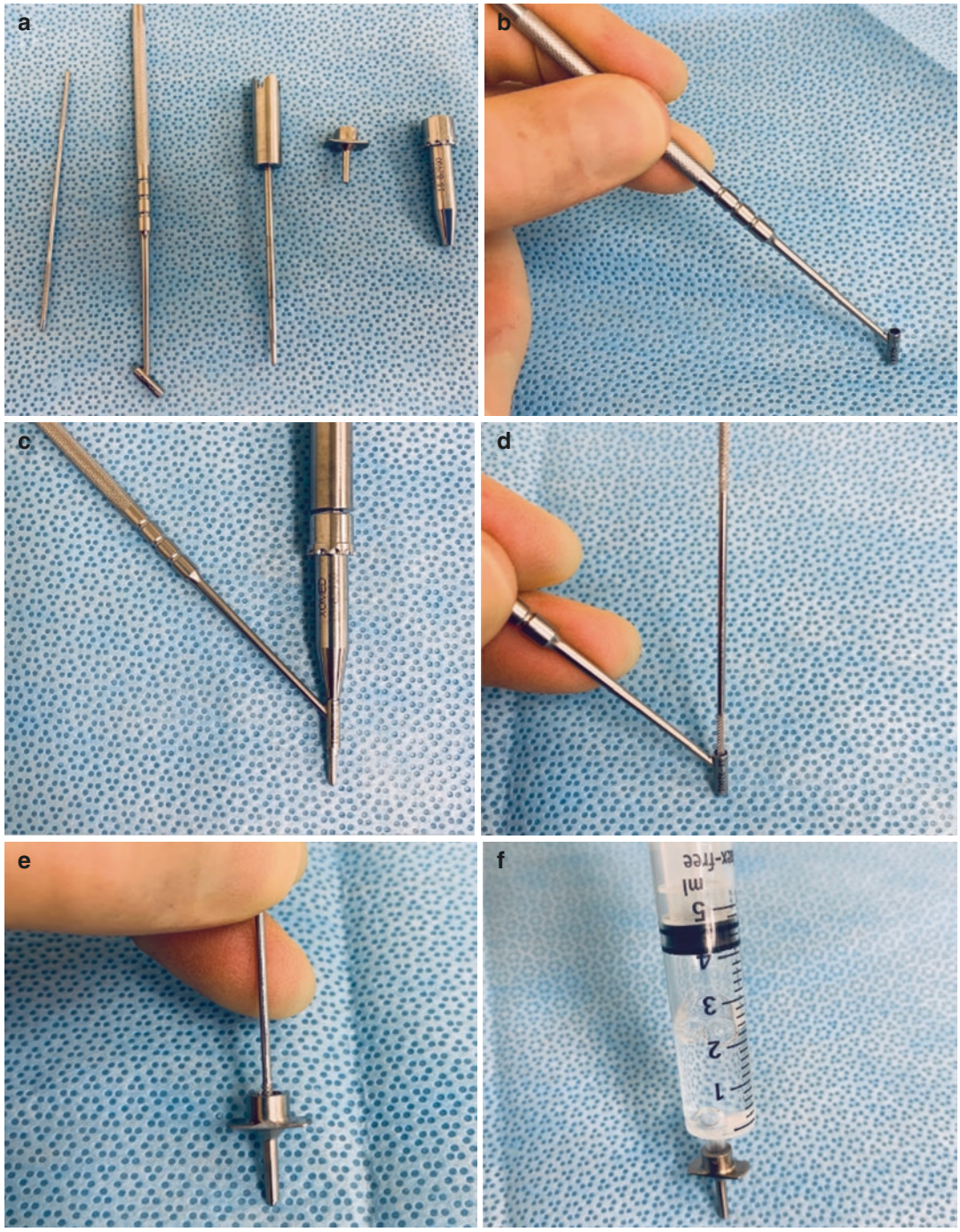

Fig. 35.6 (**a**) The Medtronic mini-trephination set (Medtronic ENT, Jacksonville, FL). Contents (left to right) guidewire, drill guide, drill bit component 1, cannula, drill bit component 2. (**b**) Drill guide. (**c**) The two drill bit components are assembled, attached to the debrider handpiece and fed over the drill guide. (**d**) After the trephine is performed, the drill guide is held in place, whilst the drill bit is replaced with the guidewire. (**e**) The cannula is then fed over the guidewire and secured into place within the trephine. (**f**) A saline-filled syringe is attached to the cannula and aspirated to confirm correct placement

age pathway, fluorescein dye (0.5 mL of 5% fluorescein in 500 mL of saline) can be instilled through the frontal cannula whilst observing the recess endoscopically from below [20]. At the end of the procedure, the cannula is gently removed from the trephine site and pressure is placed on the incision for 5 min. These small incisions are not routinely sutured but covered with a simple plaster or steri-strip and generally heal very well.

Tips

- *Initial flushing of the frontal sinus must be performed slowly with direct observation of the ipsilateral eye and immediately halted in the presence of any orbital swelling or proptosis* [20].
- *In the presence of a posterior table or superior orbital rim/lamina papyracea dehiscence, no pressure should be applied when instilling saline or fluorescein dye through the frontal trephine* [20].
- *To reduce postoperative restenosis of the frontal recess, corticosteroid cream can be instilled through the frontal cannula before removal at the end of the procedure* [20].
- *If clinically required, the frontal cannula can remain* in situ *postoperatively for up to 5 days to facilitate regular frontal sinus saline flushes or instillation with corticosteroid or decongestant drops* [20].

External Frontoethmoidal Surgery

Initially, radical surgery was thought to be the answer for chronic frontal sinus disease, and it was Kuhnt (1895) and Riedel (1898) who first described fully excising both the anterior wall and sinus floor [24]. However, this left patients with unsightly facial disfigurement, and despite modifications by Killian (1903) to improve cosmesis, these procedures were largely abandoned for more conservative techniques [24]. The frontal osteoplastic flap was first described by Schonborn in 1894, but due to the lack of radiology and concern over re-approximation of bone flaps, it was not commonly performed until the 1950s when Macbeth (1954) re-described the technique with modern concepts [25], and Goodale and Montgomery (1957) demonstrated high success rates with low levels of restenosis [26]. The procedure provided the option of obliterating the frontal sinus with fat and became very popular until the introduction of endoscopic sinus surgery. Allowing comprehensive access to all areas of the frontal sinus, the osteoplastic flap remains one of the few external frontal procedures still in use today.

Frontal Osteoplastic Flap With or Without Frontal Sinus Obliteration

The frontal osteoplastic flap is generally considered an endpoint procedure in frontal sinus surgery performed in cases where endoscopic sinus surgery either has failed or is not appropriate. The possible indications are listed in Table 35.1 [2]. Removing the anterior table allows access to all areas of the frontal sinus and provides the option of obliteration if required [18, 22, 27].

Table 35.1 Possible anatomical and pathological indications for an osteoplastic flap approach to the frontal sinuses

Anatomical	Pathological
Narrow anterior-posterior diameter associated with a small frontal sinus	*Recurrent frontal bone osteomyelitis*
Narrow or scarred frontal recess	*Neo-osteogenesis causing stenosis of frontal sinus outflow tract*
	Lateral frontal sinus disease (e.g. *large osteoma, inverted papilloma, mucocoele, mycetoma)*
	Chronic frontal sinusitis refractory to endoscopic management
	Anterior table fibro-osseous lesions (e.g. *ossifying fibroma)*
	Posterior table defect with cerebrospinal fluid leak
	Complex frontal sinus fracture

Procedure

In the past, a frontal sinus template was made either from a Caldwell radiograph or from using transillumination. More recently, CT-image guidance has been demonstrated to be more accurate, faster and safer than the original techniques [28]. Bilateral tarsorrhaphy sutures are performed to protect the eyes [26]. After infiltration with 2% Lidocaine in 1:80,000 adrenaline, a bicoronal incision is performed starting in the midline, following the hairline down to the pre-auricular fold, taking care to avoid damaging the superficial temporal artery and frontal branch of the facial nerve [26]. The bicoronal flap is raised anteriorly in the subgaleal plane. An incision is made 2 cm posterior to the supraorbital and supratrochlear neurovascular bundles, and the dissection continues anteriorly in a subperiosteal plane, raising a pericranial flap whilst exposing the entire frontal sinus (Fig. 35.7a, b) [22]. The frontal sinus is marked out using either the template or CT-image guidance (Fig. 35.7c), and the anterior wall is excised

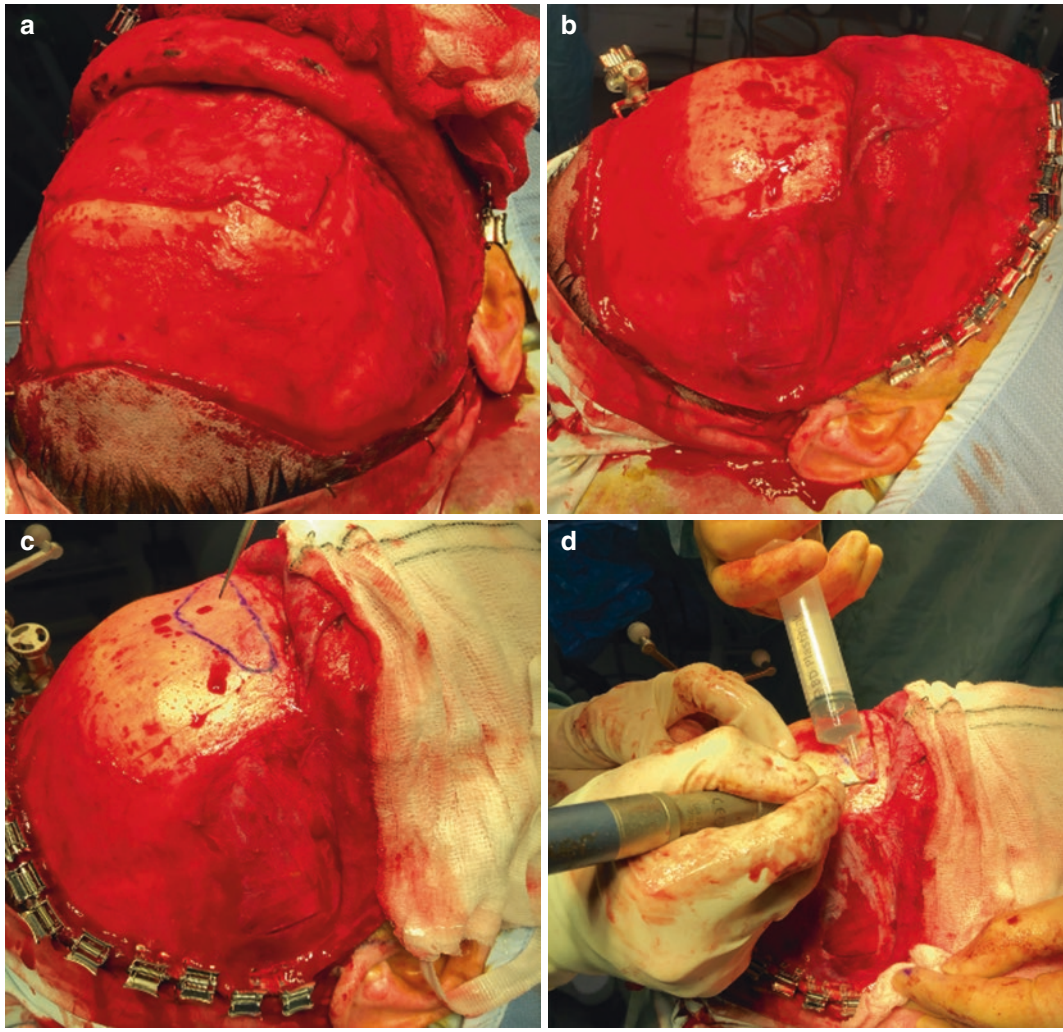

Fig. 35.7 (**a–d**) A frontal osteoplastic flap. (**a**) Following elevation of the subgaleal flap, a pericranial flap is outlined beyond the peripheral margins of the frontal sinuses. (**b**) Pericranial flap raised inferiorly. (**c**) Frontal sinus margins are mapped out using image guidance. (**d**) Using a high-speed fissure burr, the anterior table of the frontal sinus is removed

using a high-speed fissure burr. The fissure burr is preferred over a drill as this reduced the gap left between the flap and bone (Fig. 35.7d) [10, 22, 26]. However, a small oscillating saw is also useful for minimising bone loss and bevelling the bone for later flap replacement. The intersinus septum is fractured with an osteotome to release the bone flap (Fig. 35.8a, b), which is removed and placed in sterile saline [22]. The frontal sinus pathology is managed as planned. If obliteration is planned, all mucosa is removed from the sinus and bone flap and burred with a

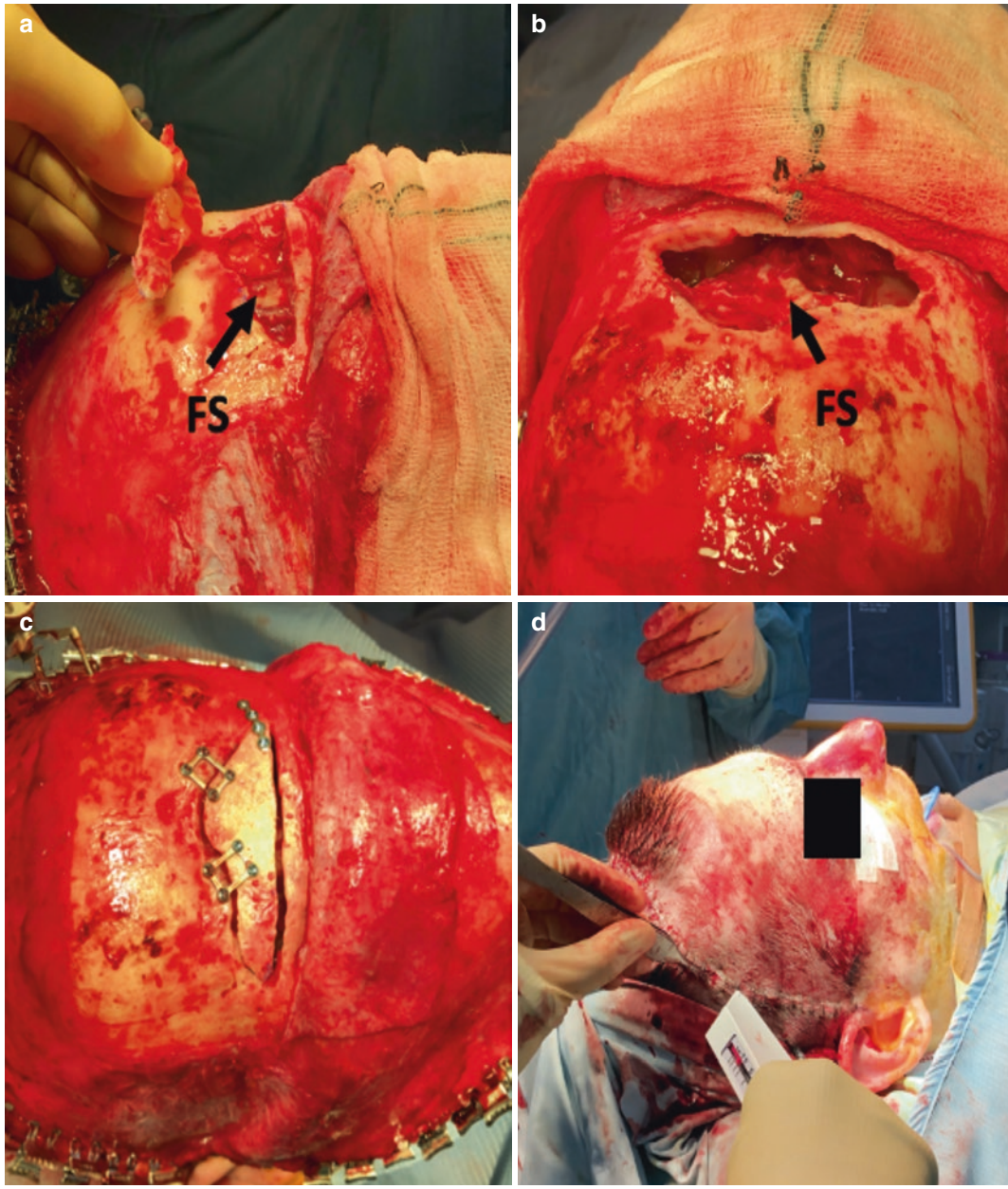

Fig. 35.8 (**a**) Elevation of anterior table exposing the limits of the frontal sinus (**b**). (**c**) Following the planned frontal sinus procedure, the anterior frontal wall is fixed in place with titanium plates. (**d**) The bicoronal incision is closed in layers

diamond drill. The frontal recess is plugged with the bone, temporalis muscle or fascia and the sinus obliterated with abdominal fat [22, 26]. However, the modern approach is to combine the osteoplastic flap with a Draf type III midline frontal sinusotomy, which allows endoscopic postoperative inspection. Obliteration is best avoided, if possible, to prevent the risk of burying mucosa or disease [26].

The bone flap is replaced and secured with titanium plates (Fig. 35.8c). The bicoronal flap is replaced and closed in layers with a drain left in place for 24–48 h (Fig. 35.8d). The tarsorrhaphy sutures are removed and a compression dressing applied for 48–72 h.

Managing Disease in the Small Frontal Sinus

With advancements in image guidance, the size of the frontal sinus has become less important than the pneumatisation and pathology of the frontal recess, which will both determine whether an adjunctive external approach is required.

Tips

- *A midbrow, lateral brow or gull-wing incision can be used in unilateral cases, but often results in poorer cosmesis, and the risk of supraorbital nerve damage is higher.*
- *Pre-drilling the screw holes for securing the titanium plates before removal of the anterior table will help to provide landmarks for re-approximation of the bone flap and increase the ease of fixation at the end of the procedure.*
- *A pericranial flap can be raised if cranialisation is planned.*
- *Riedel's procedure, the removal of the anterior table of the frontal sinus, may be required in cases of recalcitrant frontal sinusitis/osteomyelitis.*
- *Cranialisation, the removal of the posterior frontal sinus table, is generally performed by neurosurgical colleagues in complex posterior table fractures.*

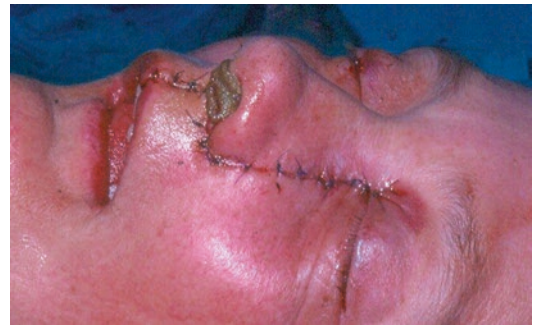

Fig. 35.9 Clinical photograph of a left lateral rhinotomy with lip split. Photographs courtesy of Mr Gerald McGarry

Lateral Rhinotomy, Midfacial Degloving and Craniofacial Resections

The lateral rhinotomy approach was traditionally used to access tumours of the middle meatus, maxillary and ethmoid sinuses. However, both the surgical access and postoperative cosmesis were poor, leaving patients with scars running from the medial canthus along the lateral aspect of the nose to the alar crease and sometimes through the lip (Fig. 35.9) [29]. Today, the lateral rhinotomy is used more often as part of more extended procedures to access and remove aggressive malignant tumours of the maxillary sinus [29]. In comparison, the midfacial degloving approach was traditionally used for tumours of the central anterior skull bases, such as juvenile angiofibromas, but in recent times, this procedure has been largely superseded by endoscopic sinus surgery [29]. Malignant tumours of the frontoethmoidal sinuses can also be accessed via an endoscopic or open craniofacial resection, but these procedures are beyond the scope of this text.

Conclusion

With huge advancements in endoscopic sinus surgery, open approaches to the paranasal sinuses have largely been abandoned. However, sinus anatomy and pathology can be very complex and occasionally beyond the capability of endoscopic

sinus surgery alone. In specific cases, the use of open-approach techniques (particularly the frontal osteoplastic flap), alone or in combination with endoscopic surgery, may be essential for a safer procedure and better outcome. It is therefore essential for the rhinologist to be familiar with these techniques in order to achieve the best surgical outcomes for their patients.

Key Learning Points

- Open approaches should be familiar to those involved with both emergency and elective surgical practices.
- There are no didactic rules as to when an open approach may be required; it is dependent on the individual patient's anatomy, the pathological process and the skillset of the surgeon.
- Pathologies of the frontal sinus, particularly neoplastic, may require an open approach for complete removal. The treating surgeon should refer to a tertiary centre if unfamiliar with these procedures.

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Surgery of the Anterior Skull Base

36

Christian Stephan Betz

Introduction

In the clinical reality of the otorhinolaryngologist, the skull base is divided into the anterior and the lateral skull base. Whereas the former refers to the parts of the skull base that abut the paranasal sinus system, the latter lie adjacent to the temporal bone. From anterior to posterior, the medial anterior skull base is thus represented by the posterior wall of the frontal sinus, the cribriform plate, the sphenoid planum, the sella and the clivus.

Anterior skull base surgery serves the purpose to resect neoplastic or non-neoplastic lesions that involve the skull base or to act as a portal for intracranial lesions. Neoplastic entities include sinonasal tumours with extension into the skull base and intracranial tumours that affect the skull base from above. The latter includes meningiomas, especially when arising within the olfactory groove, craniopharyngiomas and distant metastases of various malignant tumour entities. Non-neoplastic lesions of the anterior skull base comprise a variety of different pathologies, but meningoceles and meningoencephaloceles are the most prominent.

Anterior Skull Base Surgery

With its multitude of important vascular and neural structures in a confined anatomical space, as well as its rather remote location in the centre of the head, the anterior skull base is a challenging area for surgical interventions.

The safe surgical management of patients with anterior skull base pathologies requires a thorough, comprehensive, anatomical, functional, pathological and physiological knowledge of this complex region. Anterior skull base surgery is usually reserved for experienced surgeons and should both be planned and performed by an

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C. S. Betz (✉)
Department of Otorhinolaryngology, University Medical Centre Hamburg-Eppendorf, Hamburg, Germany
e-mail: c.betz@uke.de

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interdisciplinary team (neurosurgeons and otorhinolaryngologic surgeons ± representatives from other specialties such as maxillofacial surgery or orbital surgery). For neoplastic indications, multidisciplinary tumour boards [multidisciplinary teams (MDTs)] with a head and neck or a neurooncological focus might suffice as a proper platform to discuss these cases, but they may miss out on equally challenging non-oncological cases. Regular interdisciplinary skull base meetings of a dedicated skull base team have become the gold standard for the so-called skull base centres in many countries, even though an appropriate international standardization has not yet been undertaken.

A proper and thorough assessment of the cases before surgical treatment is thereby at least as important as the operation itself. The following points need special consideration:

- *Surgery* versus *'watch & scan' or other treatment modalities:* Not all anterior skull base lesions need to be addressed surgically as therapy of choice. For example, some benign neoplastic lesions (e.g. osteomas) can be followed via imaging, and some other lesions (e.g. certain types of sarcomas) might do better with primary conservative treatment measures.
- *Complete resection* vs. *gross total resection or subtotal resection:* The understanding of the targeted surgical resection margin for malignant neoplastic pathologies differs between the neurosurgeon and the otorhinolaryngologist. Whereas the former usually aims at a gross total resection (i.e. no tumour enhancement in postoperative imaging) whilst avoiding the so-called 'eloquent' (functionally important) areas of the brain, the otorhinolaryngologist is generally aiming for a clear resection margin of at least 5 mm in all directions. The aims of gross resection, total clearance or subtotal resection need to be carefully considered during operative planning. The surgical plan will also impact on adjuvant therapy and prognosis in oncological cases.
- *Proximity to vital structures:* Pathological skull base lesions can encroach or lie adjacent to vital anatomical structures, and lesions may surround or invade these structures. The operability of the lesion needs to be carefully considered with regard to the severity of risk, intent to cure, postoperative morbidity and mortality. The most prominent of these structures are the internal carotid arteries, the neurovascular structures of the orbital apex and the brainstem (including the basilar artery and the cranial nerves originating from it).

As for all other operative areas, surgery of the anterior skull base can be broken down into three distinct parts:

– Approach or access
– Tumour resection
– Closure of skull base defect and reconstruction

All of these components need to be considered and discussed in detail prior to surgery, ideally in the dedicated skull base MDT. Operative planning is of paramount importance and inadequate planning cannot always be compensated for at the time of surgery.

Surgery inevitably creates a breach of the barrier between the sterile intracranial and the 'clean-contaminated' (para)nasal space, irrespective of the approach. This results in a considerable risk of infective complications. A suitable prophylactic antibiotic is essential and should be planned before surgery. Cefuroxime or an agent with a similar spectrum is recommended, commencing with induction, and continued preoperatively for up to 24 h following surgery [1].

The following paragraphs describe the traditional open routes to access the skull base, novel endoscopic routes and combined approaches.

Open-Approach Surgery

Approach

Transfacial Approaches

These approaches are often suitable and sufficient for pathologies involving but not extending beyond the anterior skull base.

For benign neoplasms that may involve the anterior skull base, such as juvenile angiofibroma or inverted papilloma (and potentially a small, well-defined group of malignancies), the midfa-

cial degloving approach is advocated as the open approach of choice as it leaves no facial scars. The exposure of the anterior skull base offered by this approach is somewhat inferior to that of the lateral rhinotomy approach, but it is superior with regard to accessibility of the pterygopalatine fossa and the medial aspect of the infratemporal fossa.

For malignancies, a lateral rhinotomy is the preferred transfacial route of access. This approach can be combined with additional incisions, for example:

- An upper lip-split ('Weber-Ferguson' approach) if the lower maxilla is involved
- A supraorbital incision ('Lynch' incision) if the posterior wall of the frontal sinus is involved
- An infraorbital incision ('Dieffenbach' incision) if the infraorbital rim or the zygomatic root is involved

A temporary partial maxillectomy +/- removal of the anterior wall of the frontal sinus is recommended as long as the pathology does not involve the previously mentioned structures. This additional access facilitates wide access to the maxillary, ethmoidal and sphenoidal sinuses, the medial aspects of the orbits and the anterior skull base, extending back to the sphenoid planum. The osteotomies, as well as the extent of bone removal, need to be adapted according to the extent of the individual pathology and lesion.

Craniofacial and Subcranial Approaches

For pathologies that show an intracranial extension beyond the skull base, the so-called craniofacial approach as well as the subcranial approach are standard procedures to gain excellent access to this complex area [3].

The craniofacial approach (Fig. 36.1) combines a transfacial approach for access to the skull base from below with a frontal craniotomy for skull base exposure from above:

– Transfacial approach: usually a Weber-Ferguson incision, some form of maxillectomy and a spheno-ethmoidectomy.
– Frontal craniotomy:
  Incision: usually a bicoronal incision, less common a butterfly incision. The bicoronal incision has several advantages over a butterfly incision, such as avoidance of an obvious facial scar, and improved access for intracranial resection, and excellent access to a large, well-vascularized pericranial flap for reconstruction.
  Dimensions: vertical dimension—glabella to several centimetres above the superior edge of the frontal sinus; horizontal dimension—midpupillary line bilaterally.

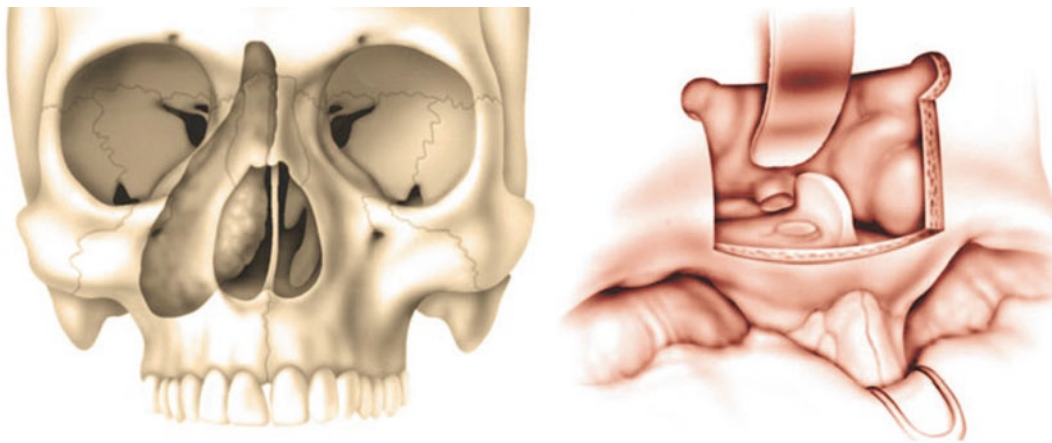

Fig. 36.1 Illustration of the craniofacial approach (left: access to the skull base from below via lateral rhinotomy and partial maxillectomy; right: access to the skull base from above via bicoronal incision and frontal craniotomy). Originally published in [3]; reprint permission granted by Springer

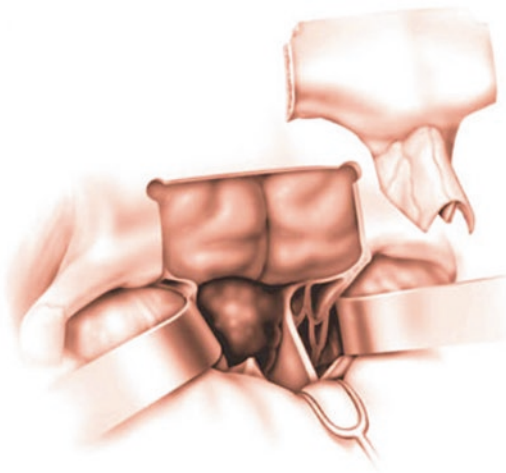

Fig. 36.2 Illustration of the subcranial approach (removal of fronto-naso-orbital bone segment following bicoronal incision). Originally published in [3]; reprint permission granted by Springer

The subcranial approach (Fig. 36.2) was originally described by Raveh as a means of treating anterior skull base fractures [4]. It offers a single access approach providing a simultaneous view of the skull base from above and below. A fronto-naso-orbital bone segment (+/- inclusion of the posterior wall of the frontal sinus) is temporarily removed following careful dissection of the supraorbital bundles and placement of adequate osteotomies. The size of the bone segment is determined individually by the actual disease.

Resection

Following the (sometimes cumbersome) open access to the skull base lesion, curative resection, if possible, is traditionally 'en bloc'. If en-bloc resection is not possible, excision is performed in two or more sections, but special care is taken to orientate each section to enable the pathologist to verify the completeness of resection and tumour margins. For malignant tumours, the safety margin should ideally be 5 mm in all directions.

It is common understanding, however, that the sacrifice of vital and functioning structures (such as eloquent regions of the brain or the optic nerve) in close proximity to the tumour needs to be weighed against the gain in oncological outcome measures such as tumour-specific survival. Histopathology of intraoperative frozen sections of resection margins can be really helpful to ascertain the completeness of resection. However, it can be hindered by (a) selection of specimens and (b) reliability of the reports, especially in pathologies that are difficult to diagnose. For malignant tumours invading or extending beyond the dura, intraoperative dural margin assessment is essential.

Reconstruction

A breach of the dura can lead to potentially life-threatening postoperative complications. The prime objective of all reconstructive measures should be a watertight dural seal, thus re-establishing an effective barrier between the sterile intracranial and the 'clean-contaminated' endonasal space.

The need to reconstruct the supporting tissues of the skull base should be considered but is often unnecessary. On occasions where support seems mandatory, split calvarial bone, bone cement, cartilage, titanium mesh or PDS plates may be used. However, the nasal cavity surface of the graft should always be covered by a soft tissue layer (ideally perfused) to prevent necrosis or infection.

In open transfacial approaches with sole exposure from below, the dural seal is usually accomplished by using a combination of both autologous (e.g. facia lata, nasoseptal flap) and fabricated material in layers, which are applied in both an underlay and an overlay technique. In open craniofacial or subfrontal approaches with good exposure, a watertight dural seal can usually be accomplished via primary closure or by suturing in either artificial (collagen-based) dural replacement material or facia lata, respectively. In larger defects, an additional onlay graft from below (such as a nasoseptal flap) may add to the stability of the closure. In very large defects or recurrent CSF leaks in pre-irradiated patients, free flaps can be used as an ultimate means of closure. In these cases, de-epithelialized radial forearm flaps are most used.

The nasal cavity is loosely packed with nasal tampons for 3–5 days to support the reconstruction from below during the postoperative phase. The author prefers to interpose a layer of gelatin sponge between the packing and the reconstruction to prevent disturbing the repair when the packing is removed.

As for closure of the access of the frontal craniotomy in craniofacial or subfrontal approaches, the preserved, well-vascularized pericranial flap is wrapped around the frontal/fronto-naso-orbital bone segment. The posterior wall of the frontal sinus is removed, thus 'cranializing' the sinus cavity. The bone segment is then reattached to the facial bones with titanium plates.

Postoperatively, the patient should have partial bed rest (toilet visits only) with a 30° elevated upper body, stool softeners and prophylactic antithrombotic treatment. A perioperative lumbar drain is not necessary or recommended in most patients. Postoperative imaging of the head should be considered should neurological symptoms or signs arise.

Endoscopic Approach Surgery

Approach and Resection

There have been tremendous developments with endoscopic techniques and equipment over recent years, such as the extended range of surgical instruments, developments of reconstructive methods specifically designed for transnasal approaches, improvements of navigation assistance and neurophysiological monitoring. Transnasal endoscopic approaches have evolved over the last two decades to become a viable alternative to transnasal microscopic approaches such as pituitary adenoma surgery and to traditional open approaches to the anterior skull base for a selected range of cases.

Transnasal endoscopic approaches of skull base lesions that extend into or beyond the dura:

- are typically performed jointly by a team approach consisting of an otolaryngologist experienced in endoscopic skull base surgery and an endoscopically trained neurosurgeon
- can almost always be subdivided into three distinct phases:
  - Purely endonasal phase, performed by otorhinolaryngologist
  - Interdisciplinary skull base/intracranial phase
  - Transnasal closure, performed by otorhinolaryngologist or interdisciplinary surgeon

The learning curve has been shown to follow quite a shallow curve, and to avoid unwanted outcomes, a stable interdisciplinary team that operates regularly together is recommended. Such a team can then slowly increase the level of complexity of the cases addressed [5].

As the indications for purely transnasal approaches are still somewhat controversial and a matter of debate, it will be much more helpful for the reader to understand the most important contraindications for such a course of action (Table 36.1):

Whilst open approaches offer a wide access that facilitates en bloc resections and conventional techniques of reconstruction, endoscopic approaches typically provide no more than a narrow corridor to the area of concern. They have thus created the need for a true 'rethinking process' of traditional surgical principles.

Similar to transnasal resections of tumours that do not affect the skull base, transnasal endoscopic surgery of skull base tumours inevitably results in 'piecemeal' rather than en-bloc resections. This, however, does not seem to negatively affect oncological outcome measures [6] so long as the most important oncological principles are respected. Margins should be kept to safe limits

Table 36.1 Contraindications to transnasal endoscopic approaches to the skull base

• Invasion of orbital contents requiring orbital exenteration
• Involvement of the skull base lateral to the medial orbital wall (some authors suggest mid-orbit)
• Invasion of the anterior wall of the frontal and/or maxillary sinus
• Invasion of the nasal bones
• Involvement of the facial skin
• Important neurovascular structures (e.g. optic nerve) crossing the path of the chosen corridor

wherever possible and checked by frozen-section margin assessments when appropriate.

The description and classification of the different corridors that are commonly used in transnasal endoscopic skull base surgery today are mostly an achievement of the skull base group at University of Pittsburgh Medical Center (UPMC) [7–9]. They have defined the corridors (Fig. 36.3) as follows:

Sagittal plane: the midline axis from anterior to posterior, which is highly amenable for endoscopic approaches.

Coronal planes (CP): the lateral extensions to both sides which pose much more difficult tasks for the operating surgeons. As this would exceed the scope of this book, the coronal planes are not addressed further in this chapter.

The different approaches in the sagittal plane are thereby termed as follows:

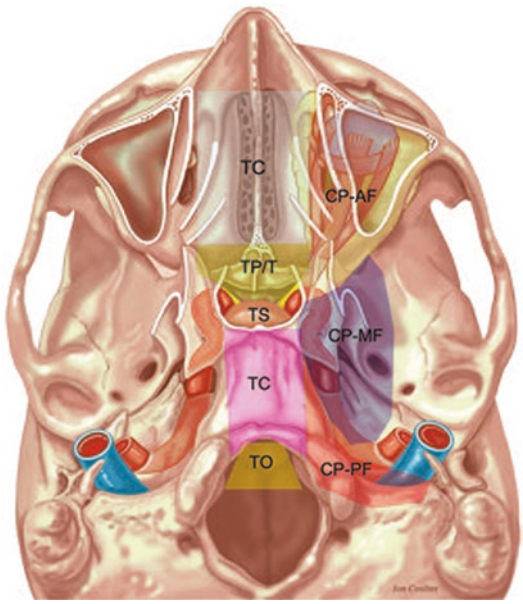

Fig. 36.3 Illustration of the sagittal plane as well as the coronal planes in transnasal endoscopic anterior skull base surgery (*TC* transcribriform, *TP/T* transplanum/transtuberculum, *TS* transsellar, *TC* transclival, *TO* transodontoid, *CP-AF* coronal plane to the anterior cranial fossa, *CP-MF* coronal plane to the middle cranial fossa, *CP-PF* coronal plane to the posterior cranial fossa). Originally published in [10]; reprint permission granted by Rockwater, Inc.

- *Transcribriform (TC):* This approach is mostly used for neoplastic lesions of the nasal cavity and/or paranasal sinuses affecting the anterior skull base with limited lateral extension. Olfactory neuroblastomas might serve as perfect examples of such lesions, as they are usually confined to the midline (Fig. 36.4, Video 36.1). The same might be true for small olfactory groove meningiomas with limited lateral extension. Similarly, benign and malignant tumours of the paranasal sinuses that reside mostly in the midline are rated as ideal candidates for transcribriform endoscopic resection.
- *Transplanum/transtuberculum (TP/T):* This approach is recommendable for the resection of craniopharyngiomas/Rathke cleft cysts, large pituitary macroadenomas with considerable suprasellar extension and a carefully selected subgroup of tuberculum sellae and planum meningiomas.
- *Transsellar (TS):* This approach has become the preferred route for many surgeons for the resection of pituitary adenomas, as the endoscope is superior to the microscope with regard to visualization of the target area (Fig. 36.5), thus minimizing the risk of postoperative pituitary dysfunction [11]. Even though it seems likely that the rate of (gross) total resections should also be higher for the endoscopic approach, this has not been proven to date.
- *Transclival (TC):* This corridor is used for the removal of various pathological entities that lie anterior to the brainstem, with clival chordomas being the most prominent.
- *Transodontoid (TO):* This approach is the most posterior one in the sagittal plane, reaching the craniocervical junction. The most relevant indications for it include bulbomedullary compression caused by basilar invagination or an os odontoideum (odontoid peg displacement) in rheumatoid arthritis.

In contrast to open-access surgery, transnasal skull base surgery is best performed with a special set of equipment including:

- A set of surgical instruments dedicated to transnasal skull base surgery (i.e. longer, finer

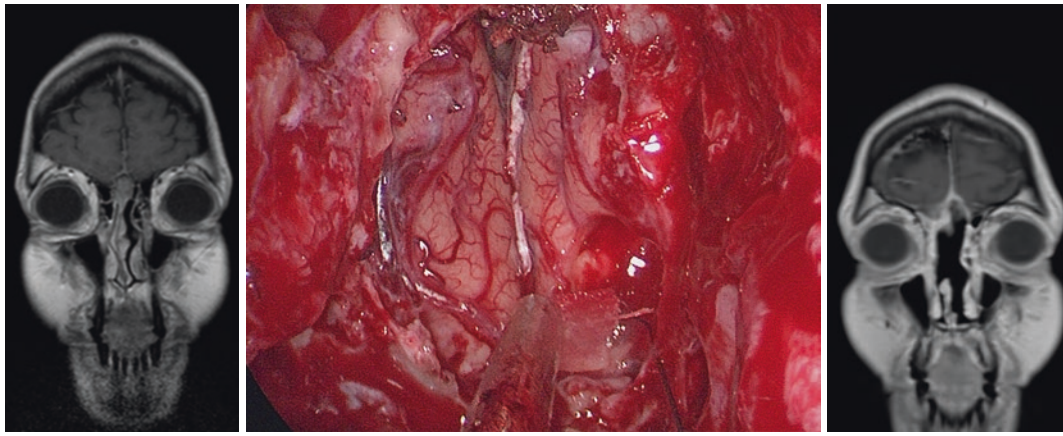

Fig. 36.4 Example of a purely transnasal, endoscopic transcribriform resection of a T3 recurrent olfactory neuroblastoma (left: preoperative MRI, middle: intraoperative image following resection of tumour ((1 Falx, 2 dural margins, 3 frontal lobes, 4 resected olfactory bulbs) right: postoperative MRI)

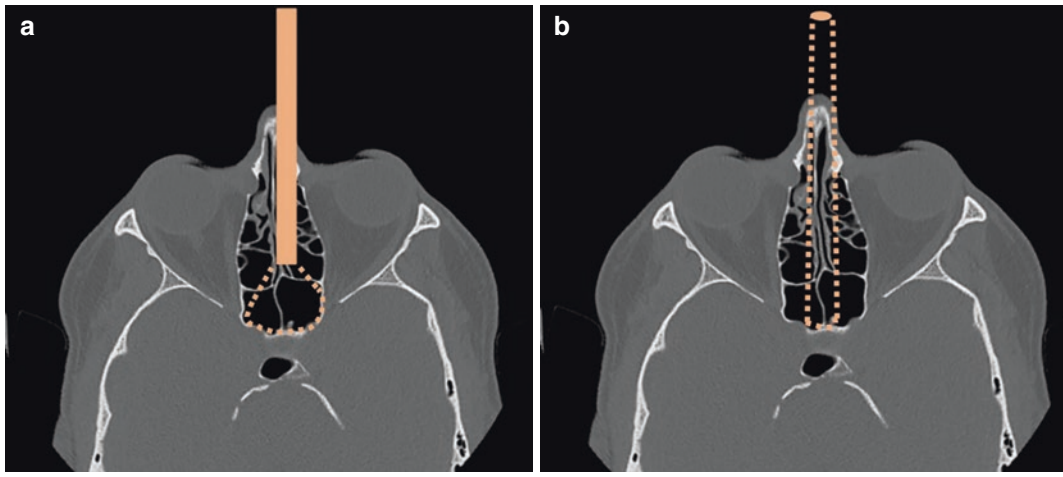

Fig. 36.5 Illustration of the field of view during endoscopic (left) and microscopic visualization (right) of the sellar region

versions of the instruments developed for paranasal sinus surgery and instruments designed especially for transnasal skull base surgery).
- A set of surgical instruments for achieving haemostasis (a transnasal applicator for haemostatic clips, fine bipolar systems that are not hindered by the narrow nasal entrance).
- A transnasal burr (± shaver) system with straight and curved blades and with integrated rinsing and suction.
- A foot-pedal operated saline-wash cleaning system for the endoscopic tip.
- A navigation system (optical or electromagnetical) that allows pre-planning of the procedure and intraoperative guidance.
- A high-resolution endoscopic camera system that allows for a detailed intraoperative visualization.

The surgical procedure itself is highly dependent on the individual features of the lesion that needs to be removed. However, some characteristic steps need to be followed:

- If a nasoseptal flap will/might be needed for reconstruction (please see below), a flap should be raised at the beginning of the surgical procedure and is then placed ('parked') in the nasopharynx for later usage.
- The next stage is to remove, if present, the endonasal portion of the disease whilst maintaining haemostasis and controlling the blood supply relevant to the chosen corridor, such as clipping of the anterior and posterior ethmoidal arteries bilaterally in a transcribriform approach.
- Depending on the location and size of the lesion that needs to be addressed, the procedure may require a bi-nostril approach; to achieve this, parts of the (remaining) septum are resected and sacrificed. This is followed by surgical definition of the borders for resection of the bony skull base. For example, during a transcribriform resection, the anterior border is the transition zone between the posterior wall of the frontal sinus and the cribriform plate (visualized by performing a Draf Type III procedure), the lateral borders are the foveae ethmoidalis (visualized by a radical total ethmoidectomy), and the posterior border is the transition zone of the cribriform plate and the sphenoid plate (visualized by a complete removal of the anterior wall of the sphenoid sinus). The bony skull base defined by these borders is then carefully removed using a coarse diamond burr, and the dura is visualized.
- For lesions that do not extend into or beyond the dura, the bony skull base (including rest of the lesion) is carefully removed followed by a reconstruction (see below).
- For all other lesions, the procedure now becomes a truly interdisciplinary one, and it is further performed using a three- or even four-hand technique. This means that the endoscope (± a tool for suction) is held by the one surgeon, whereas the other proceeds with the bimanual resection. Following dural incisions around the lesion, the intradural part of the procedure ensues, which is again highly individualized. It encompasses the (frozen section proven) resection of all intracranial disease whilst at best preserving vessels and brain tissue.

Reconstruction

As for open approaches, a watertight dural seal also needs to be accomplished in transnasal skull base surgery, whilst the placement of supporting tissue is usually not needed.

In those cases when the dura is exposed but not incised, or where areas of dehiscence are very limited, artificial material such as Tachosil® (Corza Health, Inc.) applied in an overlay technique in layers might suffice.

For all cases where a dural resection has taken place, the nasoseptal flap [12] has become the 'work-horse' for reconstruction in most centres. The nasoseptal flap, as well as other, less commonly used vascularized flaps, is placed as a component part of a multi-layer closure that may, for example, include a fascia lata as an underlay graft, Tachosil® (Corza Health, Inc.) as an overlay graft and the nasoseptal flap as an onlay graft. The principle of multilayer closure has significantly reduced the rate of postoperative CSF leaks in transnasal skull base surgery, achieving leak-free closure to a level comparable to open-approach surgery [13].

Fat tissue or fascia lata alone or in combination might suffice for a selected group of cases in the clival and sella region.

Following reconstruction, the nasal cavity is packed for 3–5 days according to the recommendation given in open-approach surgery. Special care is undertaken to assure that the reconstruction is neither disrupted or displaced during packing nor compressed to a degree that compromises the perfusion of the vascularized flap.

Postoperative recommendations are similar to those for open-approach surgery.

Should there be a high risk of a postoperative CSF leak, as may occur in patients with an intraoperative 'high-flow' leak, a postoperative lumbar drain is recommended. The lumber drain should be set with a flow of 10 mL/h for 72 h. This has been shown to reduce the rate of CSF leaks significantly in a prospective randomized trial [14].

Combined Approach Surgery

Over the last decade, combined approaches (open and transnasal) have become increasingly more

popular amongst skull base surgeons and may sometimes be considered the best option for a case. For example, tumours of the skull base with an extension both intracranially and beyond the medial orbital wall may qualify for a combination of a craniotomy approach (for a resection of the supraorbital and the intracranial part) and an endoscopic approach (for the resection of the endonasal parts).

Summary of Areas of Controversy or Uncertainty

Due to the complex preconditions in a challenging anatomical area and the multitude of different pathologies that need to be addressed, anterior skull base surgery is a relatively new field that is still undergoing constant development. As with many surgical fields, high-level evidence is missing for almost all of the burning questions with regard to decision-making and best practice.

Key Learning Points

- The anterior skull base can be surgically addressed:
  - Via open approaches
  - Via endoscopic approaches
  - Via combined approaches
- Due to its complexity, anterior skull base surgery (including treatment planning) should be performed in dedicated skull base centres only.
- If the 'dural seal' is opened or dura is resected during surgery, the defect must be closed in a watertight fashion to prevent postoperative complications.
- The decision whether to choose an open, an endoscopic or a combined approach is dependent on many factors as well as the individual patient. These can be con-

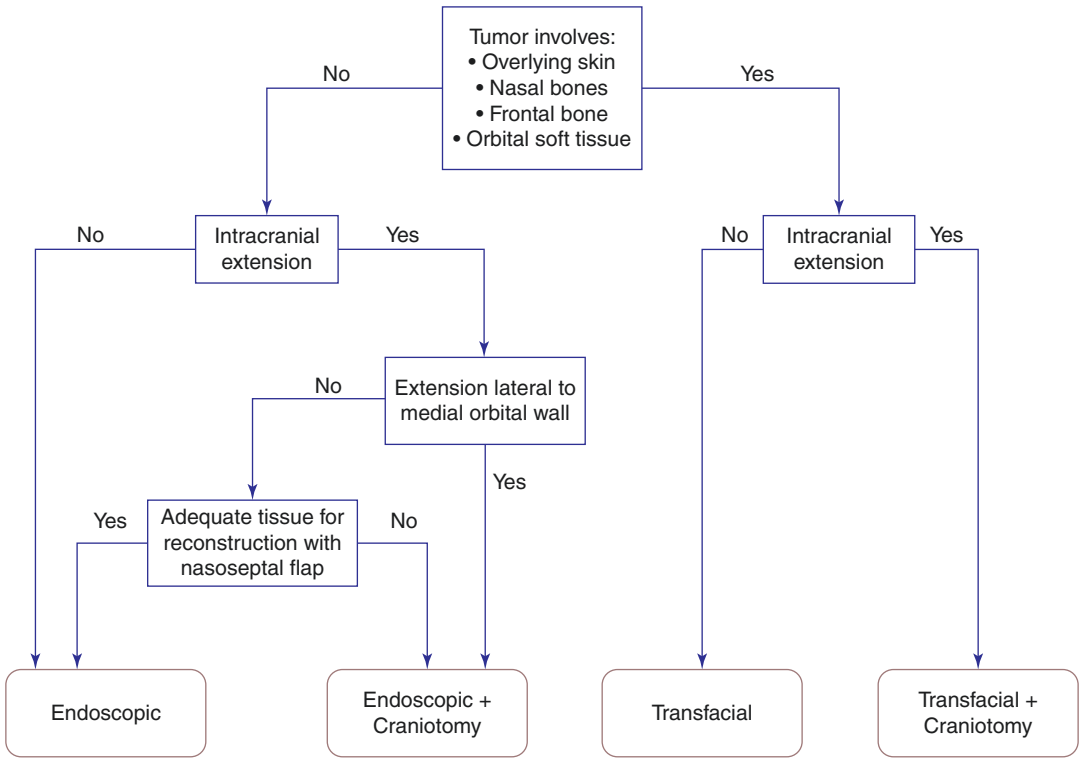

Fig. 36.6 Algorithm for the surgical approach to the anterior skull base. Originally published in [15]; reprint permission granted by Georg Thieme Verlag KG

sidered as 'intrinsic' factors, such as the location and extension of lesion, and 'extrinsic' factors that include the expertise of the local surgical team, having the correct instruments and technology available and the backup facilities to manage potential complications.

- In clinical reality, the chosen approach—more often than not—has to be adapted to the individual case.

Nevertheless, both the clinical and the scientific interest in this topic are enormous, and more controlled trials investigating those questions are currently being performed or planned.

One of the most important questions with regard to anterior skull base surgery that has not been sufficiently answered yet is how to decide on an open, endoscopic or combined approach. Apart from personal/the centre's amount of experience with each approach as well as the equipment available, the size, location and histopathological entity of a lesion should guide this decision. Figure 36.6 provides an excellent algorithm for decision-making with respect to current knowledge.

The existing knowledge on anterior skull base surgery by far exceeds the scope of this chapter. For further reading (especially on decision-making), current consensus statements of international organizations are recommended [16, 17]. In order to improve one's personal surgical skills, the formation of a dedicated skull base team as well as a participation in one or more skull base courses is mandatory.

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37 Transorbital Endoscopic Surgery of the Paranasal Sinuses and Skull Base

Darlene Lubbe and Nicholas Goncalves

Introduction

Gentle displacement of the orbit allows for the creation of surgical portals between the bony walls of the orbit and periorbital fascia. An endoscope and instruments can be passed through these greater than 1-cm-wide portals to access pathology within the orbit or its four walls. By breaching the orbit's bony boundaries, the sinuses and difficult-to-reach skull base spaces can be accessed through a minimally invasive transorbital approach (Fig. 37.1).

Since Kris Moe popularized this technique in 2010, numerous advances in instrumentation and closer interdisciplinary cooperation have led to transorbital surgery being performed regularly and safely in many skull base units across the world. A multidisciplinary approach is required, starting with a discussion between the otolaryngologist, ophthalmologist and neurosurgeon. A decision is made on the best surgical approach and which team members should be involved at which stage of the surgery. If the periorbital fascia is breached to address a lesion within the orbit itself, an ophthalmologist should always be involved. Similarly, when the dura is breached to address an intracranial lesion, a neurosurgeon should form part of the surgical team.

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D. Lubbe (✉) · N. Goncalves
Division of Otolaryngology, Groote Schuur Hospital, University of Cape Town, Cape Town, South Africa
e-mail: darlene.lubbe@uct.ac.za

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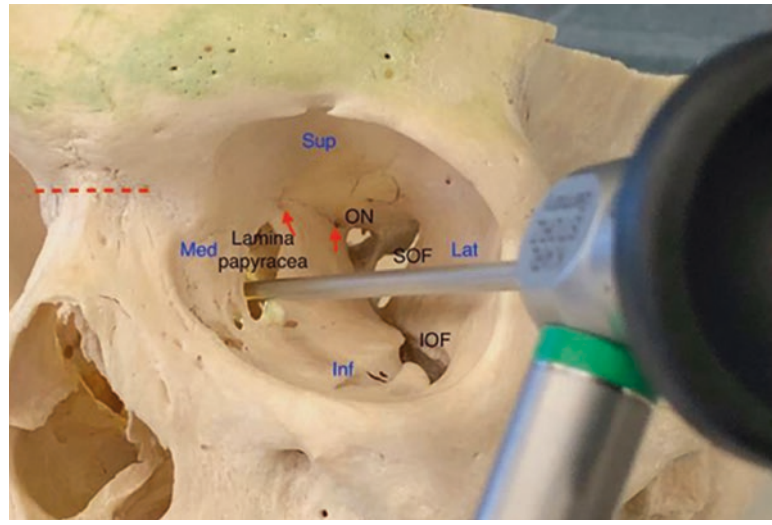

Fig. 37.1 Orbital osteology; the four walls of the bony orbit can be breached to reach skull base spaces. The endoscope is passed through the lamina papyracea (medial wall) to the ipsilateral ethmoids and contralateral sphenoid sinus. Nasion (red interrupted line) lies at the same level as the anterior ethmoidal artery (AEA) and the posterior ethmoidal artery (PEA) (red arrows). Key: *ON* Optic nerve, *SOF* Superior orbital fissure, *IOF* Inferior orbital fissure

Rationale for Transorbital Surgery

Whilst endoscopic endonasal surgery allows access to all the paranasal sinuses, medial orbit, pterygopalatine and infratemporal fossa, midline anterior skull base structures from cribriform area to pituitary fossa and beyond, certain areas are best accessed with a minimally invasive transorbital approach [1–3].

Certain open procedures can be replaced with a transorbital approach, e.g. the Lynch-Howarth incision for accessing the ethmoidal arteries. The precaruncular approach has the advantage of leaving no external scar and provides quick direct access to the vessels without traumatizing the orbicularis muscle or surrounding neurovascular structures.

Transorbital surgery allows access to all paranasal sinuses and is a useful adjunct to addressing lesions that cross surgical boundaries. Each orbit has four surgical portals and together with the two nasal corridors, multiportal surgery is possible using any of the ten portals in various combinations (Fig. 37.2). This allows different trajectories to the target area—not only for visualization with a zero-degree endoscope but also for manipulating instruments at different angles. Thus, a tumour of the maxillary sinus invading the orbital floor, inferior orbital structures and extending along the infraorbital nerve would be eminently accessible with these approaches. Multiportal surgery utilizing an inferior orbital portal together with an endonasal approach allows for resection of such lesions. It is important to remember that oncologic principles should always be followed, regardless of the surgical approach.

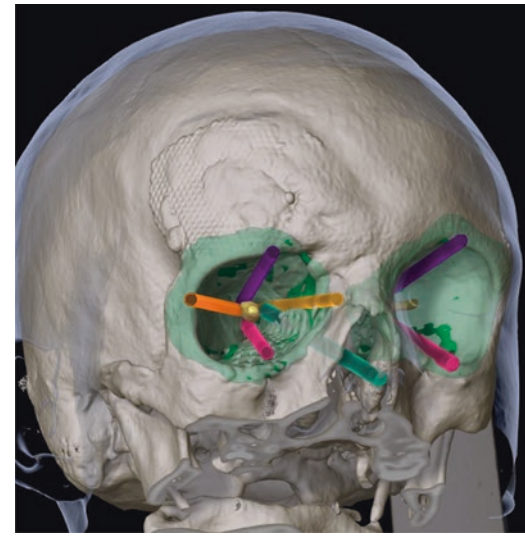

Fig. 37.2 Each orbit has four transorbital portals, and together with the two nasal portals, the ten portals can be used in various combinations

Indications for the Otolaryngologist

The key approaches are as follows:

1. Superior-lateral portal
2. Medial portal
3. Inferior portal

Superior-Lateral Portal

It can be difficult to access the lateral aspect of a well-pneumatized frontal sinus using a purely endonasal approach. A modified endoscopic Lothrop/Draf procedure may allow for good visualization of the lateral aspect of a well-pneumatized frontal sinus, but often an angled endoscope is required. In these cases, even a 70° Lothrop drill burr may not reach the lateral wall of the frontal sinus to remove bone infiltrated by an inverting papilloma for instance. Another external surgical approach is often needed to ensure complete clearance. The superior orbital approach is useful in these cases. The only advantage over the eyebrow approach is cosmesis, and either approach could be used as part of multiportal surgery.

The superior-lateral incision is favoured where wide access is required to the orbital roof, superior orbit, frontal sinuses and anterior cranial fossa (lateral to cribriform plate). An extradural empyema secondary to a frontal sinusitis can be safely drained through a transorbital approach, avoiding a craniotomy.

The author prefers the extended eye crease incision in most instances since it allows for better inferior and medial retraction of the orbital contents. Where pathology is limited to the superior orbit, anterior cranial fossa or medial aspect of the frontal sinus, the incision does not have to extend beyond the lateral canthus of the eye.

The extended superior eyelid crease incision (Fig. 37.3) spares the lateral canthus and allows for minimal morbidity and increased patient comfort. This extended incision is required to access the lateral portal to address lesions of the lateral aspect of the eye itself (e.g. cavernous haemangioma, pseudotumours), lateral orbital wall (e.g. in thyroid eye disease for lateral decompression) and infratemporal fossa (angiofibroma) and during sphenoid wing meningioma surgery where the middle cranial fossa is exposed (Fig. 37.4 and 37.5). The superior and inferior orbital fissure can be accessed through this portal and typically forms the limit of the dissection in patients with normal neurological function (CNs III, IV, V_1, VI).

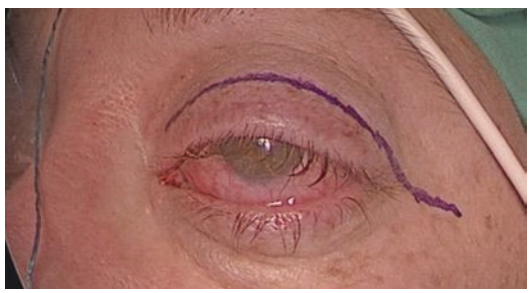

Fig. 37.3 Extended superior eyelid crease incision of the left eye

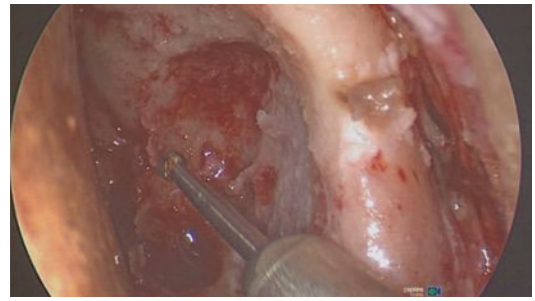

Fig. 37.4 Left orbital portal with temporalis muscle exposed laterally and greater wing of sphenoid drilled away

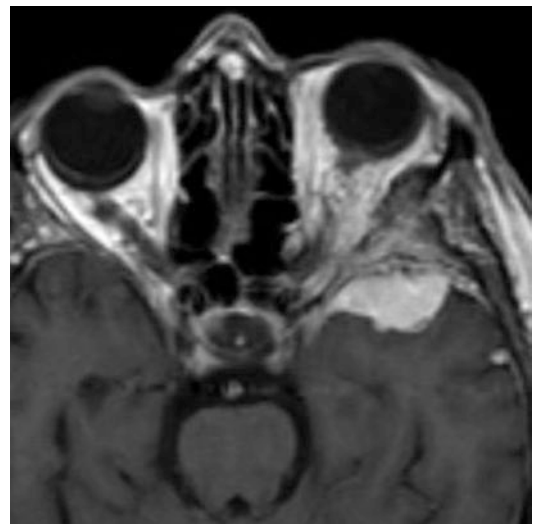

Fig. 37.5 Sphenoid wing meningioma infiltrating the middle cranial fossa, lateral orbital wall and orbit itself

Medial Portal

The medial portal is ideal for accessing the anterior ethmoidal artery (AEA) and posterior ethmoidal artery (PEA). These arteries often need ligation in patients with epistaxis secondary to a nasoethmoid fracture or to assist with haemosta-

sis during tumour surgery. The optic nerve can be found 6 mm posterior to the posterior ethmoidal artery and great care must be taken to ensure that the optic nerve is not damaged during bipolar cautery to the vessels. It is important to note that the posterior ethmoidal artery can be absent or that there may be accessory ethmoidal vessels. In the event of a traumatic optic nerve injury, the medial portal gives good access to the medial optic canal if a bony spicule requires removal or if an optic nerve decompression is required.

Together with an ophthalmologist, medial orbital tumours can easily be accessed through this route. Both intra- and extraconal lesions can be resected through a precaruncular approach. A standard transnasal approach is often used to resect medially located orbital cavernous haemangiomas, but this approach requires extensive resection of normal sinuses, removal of the lamina papyracea, breach of periorbita and mobilization of the medial rectus muscle. The precaruncular approach avoids this extensive dissection of normal tissues and obviates the need for reconstruction since the lamina papyracea is left intact.

The ipsilateral sphenoid sinus can quickly be entered using the medial corridor. This is useful in cases where an optic nerve decompression is performed using a multiportal approach (endonasal and precaruncular).

The contralateral sphenoid can also be entered by breaching the lamina papyracea, performing an ethmoidectomy and posterior septectomy, thus facilitating a direct view of the lateral wall of a well-pneumatized contralateral sphenoid sinus. This approach is especially useful in patients with spontaneous cerebrospinal fluid leaks secondary to a Sternberg canal defect. The huge advantage of this approach is that it offers a direct view of the lesion, the ability to use a zero-degree endoscope and standard straight FESS instruments to repair the defect.

The anterior cranial fossa can be entered via the medial orbital wall superior to the frontoethmoidal suture line. The AEA and PEA are excellent landmarks as they run within this suture line. The approach facilitates repair of cerebrospinal fluid leaks, utilizing standard techniques of fat plugging with an underlay fascia or cartilage graft. This transorbital approach to the anterior cranial fossa requires further clinical investigation and studies.

The precaruncular approach is very useful during optic nerve decompression, especially where patients have had a previous medial orbital decompression or where significant proptosis is present. Combining the precaruncular approach with an endonasal approach has some advantages over using a one- or two-nostril endonasal approach. Firstly, a malleable retractor can be placed through the medial portal to retract the orbital contents, especially if fat is herniating into the ethmoidal cells. Extensive herniation of orbital fat makes it difficult to perform optic nerve decompression, especially in patients who have had previous orbital decompressions, even when using the contralateral nostril. Retraction of the fat via the precaruncular portal facilitates good visualization of the optic canal, using either ipsilateral or contralateral endonasal approaches.

The second advantage of using the medial portal is it obviates the need for doing a posterior septectomy in order to get more instruments at the target site using the binostril approach. The precaruncular approach can be combined with an ipsilateral endonasal approach, thereby preserving the nasal septum.

Inferior Portal

The inferior conjunctival incision allows for access to the floor of the orbit, the inferior orbital fissure and the infraorbital nerve and for lesions of the orbit itself. Using the endoscope through this portal allows for direct visualization and repair of blowout fractures. For smaller fractures, plating can be avoided by inserting septal cartilage over the defect. Entrapped muscles can be released under direct vision.

This route allows for reconstruction/elevation of the orbital floor patients with imploded maxillary sinuses/silent sinus syndrome, once a middle meatal antrostomy has been performed.

Transorbital Surgery: Surface Anatomy

Superior and Lateral Orbital Portals

An extended superior eyelid crease approach is used to gain access to the superior and lateral

orbital portals. The levator palpebrae superioris muscle attaches to the tarsal plate to form the upper eyelid crease. The surgical incision is made in the crease, allowing for a cosmetically acceptable hidden scar (Fig. 37.3). The incision transects the skin and orbicularis muscle so that the dissection is carried out in a sub-orbicularis plane, staying superficial to the orbital septum and the aponeurosis of the levator muscle as it attaches to the upper tarsal plate (Figs. 37.6 and 37.7).

Dissection is aimed superiorly until the periosteum of the superior orbital rim is reached. Dissection then continues in a subperiosteal plane. Care must be taken not to apply excessive traction superiorly as it may injure the levator aponeurosis and result in an aponeurotic ptosis.

The lateral portal is bound by the orbit contents medially and lateral orbital wall laterally. The lateral canthus is where the upper and lower eyelids converge laterally. The lateral canthal tendon is composed of fibrous tissue from the upper and lower tarsi and the common tendon known as Whitnall's ligament, which inserts onto a bony protuberance on the lateral orbital wall. During the lateral approach, it is important to dissect in the subperiosteal plane as not to damage the lateral canthal tendon. In addition, the periosteum must be sutured back into place to preserve the angle and height of the lateral canthus. The function of the lateral canthus is to direct tears towards the medial canthus and lacrimal canaliculi. If the lateral canthal tendon is damaged, it may result in lateral ectropion, which may cause pooling of tears and epiphora.

The recurrent branch of the middle meningeal artery (MMA) (also referred to in the literature as the meningolacrimal artery/orbital branch of the middle meningeal artery/sphenoidal artery) enters the lateral orbit through the meningo-orbital foramen (sometimes referred to as Hyrtl canal) [4] (Figs. 37.8, 37.9 and 37.10). This artery is a constant landmark when using the lateral portal and helps to identify the superior orbital fissure (SOF) that lies approximately 1 cm posterior to the artery as it exits the canal in the superior-lateral orbit (Fig. 37.8) [3].

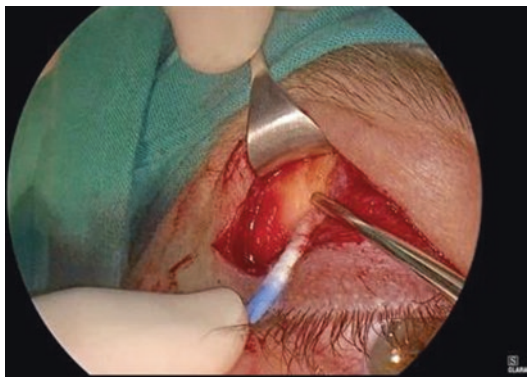

Fig. 37.6 Dissection in the sub-orbicularis plane and exposure of periosteum in a right eye

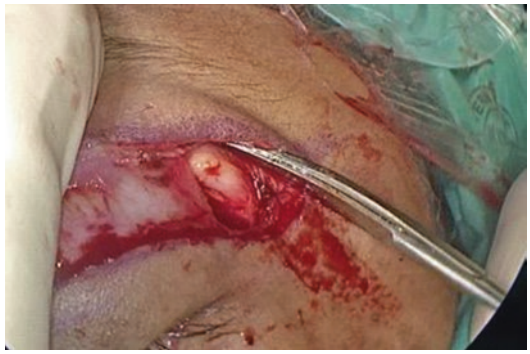

Fig. 37.7 Left superior eyelid approach with rim exposed

Fig. 37.8 Left orbit with arrow pointing to the meningo-orbital foramen on the lateral orbital wall where the recurrent branch of the middle meningeal artery (MMA) exits

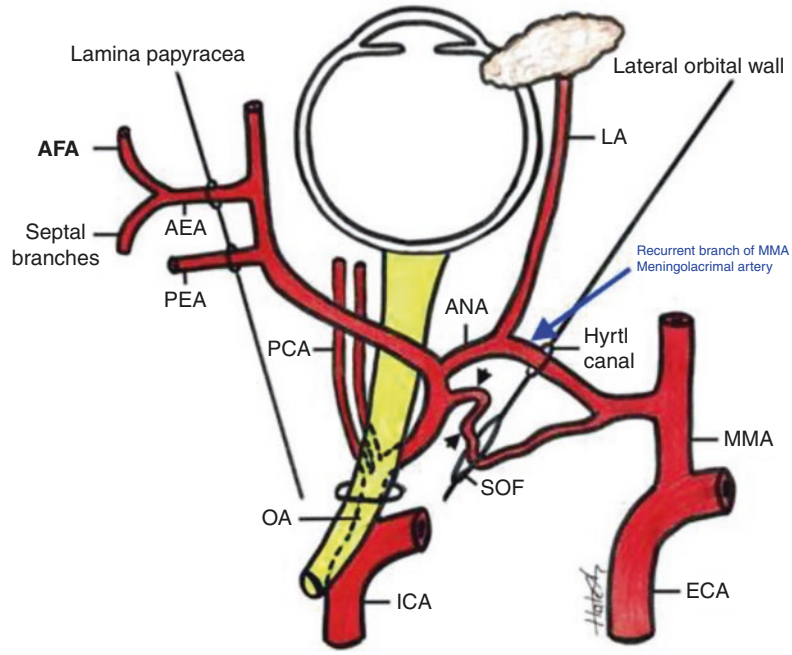

Fig. 37.9 Blue arrow showing the recurrent branch of the middle meningeal artery (MMA) exiting through the meningo-orbital foramen (Hyrtl canal) in the lateral orbital wall, 1 cm anterior to the superior orbital fissure (SOF). Key: *ECA* External carotid artery, *MMA* Middle meningeal artery, *LA* Lacrimal artery, *ANA* anastomotic branch, *ICA* Internal carotid artery, *OA* Ophthalmic artery, *PCA* posterior ciliary arteries, *PEA* Posterior ethmoidal artery, *AEA* anterior ethmoidal artery, *AFA* anterior falx artery

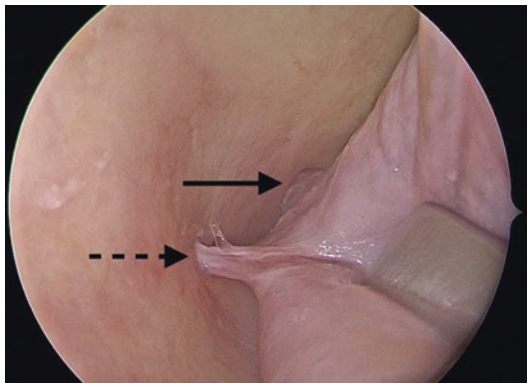

Fig. 37.10 Recurrent branch of right middle meningeal artery (MMA)/meningolacrimal artery (broken arrow). Note this artery lies 1 cm anterior to the lateral superior orbital fissure (SOF) (solid arrow)

Excessive traction on the orbit medially may potentially result in a superior orbital fissure syndrome with functional impairment of cranial nerves III, IV, V_1 and VI.

Medial Orbital Portal

The medial orbital portal is a potential space between the medial periorbital fascia and medial orbital wall. The medial wall is comprised of ethmoid bone (lamina papyracea), lesser wing of the sphenoid, lacrimal bone and frontal process of the maxilla. Posteriorly the medial orbital portal ends at the optic nerve foramen (Fig. 37.1). In order to gain surgical access to the medial portal, the lacrimal caruncle and medial canthus must be identified. The lacrimal caruncle is a mucosal structure located at the medial palpebral commissure occupying the lacus lacrimalis (triangular space of conjunctiva at the medial aspect of the eye).

Approaches to the medial orbital portal include the precaruncular or transcaruncular approach. The medial canthus is made up of tendon attachments to the orbicularis oculi muscle and tarsus. It attaches to the anterior lacrimal crest on the frontal process of the maxilla.

Horner's muscle (more recently termed Horner-Duverney muscle) is a historical term that refers to deeper fibres of the lacrimal portion of orbicularis oculi that attach the tarsus to the posterior lacrimal crest.

It is important to identify the superior and inferior canaliculus of the lacrimal system as it lies superficial to the plane of dissection when accessing the medial orbital portal. It is recom-

mended for the novice to probe the lacrimal system prior to dissection of the pre- or transcaruncular approach to the medial orbital portal. Once the medial portal has been accessed and periosteum of the medial orbital wall elevated, the first structure identified is the anterior ethmoidal artery (AEA) and anterior ethmoidal nerve. The traditional 24:12:6 rule for identifying the AEA, PEA and optic nerve, i.e. the AEA lies 24 mm posterior to the anterior lacrimal crest, the PEA lies 12 mm posterior to the AEA and the optic nerve lies 6 mm posterior to the PEA, has little clinical relevance intraoperatively during the medial approach until the AEA is reached. This is because intraoperatively the anterior lacrimal crest is not dissected or identified in order to preserve the lacrimal sac. In addition, the frontoethmoidal suture line is not a reliable landmark to identify these structures as it has been found to only be clearly visible in up to 50% of cases [5]. Instead, the level of the nasion that corresponds with the level of the base of skull can be used as a guide to identify the level of the AEA and PEA during the precaruncular approach (Fig. 37.1).

Inferior Portal

The inferior orbital portal accesses the area between the eye and the orbital floor or roof of the maxillary sinus. The orbital septum merges with the capsulopalpebral fascia, which is formed from the fibres of the inferior rectus muscle, to attach to the lower end of the tarsal plate. The tarsal plate of the lower eyelid is shorter than its superior counterpart by an average of 4 mm. A lower eyelid transconjunctival approach is used to gain access. The approach may be preseptal or postseptal, with the preseptal being more favourable as it avoids herniation of fat into the surgical field. Care is taken to remain in the subperiosteal plane to avoid injuring the inferior oblique muscle that arises just lateral to the lacrimal groove in the anterior margin of the floor of the orbit.

Preoperative Planning

A multidisciplinary approach is essential with all cases being discussed between specialties to ensure the best approach is chosen. The best approach will be the one giving best access to the lesion for complete resection and the most direct approach to the target area without causing collateral tissue damage to normal uninvolved structures. It is important to have a full visual assessment - visual acuity, fundoscopy, intraorbital pressure and proptosis measurement prior to transorbital surgery.

Imaging will often include CT and MRI of the orbits depending on the pathology.

Contraindications to surgery need to be excluded and patients need to be warned against using aspirin or other anticoagulants prior to surgery. Image guidance is often useful although not essential. Electromagnetic navigation is preferred to avoid line of sight issues.

Contraindications

In general, intraocular surgery within a 6-month period is a relative contraindication as it may increase the risk of wound rupture during retraction of the globe. Other relative contraindications include corneal ectasia, glaucoma, shallow orbit, single-eye patients and a previous retinal or optic nerve vascular event.

Absolute contraindications include intraocular surgery within 6 weeks (high risk of wound dehiscence), advanced glaucoma, severe corneal ectasia, scleromalacia and ocular ischemic syndrome.

Acute infective conditions such as acute dacryocystitis or conjunctivitis need to be treated prior to transorbital surgery. The risks with ocular pathology need to be weighed against the benefits of transorbital surgery in each individual patient. Consultation with an ophthalmologist is essential if concurrent ocular pathology exits prior to transorbital surgery.

Surgical Technique and Tips

Intraoperative Preparation

The positioning of the patient is the same for all four approaches, and similar to standard endoscopic sinus surgery, with the head slightly flexed and turned towards the surgeon. The only exception is frontal sinus pathology when the head needs to be extended as for a modified Lothrop operation to get the correct angle to access the frontal sinus.

TIVA is recommended since multiportal surgery is often combined with the endonasal route.

After the patient is draped, local anaesthesia is administered (lidocaine hydrochloride 2% and adrenaline 1:80000) into the incision site. It is useful to use a marking pen to delineate the superior eyelid crease prior to infiltration.

The eyes should be lubricated throughout the procedure and the pupils need to be observed, especially during retraction of the orbit. The pupil can change shape and size from increased intraorbital pressure or traction on neurovascular structures, and retraction by the malleable retractor should then be relaxed for a few seconds until the pupil returns to normal.

The surgeon normally stands to the right of the patient (as with FESS) for the superior-lateral and medial approach and at the head of the patient (as for tonsillectomy) for the inferior approach. However, during the initial incision, it can be easier to stand on the same side as the eye being operated on, but once the endoscope is used within the corridor, it is easier to operate on the right side of the patient.

Surgical Instruments

Essential instruments include the following, in the order in which they will be required:

- Dental syringe for injecting local anaesthetic
- Sharp-tipped curved iris scissors
- Fine-tipped forceps
- Malleable retractors—sizes 8, 10, 12 and 15 mm diameter
- Suction elevator, Freer elevator and Cottle elevator
- Standard FESS set
- High-speed endonasal drill with short-shafted burrs (to prevent shaft catching orbital fat and muscle)

Surgical Steps and Tips

Superior Lateral Portal

Using loupes, the natural superior eyelid crease is identified approximately 6 mm above the superior eyelid margin, marked and infiltration applied to assist with haemostasis. A no. 15 surgical scalpel blade is used to cut through the skin and the thin orbicularis oculi muscle. Dissection is continued superiorly, staying just deep to the orbicularis muscle and superficial to the orbital septum. The septum must not be breached for this will put the levator palpebrae muscle at risk and cause orbital fat to herniate into the surgical field. Once the superior orbital rim is reached, the periosteum is incised just inferior and posterior to the orbital rim. Subperiosteal dissection continues using a Freer elevator, and depending on the target area, the surgical portal is enlarged to expose the necessary area. In the superior medial orbital rim, the supratrochlear and supraorbital nerves will be identified and must be preserved by mobilizing the nerves out of their bony canal or foramen if indicated (Fig. 37.11). The whole orbital roof will be visible and can be removed for access to the anterior cranial fossa. The optic nerve can be found at the orbital apex.

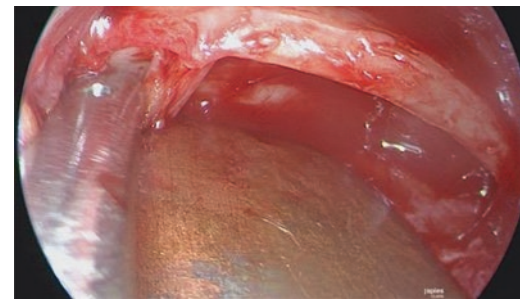

Fig. 37.11 Supratrochlear nerve exposed during superior transorbital approach in the left eye

If lateral access is required for a lateral orbital decompression or to gain access to the temporal fossa, superior orbital fissure or middle cranial fossa, the extended superior eyelid incision is made. This incision continues laterally from the eyelid crease incision within a natural crease to spare the lateral canthus of the eye. A Colorado microdissection needle can be used to cut through the orbicularis muscle onto the bone just lateral to the orbital rim. The periosteum is incised and elevated in a lateral to medial direction over the rim of the orbit. This ensures a subperiosteal dissection and elevation of the ligaments that attach to Whitnall's tubercle (described in 4.1). The first neurovascular structure encountered laterally is the recurrent branch of the middle meningeal artery. This structure can be cauterized using bipolar forceps. The superior orbital fissure can be found just 1 cm posterior to this vessel.

A decision to resect the lateral wall of the orbit is dependent on the pathology to be addressed. A bony margin of at least 5 mm of lateral orbital rim should be preserved.

The temporalis muscle can be exposed anterior laterally and the middle cranial fossa dura more posteriorly as bone is drilled away up to the lateral superior orbital fissure.

Care must be taken not to cause a cerebrospinal (CSF) leak posteriorly (middle cranial fossa) or superiorly (anterior cranial fossa dura). Any CSF leak can be closed using fat harvested from the abdomen or upper thigh with or without fascia lata as an underlay graft.

It is important to suture the periosteum of the superior orbital rim to prevent ptosis and the lateral orbital periosteum to replace the ligaments attaching to Whitnall's tubercle.

Medial Portal

The caruncle is retracted laterally, and the iris scissors used to cut through the caruncle or between the caruncle and skin (Figs. 37.12 and 37.13). The lacrimal system lies superficial to the dissection so a transcaruncular incision may be safer for those not familiar with dacryocystorhinostomy. Lacrimal probes can be inserted into the canaliculi to prevent damage to the lacrimal system. The tip of the iris scissors is aimed at the medial orbital wall bone at the level of the nasion or just below (Fig. 37.1). The nasion is the landmark for finding the height of the AEA, and care must be taken not to breach the surrounding bone: A breach below this level, through the lamina papyracea, will lead directly to the ethmoids; a breach above the AEA will open the anterior cranial fossa and cause a CSF leak (Figs. 37.1 and 37.14).

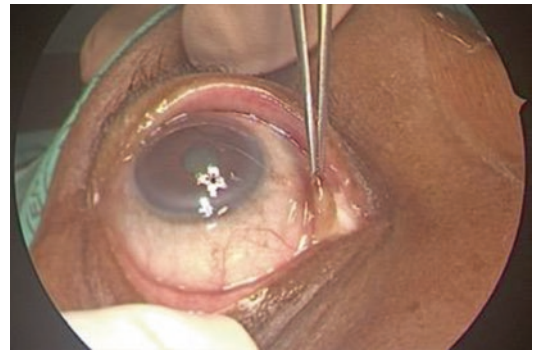

Fig. 37.12 Right eye, forceps retracting caruncle laterally in preparation for transcaruncular or precaruncular incision

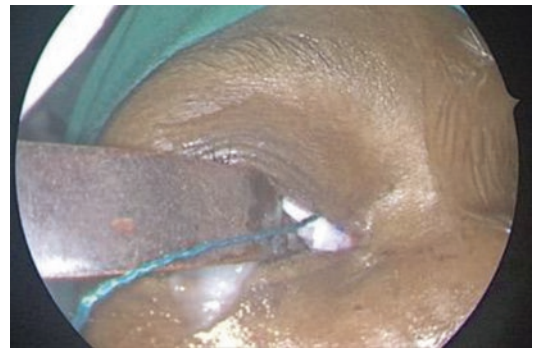

Fig. 37.13 Right eye, malleable retractor in precaruncular corridor for anterior ethmoidal artery (AEA) ligation

Once the bone is reached, a suction Freer is used to dissect in a subperiosteal plane, staying at the level of the nasion. The AEA can be cauterized using bipolar forceps or a ligaclip can be applied. The PEA can be found 12 mm posterior to the AEA and the optic nerve 6 mm posterior to the PEA. Depending on the pathology to be addressed, the lamina can be removed to enter the ethmoids or the sphenoid can be entered below the level of the PEA and optic nerve. Good access

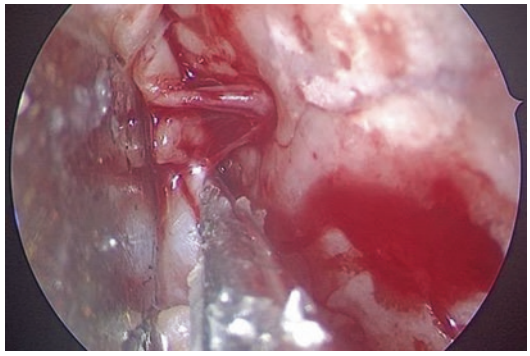

Fig. 37.14 Anterior ethmoidal artery (AEA) in the right eye in frontoethmoidal suture line, which is in line with the nasion

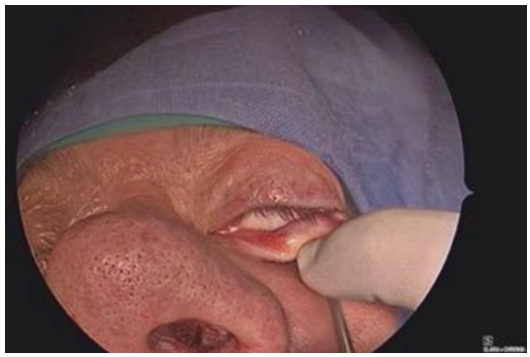

Fig. 37.15 A transconjunctival incision is made at least 2 mm inferior to the tarsus

is provided to the medial orbit for intraconal and extraconal lesions such as cavernous haemangiomas. The precaruncular incision does not require closure. Chloromycetin ointment is placed in the medial canthus postoperatively.

Inferior Portal

Standing at the head of the patient, a transconjunctival incision is made at least 2 mm inferior to the tarsus (Fig. 37.15). The incision is directed to the inferior orbital rim and can then be extended medially or laterally depending on the indication for the surgery. A subperiosteal dissection must be carried out to avoid damaging the inferior oblique muscle that originates at the medial aspect of the orbital rim (Fig. 37.16). The inferior orbital fissure forms the lateral limit, and medially the dissection can extend to the medial orbital wall/lamina papyracea.

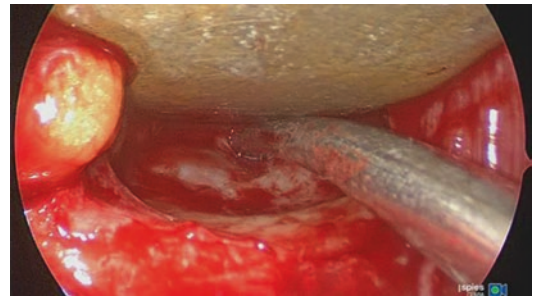

Fig. 37.16 Left orbital floor exposed using inferior transconjunctival approach

The infraorbital nerve is found in the floor of the orbit and is usually covered by a layer of bone. The orbital floor can be resected, inferior orbital tumours removed or the infraorbital nerve followed back in malignant pathologies, according to the pathology that needs to be addressed.

The floor can be reconstructed with cartilage or polydioxanone sheeting for small defects and preformed bare titanium implants covered with 0.25-mm polydioxanone sheeting for larger defects. It is usually not necessary to close the incision. A temporary tarsorrhaphy suture can be placed in patients with chemosis.

Postoperative Management

Specific postoperative care is essential to ensure good outcomes and reduce recovery times. Local lubricant eye ointment is used to prevent dry eye. Ice packs are used directly over the eye for a few minutes every hour for 24 h to reduce swelling and orbital ecchymosis.

A small suction drain is recommended to prevent a lateral orbital haematoma when using the superior lateral approach, unless a CSF leak has been repaired, when a suction drain is contraindicated [6].

Postoperative care of excessive chemosis (usually encountered preoperatively with proptosis) is treated with a suspension (Frost) suture. Postoperative antibiotic prophylaxis is given for 24 h if both the orbit and nasal cavity are entered during the procedure. An ophthalmology clinical review is required postoperatively to assess vision.

Complications

Only a few units perform regular transorbital surgery and few complications have thus far been reported. In the author's experience, complications are only likely to occur due to the following:

- Too much retraction on the eye by the assistant trying to provide a wider surgical corridor. It is important that the surgeon check the pupil regularly for changes in shape and size and relax the retraction every few minutes. Excessive retraction during the superior lateral approach can lead to a superior orbital fissure syndrome with CN III, IV and VI palsies and blindness if the optic nerve itself is damaged by a retractor.
- Upper eyelid retraction can lead to temporary damage of the levator palpebrae muscle with ptosis. Dissection through the orbital septum can lead to permanent damage to the muscle that will require a blepharoplasty.
- CSF leaks can ensue if the anterior cranial fossa is breached during the precaruncular or superior approach and the middle cranial fossa during the lateral approach.
- Enophthalmos can occur if reconstruction of the floor or medial orbit is required post resection of these walls in patients without exophthalmic conditions (such as thyroid eye disease). The need for orbital wall reconstruction needs to be discussed and considered both preoperatively and intraoperatively.
- The lacrimal system can be injured if the dissection is too superficial during the precaruncular approach. Inserting probes into the canaliculi can prevent injury.

Areas of Controversy

Transorbital surgery for sphenoid wing meningiomas is a relatively new approach. There is no doubt that an optic nerve decompression prior to resection of the intracranial and lateral orbital component enhances postoperative visual improvement [7, 8]. There is uncertainty whether complete surgical resection is possible with the transorbital route alone when compared to a pterional approach. Which patients should be offered transorbital surgery versus a craniotomy is not clear, and further studies with long-term outcomes need to be examined to ascertain the role of transorbital surgery for these lesions.

Access to the anterior and middle cranial fossa through the superior lateral approach is relatively easy, but whether neurosurgeons can utilize these portals to address pathology of the frontal and temporal lobes remains to be seen.

Key Learning Points

- Multidisciplinary input is essential if transorbital surgery is contemplated.
- Before embarking on transorbital surgery, training is essential and special instruments/retractors are required.
- Multiportal surgery allows resection of lesions crossing surgical boundaries.
- A subperiosteal tissue plane preserves neurovascular structures and orbital muscles.
- Suturing of the periosteum is important to avoid ptosis and lateral canthal dystopia.

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CSF Rhinorrhoea and the Anterior Skull Base

38

Hans Rudolf Briner and Andrew C. Swift

CSF Physiology

Cerebrospinal fluid (CSF) surrounds and protects the central nervous system (brain, spinal cord and adjacent nerves). The fluid is unique and consists of 99% water and actively regulated balanced electrolytes and proteins (Fig. 38.1) [1]. CSF not only provides hydromechanical protection but maintains an optimal neural microenvironment that supports the clearance of brain metabolites, creating a microenvironment essential for normal brain development, function and health.

The volume of CSF in adults is normally about 150 mL, with about 75 mL contained within the spinal subarachnoid space. CSF is produced mainly by the choroid plexus of the lateral ventricles and the tela choroidea of the third and fourth ventricle. The CSF is completely replaced about three to four times per day, which equates to a volumetric production of about 400–600 mL/day.

Following circulation, the CSF is resorbed via arachnoidal villi, which evaginate into the cerebral sinuses, mainly the superior sagittal sinus, but also via arachnoid villi in the spinal nerve roots. What is less well known is that a significant part of CSF resorption takes place via extra-arachnoid pathways, such as the brain parenchyma, meningeal lymphatic vessels around the dural sinuses and the cribriform plate, and via perineural sheaths of the cranial nerves [2].

The pressure of CSF is variable and is dependent on several physiological factors such as posture, blood pressure in the carotid arteries, jugular venous pressure, respiration, intraabdominal pressure and physical activity. In an adult lying on the left side, the pressure of CSF is approximately 10–15 cmH2O [1].

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H. R. Briner (✉)
Center for Otorhinolaryngology, Head and Neck Surgery, Hirslanden Clinic, Zurich, Switzerland
e-mail: briner@orl-zentrum.com

A. C. Swift
Liverpool Head and Neck Centre, Liverpool University Hospitals Foundation Trust, Liverpool, UK

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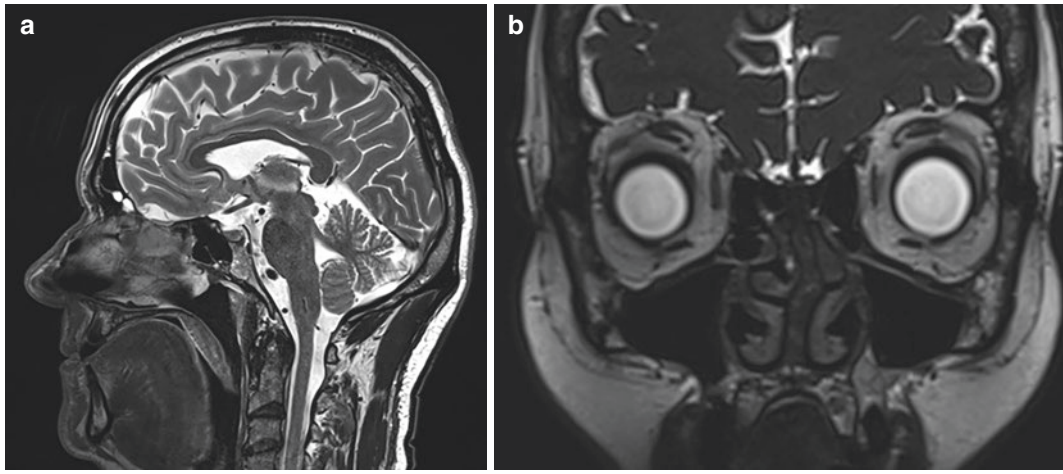


Fig. 38.1 (**a, b**) MR image (T2 TSE sagittal (**a**), T2 space coronar (**b**)) that shows cerebrospinal fluid (CSF) surrounding the brain and spine *(images by B. Schuknecht, MRI Institute, Zurich, Switzerland)*

Table 38.1 Aetiological classification of CSF leaks

CSF leak	Traumatic			Non-traumatic		
	External trauma	Surgery		Anatomical malformation	High intracranial pressure	Other causes (tumour, no cause identifiable)
		Planned opening of the dura in endoscopic skull base surgery	Inadvertently during endoscopic sinus surgery			
Remarks	Most common	Repair part of the surgical plan	Repair as soon as possible	Rare	Common: idiopathic intracranial hypertension	Rare

Classification of CSF Leaks

CSF rhinorrhoea can be categorised into two main groups – traumatic leaks and non-traumatic leaks [3].

Traumatic leaks: These account for approximately 95% of all CSF leaks [4]. Traumatic leaks can further be divided in leaks caused by external trauma (e.g. head injury) and leaks caused by surgery. This surgical subgroup includes pituitary surgery, transnasal skull base surgery and complications of endoscopic sinus surgery.

Non-traumatic leaks: CSF leaks in this subgroup are less common and can be found in approximately 5% of patients with CSF rhinorrhoea. The aetiology of non-traumatic leaks includes rare congenital anatomical malformations, CSF rhinorrhoea with high intracranial pressure, skull base tumours and cases where no cause for the leak can be found (Table 38.1).

CSF leaks can also be classified according to anatomical localisation, such as the posterior/dorsal wall of the frontal sinus, the ethmoidal roof, the cribriform plate, the sphenoid or the skull base adjacent to the temporal bone (Table 38.2).

The aetiological classification can be combined with the anatomical classification to facilitate a precise description for clinical practice. Figure 38.2 illustrates a clinical example of a 'non-traumatic CSF leak of the left cribriform plate due to an arachnoid protrusion associated with idiopathic intracranial hypertension' (Fig. 38.2a–e).

Table 38.2 Anatomical classification of CSF leaks

CSF leak	Anterior skull base				Lateral skull base
	Frontal sinus (dorsal wall)	Ethmoid roof	Cribriform plate	Sphenoid	Temporal bone (mastoid, middle ear)
Remarks	Traumatic leaks	Most common location of inadvertent leaks during endoscopic sinus surgery	Common, traumatic and non-traumatic CSF leaks	Arachnoidal cysts in the lateral sphenoidal recess, associated with intracranial hypertension	CSF rhinorrhoea via Eustachian tube

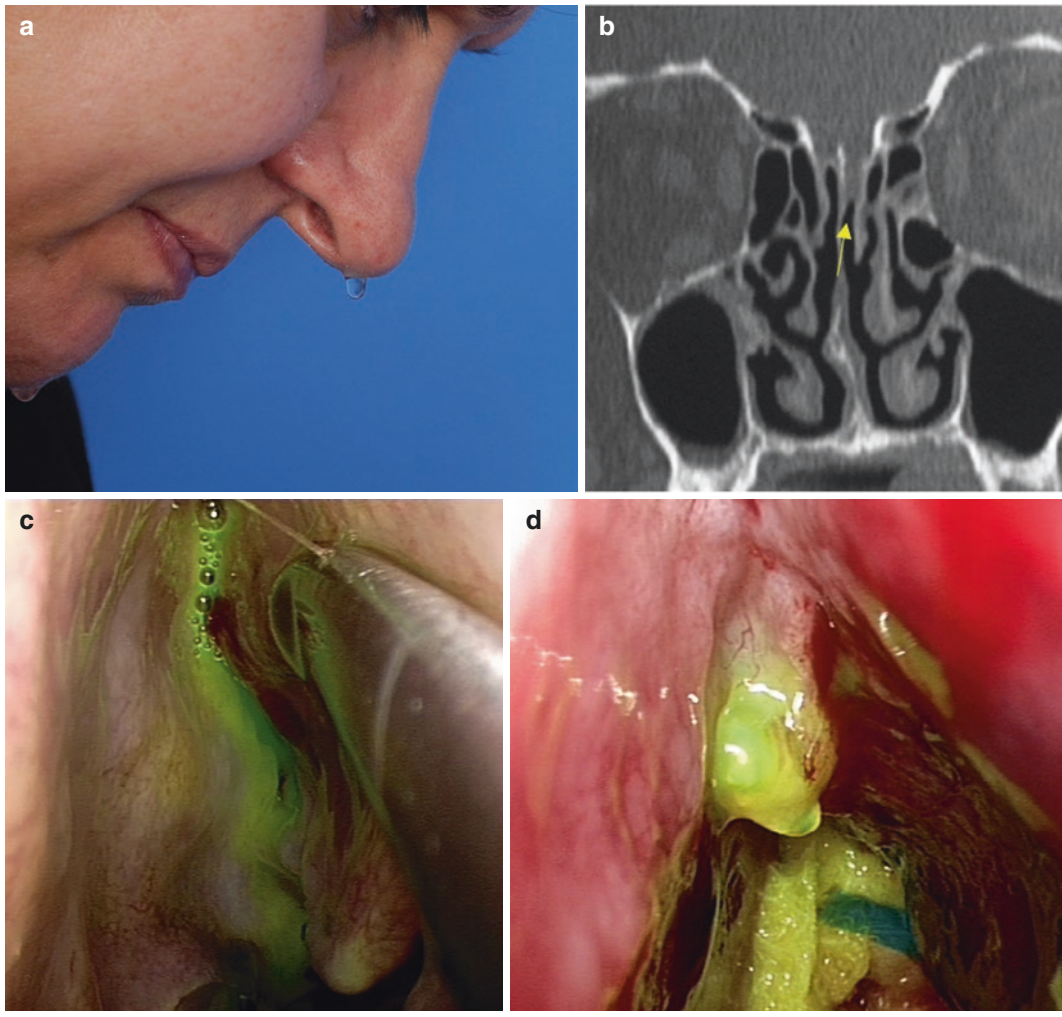


Fig. 38.2 (**a**) Patient with spontaneous, non-traumatic CSF rhinorrhoea on the left side, provoked by bending the head forward. (**b**) Coronal CT scan of the same patient with a non-traumatic CSF leak of the left cribriform plate due to an arachnoid protrusion (arrow) into the left olfactory rim associated with idiopathic intracranial hypertension *(image by B. Schuknecht, MRI Institute, Zurich, Switzerland)*. (**c**) Nasal endoscopy demonstrates CSF rhinorrhoea originating from the left olfactory cleft. The CSF is yellow due to intrathecal application of fluorescein sodium by a lumbar puncture before endoscopy. (**d**) Endoscopic view of the non-traumatic CSF leak of the left cribriform plate during endoscopic repair. The arachnoidal protrusion appears yellow because of the intrathecal application of fluorescein sodium. (**e**) Endoscopic view of the same lesion with the blue light filter. The CSF appears green due to fluorescein sodium and the leakage is more obvious

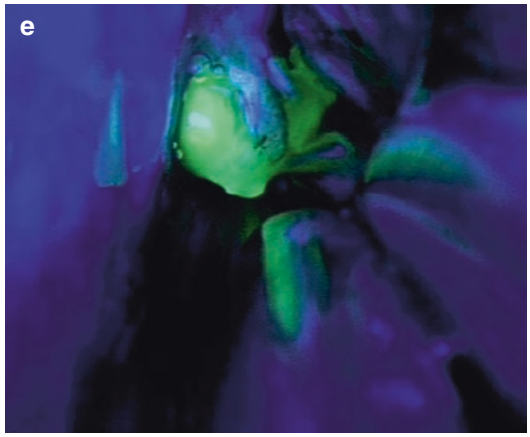


Fig. 38.2 (continued)

Complications of CSF Leaks

The dura is a watertight anatomical layer that prevents CSF from leaking into the surrounding tissue. A dural defect will result in a CSF leak, and should this occur in the anterior skull base or travel along the Eustachian tube from a temporal bone defect, it will present as CSF rhinorrhoea.

A profuse loss of CSF will induce low intracranial pressure that presents with headache and non-specific neurological symptoms such as visual disturbances, hearing abnormalities or cognitive deficits [5].

A breach in the dura can also act as a conduit for bacterial migration from the nasal cavity, paranasal sinuses or mastoid cells into the intradural space to cause meningitis. The incidence of meningitis depends on various factors such as the cause and the size of the dural defect and the duration of the leak. There is an ever-present cumulative risk of meningitis with an active CSF leak, irrespective of the site of the dural defect. Recurrent bacterial meningitis may occur over many years in the presence of a dural defect, and the latter may not be recognised as a cause of recurrent meningitis.

A dural defect may also allow air to enter the intracranial cavity and intradural space leading to pneumocephalus. Risk factors for pneumocephalus include large dural defects, raised intranasal air pressure induced by nose blowing and a lumbar drain. Pneumocephalus frequently causes headaches and may lead to non-specific neurological symptoms such as an altered mental status. A tension pneumocephalus is a serious, potentially life-threatening complication associated with CSF rhinorrhoea caused by the dural defect acting as a valve [6].

Indication for CSF Leak Closure

Every persistent CSF leak must be closed to prevent development of severe, possibly life-threatening complications, particularly where the CSF leak is profuse. Repair of large dural defects should be performed as soon as possible to prevent complications such as intracranial hypotension, meningitis and pneumocephalus.

A dural defect may cause minimal episodic, intermittent CSF rhinorrhoea, but such leaks are not so innocent and carry an inherent increased long-term cumulative risk of meningitis. The defect should be identified and repaired in all such cases.

The timing of closure depends on the clinical situation and the estimated risk of developing a complication.

Post-traumatic CSF rhinorrhoea after a skull base fracture may stop spontaneously, but exploration and dural repair remains a subject of debate. Spontaneous healing of small post-traumatic dural defects and the surrounding tissues is relatively common. However, there is still a potential long-term risk of meningitis, especially after fractures of the frontal skull base where spontaneous healing may not be as robust as in fractures of the temporal bone [4]. A healed skull base fracture may leave a bony dehiscence where the scar tissue may become tenuous and lead to dural herniation and a CSF leak many years after the initial head trauma.

Clinical Features of CSF Leaks

CSF rhinorrhoea can present with a range of clinical feature, such as profuse positional rhinorrhoea following trauma to infrequent episodes of minimal rhinorrhoea where the diagnosis can be challenging. As a general principle, the diagnosis of CSF rhinorrhoea should ideally be proven and the site located prior to surgical exploration.

Careful assessment of the medical history is key in establishing the diagnosis of CSF rhinorrhoea. Typically, it presents as unilateral clear, watery rhinorrhoea, provoked by bending the head forward or by physical activity leading to increased intracranial pressure (Fig. 38.2a). The rhinorrhoea can vary from infrequent episodes with minimal leakage to frequent profuse watery rhinorrhoea. CSF rhinorrhoea usually continues when the patient is asleep and may lead to visible 'water stains' or a halo sign on the pillow. Patients with profuse rhinorrhoea often describe a 'salty taste', but this symptom is non-specific.

Specific enquiry with leading questions should include the following: previous head trauma, even from many years ago; previous sinus surgery; and previous meningitis; especially if recurrent.

Non-traumatic spontaneous CSF rhinorrhoea may be associated with idiopathic intracranial hypertension in some patients and this should always be considered (IIH: vida infra).

Occasionally, patients will complain of non-specific accompanying symptoms such as headache, visual disturbances, dizziness or tinnitus. These non-specific symptoms are mostly explained by other, mainly neurological conditions and not by a CSF leak. However, it is important to appreciate that non-specific symptoms may occasionally be associated with increased intracranial pressure in addition to a CSF leak.

Watery Rhinorrhoea That Mimics CSF Leaks

Severe allergic rhinitis can cause episodes of profuse rhinorrhoea that may be similar to CSF rhinorrhoea. The diagnosis can be easily confirmed by analysing the fluid for beta-2 transferrin and/or beta-trace protein.

CSF rhinorrhoea can also be mimicked by water collecting in the maxillary sinus after nasal rinsing or water sports, particularly after endoscopic surgery.

Occasionally, patients can present with episodic watery rhinorrhoea that is associated with exercise or eating. The nasal drip in these instances is physiological and more likely in more senior age groups. Head injury may, on rare occasions, cause watery rhinorrhoea induced by emotion or exercise. This condition is known as a pseudo-CSF leak and is the result of an altered autonomic response.

Clinical Examination

CSF rhinorrhoea may be demonstrated during clinical examination and its origin may be determined by nasal endoscopy. Endoscopy may reveal other causes of rhinorrhoea such as chronic rhinitis or rhinosinusitis, as well as assess operative access and anatomical anomalies of the septum and middle turbinates.

Otoscopy and microscopy should be performed with suspected CSF rhinorrhoea to exclude a temporal bone defect with CSF tracking along the Eustachian tube.

In patients with infrequent or minimal leaks, it is helpful to try to induce a leak by placing the patient prone on a couch, flexed at the waist with the hands on the floor, in a head-down position.

Investigations

Beta-2 Transferrin and Beta-Trace Protein

In patients without an obvious CSF leak that can be localised with nasal endoscopy, a CSF leak should always be confirmed by identification and analysis of two CSF-specific proteins: beta-2 transferrin and beta-trace protein; both have high sensitivity and specificity for CSF [7–9].

Beta-2 transferrin: This is a glycoprotein found in CSF, perilymph, aqueous and vitreous humour of the eye. The concentration in nasal secretion, tears and serum is normally very low, so detection of beta-2 transferrin in nasal liquid suggests the presence of CSF. Depending on the assay used, only small amounts (10 μL) of liquid are sufficient to detect the protein. Detection of beta-2 transferrin in the collected liquid is possible for up to 14 days if it is stored in the refrigerator. A serum sample should be analysed alongside the nasal liquid as the serum concentration may occasionally be elevated and lead to a false-positive result, particularly in patients with chronic liver, kidney disease, alcoholism and rare glycoprotein metabolic disorders. False-negative results can occur when the amount of liquid is below the detection threshold of the assay or when there is bacterial contamination.

Beta-trace protein: This is prostaglandin D synthase produced in the choroid plexus and the meninges and has a high CSF to serum ratio. The assays for beta-trace protein are faster, cheaper and more automated than beta-2 transferrin assays and have a very high sensitivity and specificity in detection of CSF. Beta-trace protein is reported as an actual level that can be interpreted as either 'unlikely, equivocal or definite' presence of CSF in the collected sample. Small amounts (200 μL) of liquid – which can be collected also by placing absorbent foam swabs within the nose – are sufficient for the detection of the protein. Renal insufficiency and bacterial meningitis may lead to higher levels of beta-trace protein in serum and lower levels in CSF, leading to false-positive results. As with beta-2 transferrin, the nasal liquid to serum beta-trace protein ratio should be measured to achieve higher reliability. Beta-trace protein and beta-2 transferrin tests can also be combined for further accuracy.

Historically, a glucose oxidase test was used to differentiate CSF from nasal secretion, but the sensitivity and specificity is low and the test is no longer recommended.

Imaging

The modern possibilities of imaging allow a detection and precise localisation of most CSF leaks. High-resolution computed tomography (HRCT) and magnetic resonance imaging (MRI) are the two principal examination methods that are complementary [8, 10, 11]. Imaging will help with preoperative planning and identify other pathologies such as signs of intracranial hypertension or other intracranial/sinonasal pathologies.

HRCT of the skull, anterior skull base, paranasal sinus system and the temporal bone is the prime examination in CSF rhinorrhoea. Multiplanar reconstruction with a bone window algorithm allows detection of even small bony defects associated with CSF leaks at almost every location (Fig. 38.3a, b). Secondary signs of CSF rhinorrhoea such as intracranial air, mucosal reaction to CSF or liquid in adjacent sinuses can be of help in confirming the diagnosis.

MRI is superior to HRCT in differentiating soft tissue pathologies such as herniation of brain tissue in a meningoencephalocele, but not as good in detecting small bony skull base defects. Secondary signs of a CSF leak, such as liquid in the adjacent sinuses, are easy to detect (Fig. 38.3c, d). MRI may also show signs of increased intracranial pressure, such as an 'empty' sella or widened optic nerve sheaths.

Modern technology offers the option of fusion of HRCT and MRI imaging (Fig. 38.4a, b). However, for this to be successful, the MRI has to be performed with the acquisition of fine detail to facilitate adequate image fusion, and it is advisable to let the radiologist know of the intent on how the images will be utilised.

CT cisternography with intrathecal application of contrast is an option if a leak is difficult to detect, but this has largely been replaced by less invasive MRI sequences such as MR cisternography with intrathecal gadolinium.

Historically, CSF rhinorrhoea was often confirmed by radionuclide cisternography after intrathecal injection of a radionuclide, but modern scanning techniques have made this technique defunct.

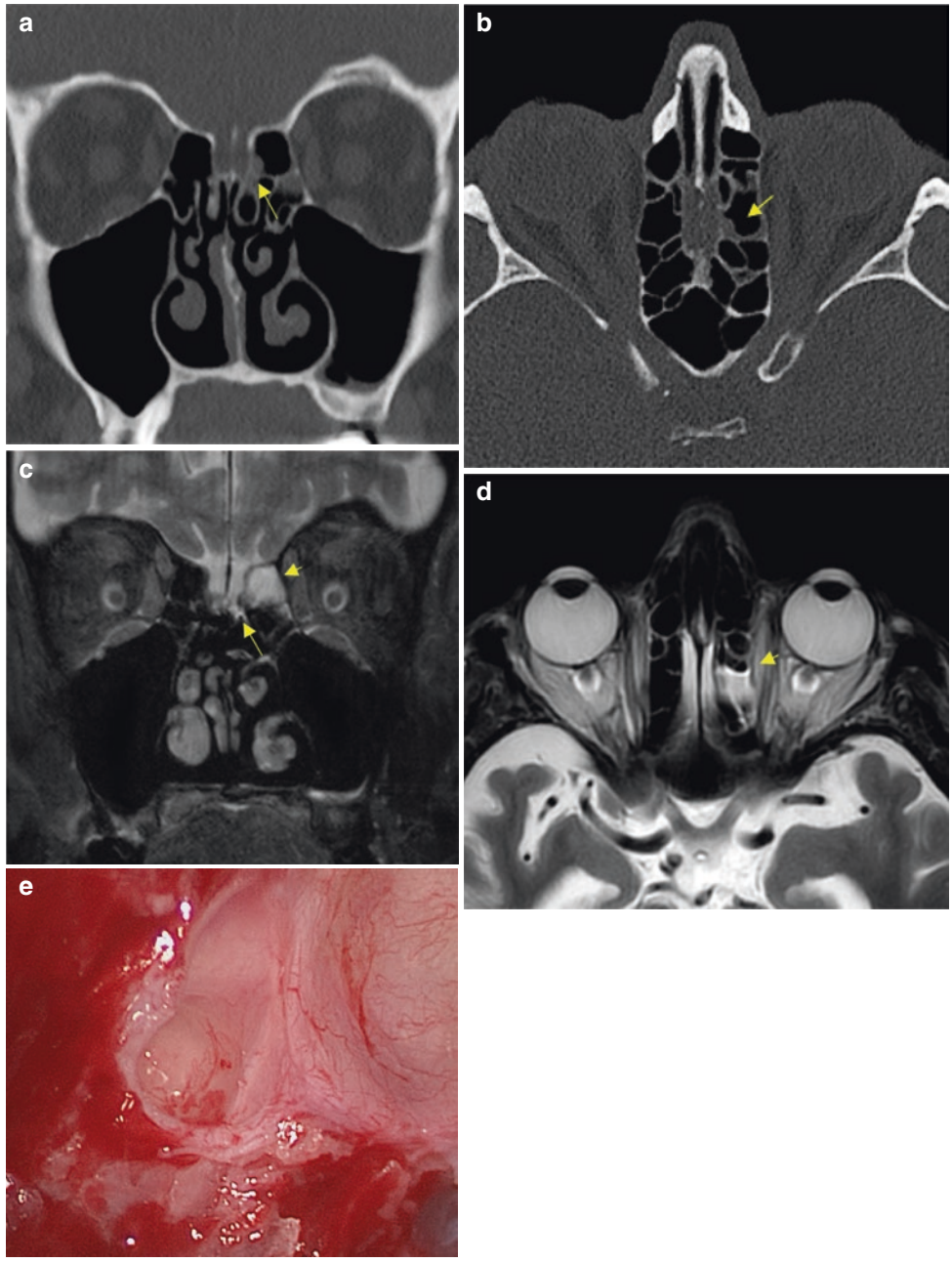


Fig. 38.3 (**a**) Patient with non-traumatic rhinorrhoea on the left side associated with increased intracranial pressure after irradiation of brain metastasis of a kidney cell carcinoma. HRCT (coronal, bone window) shows a small arachnoid herniation (arrow) at the lateral lamella of the left cribriform plate (*image by Neuroradiology Hirslanden Clinic, Zurich, Switzerland*). (**b**) On the axial scan, the small arachnoid herniation (arrow) at the lateral lamella of the left cribriform plate is visible with a slight thickening of the adjacent 'soft tissue', corresponding to liquid or mucosal thickening (*image by Neuroradiology Hirslanden Clinic, Zurich, Switzerland*). (**c**) Coronal MRI (T2, fat suppressed) shows liquid with the same signal quality as CSF in an ethmoidal cell adjacent to the arachnoid herniation (arrow) in the lateral lamella. In addition to the arachnoid herniation, fluid in the adjacent ethmoid cell (arrowhead) is an indirect sign of the CSF leak (*image by Neuroradiology Hirslanden Clinic, Zurich, Switzerland*). (**d**) Axial MRI (T2) is also able to demonstrate a fluid level in the ethmoidal cell adjacent to the CSF leak (*image by Neuroradiology Hirslanden Clinic, Zurich, Switzerland*). (**e**) Close endoscopic view of the arachnoidal herniation at the lateral lamella of the left cribriform plate during endoscopic repair

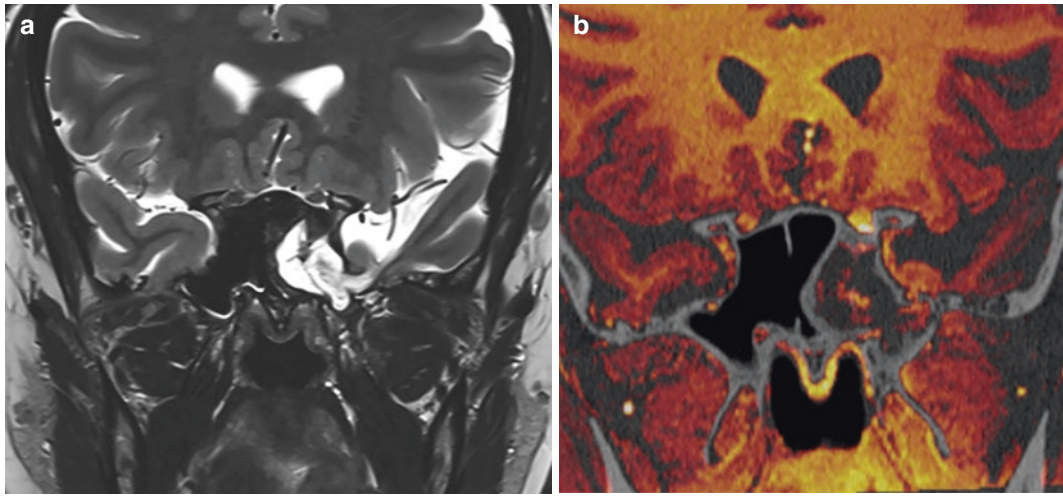


Fig. 38.4 (**a**) Coronal MRI (T2 TSE) of a non-traumatic CSF leak associated with idiopathic intracranial hypertension in the lateral recess of the left sphenoid sinus (*image by B. Schuknecht, MRI Institute, Zurich, Switzerland*). (**b**) CT-MRI fusion with precise delineation of the CSF leak to the lateral recess of the left sphenoid (*image by B. Schuknecht, MRI Institute, Zurich, Switzerland*)

Table 38.3 Recommendations for the diagnostic use of intrathecal sodium fluorescein

Intrathecal use of sodium fluorescein	Remarks
Informed consent	Off-label use
Lumbar puncture	Small needle to prevent headaches
Aspiration of 10 mL CSF	
0.5 mL of 5% sodium fluorescein suitable for intrathecal use	25 mg, maximal dose should not exceed 50 mg
Slow injection of 0.5 mL 5% sodium fluorescein that is diluted with 10 mL CSF	Monitor for neurological adverse effects (headaches, nausea, numbness of lower limbs, seizures)
Allow colour to reach cranial portion of CSF	Diffusion depends on individual situation, reliable after 4 h
Endoscopy, CSF shows yellow colour	Blue light filter enhances contrast

Sodium Fluorescein

Sodium fluorescein stains CSF yellow-green and injecting this intrathecally via a lumbar puncture can greatly enhance the detection of CSF. An active leak would be clearly seen by nasal endoscopy and the source identified during surgical exploration, especially in patients where the leak is difficult to localise (Fig. 38.2c, d). The fluorescence and contrast of fluorescein-stained CSF is greatly enhanced by blue light filter in minimal CSF leaks (Fig. 38.2e).

Once injected intrathecally, the sodium fluorescein must circulate intracranially prior to endoscopic surgical exploration. A circulation time of 4 h was recommended for reliability, but circulation occurs much more quickly if the patient is placed in a supine head-down reverse-Trendelenburg position, as fluorescein is hygroscopically denser than CSF.

Sodium fluorescein is neurotoxic, and toxicity increases with higher concentrations. The maximum dose of sodium fluorescein should not exceed 50 mg, but nowadays, it is generally recommended to use 25 mg (0.5 mL of a 5% solution) of highly purified sodium fluorescein, diluted with 10 mL of CSF and re-injected relatively slowly (Table 38.3).

Whilst this is unlicensed and required informed consent, it has been tried and tested over many years [12, 13]. Complications rarely occur, but there is a remote risk of anaphylaxis, and preoperative skin testing has been recommended. Reported transient adverse effects of intrathecal sodium fluorescein are headaches, nausea, dizzi-

ness, numbness of the lower limbs and seizures, but a fatal reaction is highly unlikely [14].

The Principles of Management of CSF Rhinorrhoea

CSF rhinorrhoea may present in four broad clinical scenarios. Whilst the principles of management remain the same, there are some possible variations in the management algorithm:

(a) The patient with an active CSF leak
(b) The patient with a suspected subclinical CSF leak
(c) The patient with a traumatic CSF leak
(d) CSF leak as a surgical complication

The Active Leak

In active leaks, the diagnosis is typically easy and the location identified by nasal endoscopy and imaging. However, it is still best to confirm the diagnosis by beta-2 transferrin/beta-trace protein analysis, not least for medicolegal reasons. All active CSF leaks need closure.

The Subclinical Leak

Some patients present with infrequent episodes of a possible 'leak' and minimal amounts or no provocable rhinorrhoea. These patients pose a clinical challenge.

It is important to try and obtain a sample of the nasal fluid for beta-2 transferrin and/or beta-trace protein analysis in patients with a suspected subclinical leak. The sample bottles can be taken home and kept refrigerated until enough fluid has been collected (normally a minimum of 0.5 mL). An alternative technique in patients with minimal leaks is to insert absorbent dressings within the nasal cavities for several hours and to send these for fluid analysis.

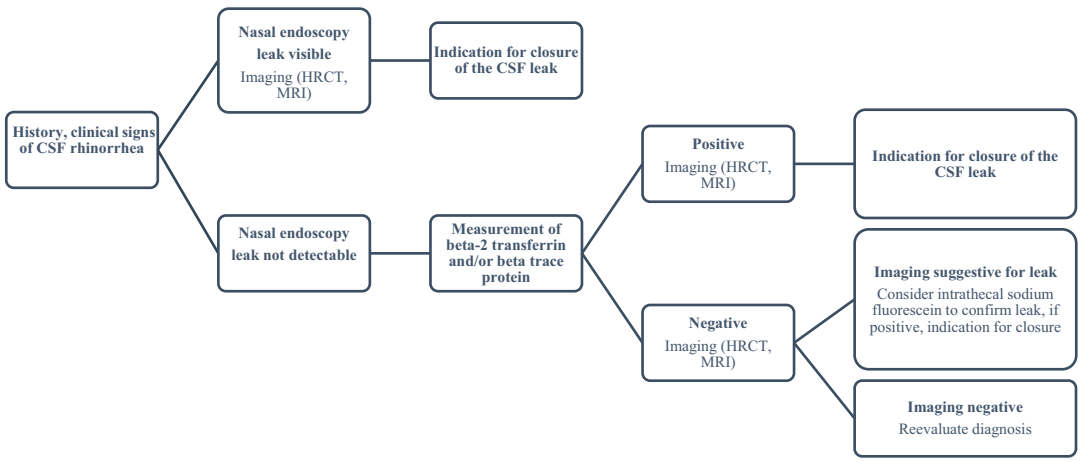
Both HRCT and MRI should be requested and may demonstrate a small defect or exclude signs of intracranial hypertension.

Nasal endoscopy after intrathecal sodium fluorescein should also be considered if a CSF leak is suspected.

There may be a reasonable argument to explore the anterior skull base endoscopically in certain situations where a suspected CSF leak cannot be confirmed. This is a matter of clinical judgement. Whilst endoscopic exploration does carry a risk, this is controlled and may be less than the risk of meningitis at a later day. It can also carry the advantage of confirming or excluding a CSF leak that affects future prognosis and management.

If there is real cause for concern, such as previous episodes of meningitis, endoscopic exploration of the skull base with intrathecal fluorescein should be considered (Table 38.4). The latter is especially true in recurrent bacterial meningitis, even in the absence of a CSF leak.

Table 38.4 Diagnostic algorithm for suspected CSF rhinorrhoea



The Traumatic CSF Leak

CSF leaks are most likely to occur from complex skull fractures affecting the mid-face and anterior skull base. These fractures may include the posterior wall of the frontal sinus, ethmoidal roof and sphenoid sinus and can be bilateral and at multiple sites. CSF leaks can also occur following a penetrating injury.

CSF leaks following direct head injury often resolve once the fracture sites have been reset, especially if secured by fixation plates.

Endoscopic exploration soon after trauma is probably unnecessary and will generally be accompanied by mucosal bleeding and an unclear view of the skull base. Frontal sinus defects would need an external approach, but a limited endoscopic procedure through a small external access point is a possibility prior to proceeding with a wider approach or an osteoplastic procedure.

The patient is best reviewed once initial healing has occurred. If there is an element of doubt as to the integrity of the anterior skull base, or a persistent CSF leak, then further detailed imaging and exploration should be considered.

CSF Leak as a Surgical Complication

A CSF leak at the time of endoscopic sinus surgery is fortunately unusual, but highly stressful for the surgeon should this occur. The risk is increased with revision surgery, especially with osteoneogenesis or altered sinus anatomy. The dural tear should be relatively small, but those caused by avulsion or a microdebrider can be substantial. There is also a risk of intracranial bleeding, especially if a penetrating injury was caused by a microdebrider.

This complication carries a significant risk of intracranial infection and should be recognised at the time of surgery or very shortly afterwards. During surgery, the surgeon should initially inform the anaesthetist, keep the patient horizontal to prevent air-embolus and proceed to repair the defect. If recognised after surgery, repair is recommended as soon as possible, particularly if a pneumoencephalus is present as well.

The principles of repair are exactly the same as those for repairing CSF leaks electively. The bone defect should be cleared of surrounding mucosa and the defect repaired. Small defects are suitable for a fat plug, but larger ones may require a composite multilayer closure.

Should the complication arise at the time of surgery, it is recommended that the surgeon discusses the problem with an experienced colleague to plan the management and avoid irrational decision-making.

Postoperatively, the patient should have regular neuro-observations and a CT scan of the head should be obtained to exclude a pneumoencephalus and intracranial bleeding. Prophylactic antibiotics are recommended. Standard measures such as avoidance of nose blowing and stool softeners apply. The surgeon has a duty of candor in this situation and will need to explain the injury to the patient.

Should a defect go unrecognised or left untreated, then there is a significant risk of pneumoencephalus, meningitis, intracranial infection and cerebral abscess.

Prevention of Meningitis by Vaccination

A dangerous complication of CSF rhinorrhoea is bacterial meningitis, especially due to *Streptococci pneumoniae*. Vaccination with 13- and 23-valent pneumococcal conjugate vaccine has been shown to be effective in reducing the incidence of pneumococcal meningitis. It is therefore recommended that patients with CSF leaks are vaccinated with pneumococcal vaccine [15], especially if surgical repair is delayed or a CSF leak is seriously suspected but impossible to prove.

Vaccination can be extended to include *Haemophilus influenzae*, but the most important priority is to cover the risk posed by the pneumococcus serotypes.

It is also important to warn patients of the risk of meningitis and the initial symptoms, so that urgent medical intervention and antibiotics are not delayed should such a complication ever occur, thus minimising the risk of serious consequences.

Timing of Surgery for Long-Term CSF Leaks

Urgent repair: In patients with active and profuse rhinorrhoea, the leak should be closed as soon possible to minimise the possibility of pneumocephalus or bacterial meningitis.

Repair within several weeks: In patients with less pronounced intermittent CSF rhinorrhoea, the risk of meningitis is relatively low but cumulative and still significant. Elective repair should be done as soon possible and generally within a few weeks.

Explore within months: The timing of surgery is less urgent in patients with minimal intermittent CSF rhinorrhoea, especially when the diagnosis and localisation cannot be easily confirmed.

Defer repair: Should the CSF leak remain undiagnosed, surgery is not recommended.

There are rare occasions where surgery may carry a greater risk to health than the risk of meningitis. Should the patient have serious coexisting comorbidities or morbid obesity, general anaesthesia may carry significant risk to life.

Patients awaiting diagnostic confirmation should be informed about the potentially increased risk of meningitis as above. Decision-making in some of these patients is complex and discussion with colleagues is recommended.

Repair of CSF Leaks

As a basic principle, every CSF leak should be repaired. Different surgical approaches, techniques and methods of reconstruction of skull base defects are available, according to the size and site of the defect.

Surgical Approach

There are two principal surgical approaches to defects of the anterior skull base – 'external' approaches, which can be extradural or intradural, and transnasal endoscopic approaches.

External approaches: An external extradural approach implicates temporary removal of the external wall of the frontal sinus and is indicated for leaks of the frontal sinus that are far lateral and therefore difficult to control endoscopically.

An external intradural or transcranial approach requires a craniotomy and gives access to dural defects from the endocranial side of the leak. This approach allows the reconstruction of large defects of the anterior skull base that cannot be reconstructed reliably by an endonasal approach, for example, after resection of extended tumours. Further indications for this approach are leaks at anatomical areas that are difficult to access transnasally, such as far-lateral recesses of a very pneumatised sphenoid sinus or lateral skull base.

Transcranial approaches have a higher morbidity due to the opening of the endocranial space and the temporary dislocation of the frontal lobe and the olfactory bulb [16].

Endoscopic approaches: Transnasal endoscopic approaches are suitable for most of the CSF leaks and have a high success rate, typically above 90%, and a low 'approach-related' morbidity. Transnasal endoscopic approaches are therefore the preferred technique of choice, except for situations where the defect cannot be controlled reliably by the endoscopic technique.

A CSF leak from a dural defect in a laterally pneumatised sphenoid sinus (via Sternberg's canal) is a challenging situation, but good access can be obtained via the posterior wall of the maxillary sinus into the pterygomaxillary fossa and infratemporal fossa (transpterygoidal approach).

Reconstruction Material

The reconstruction of a CSF leak requires material to seal the dural defect and integrate with the surrounding tissue. Autologous tissue, such as nasal mucosa, fat, muscle or fascia, is preferable.

Autologous grafts and flaps: Nasal mucosa can be used as a free flap in small defects or as vascularised pedicled flap, such as a nasoseptal flap, in larger defects [17]. Fat is particularly suitable for reconstruction due to its plasticity and sealing properties.

Fat is also easily harvested from the abdominal wall, thigh or ear lobule. Ear lobe fat is more fibrous and easier to manipulate.

Fascia can be harvested from the lateral thigh (fascia lata), the rectus abdominis or temporalis muscles. Rectus abdominis fascia is ideal for a medium-sized defect, but the thicker fascia lata is best for large defects (Fig. 38.5a–d).

Other autologous tissue, such as cartilage from the nasal septum or external ear, and bone, may be used to provide greater stability.

There are various reconstruction techniques, such as pericranial flaps, available for extensive defects after anterior skull base surgery (please see Chap. 36).

Heterologous grafts: Various types of collagen matrix sheets are available. They can help to achieve a watertight reconstruction and add stability in combination with autologous material. However, heterologous material is 'non-vital'. Healing and integration with the surrounding tissue takes longer compared to autologous tissue.

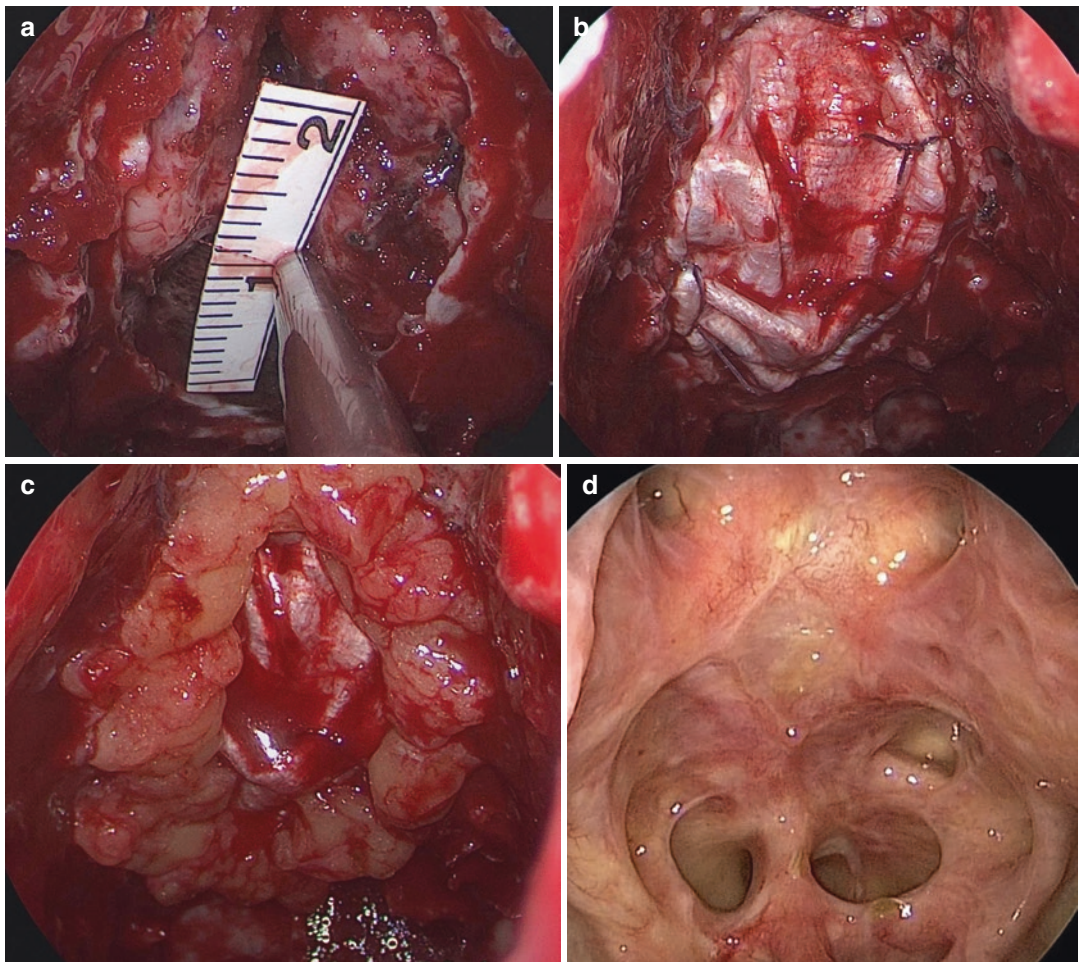


Fig. 38.5 (**a**) Large defect of the anterior skull base after resection of an olfactory neuroblastoma. (**b**) Defect reconstruction with fascia lata of the lateral part of the upper thigh. The fascia is sutured to the dura to improve stability. (**c**) The margins of the defect reconstruction site are sealed with abdominal fat. (**d**) Anterior skull base 3 years after reconstruction with optimal integration of the reconstruction material

Technique of Repair

The goal of CSF leak reconstruction is to achieve a watertight and mechanically stable closure. A persistent CSF leak will hinder a stable, watertight fusion of tissue and may lead to failure of the reconstruction. If the repair is watertight, fibroblasts and vessels grow into the contact zone between the margins of the defect and the reconstruction tissue within a few days, sealing the repair. The repair then gains strength and becomes robust over the ensuing weeks.

Whilst there are several methods of reconstruction, the optimal technique depends on the size and location of the defect.

Small leaks: The leak can be closed by inserting fat or fascia directly into the defect, like a 'bath plug' [18]. Whilst fat grafts are often very effective at sealing smaller defects, they are not easy to position in very tiny defects. In such situations, a seal is best obtained by initially laying fascia over the defect and pushing part of this directly into the defect with a fine ball probe. The repair can then be supplemented fat, fascia and/or mucosa where appropriate.

Larger leaks: The defect is best closed by a multilayer technique. A tissue graft is placed through the defect as an intracranial 'underlay', and a second graft is placed as an 'overlay' on the nasal side of the defect.

Large defects: Large skull base defects are best repaired with multilayer fascia lata, possibly with cartilage grafts as well, if appropriate. The repair should be fixed and stable. Although technically demanding and not always feasible, suturing of the fascia to the dura provides optimal stability (Fig. 38.5b). Resorbable or non-resorbable packing provides additional stability for the healing period (Fig. 38.6a–c).

In situations where dura has herniated through a defect, it is usually possible to reduce the herniation after dissection and mobilisation. Diathermy may be used to seal the defect but should be used sparingly and with caution. Brain tissue is likely to be present in large herniations, and if deemed non-functional, it can be excised if reduction intracranially is not possible.

Graft fixation: Fibrin glue (concentrated fibrinogen activated by thrombin and calcium chloride) or a similar agent is used to fix the reconstruction. Intrathecal fluorescein is recommended to confirm the extent of the defect, to identify multiple defects and to provide confirmation that the repair is watertight.

Tips and Tricks

For a successful closure of a dural leak, the graft must adhere with the margins of the defect. The graft will not adhere to mucosa that must be cleared and the bone around the defect exposed. The cleared margins should be wide enough (> 2–3 mm) to generate a stable zone of fusion.

Autologous, vital reconstruction tissue has faster healing properties compared to heterologous material. Vascularised mucosal flaps offer the best solution to achieve a fast and stable fusion with the defect margins and are the method of choice for larger and 'difficult-to-close' leaks.

If fascia lata or other tissues from the thigh have been utilised, the fascial defect should be repaired with a non-resorbable or even a resorbable mesh (Fig. 38.7a, b). Failure to repair a defect in the fascia lata can lead to muscle herniation and prolonged leg soreness.

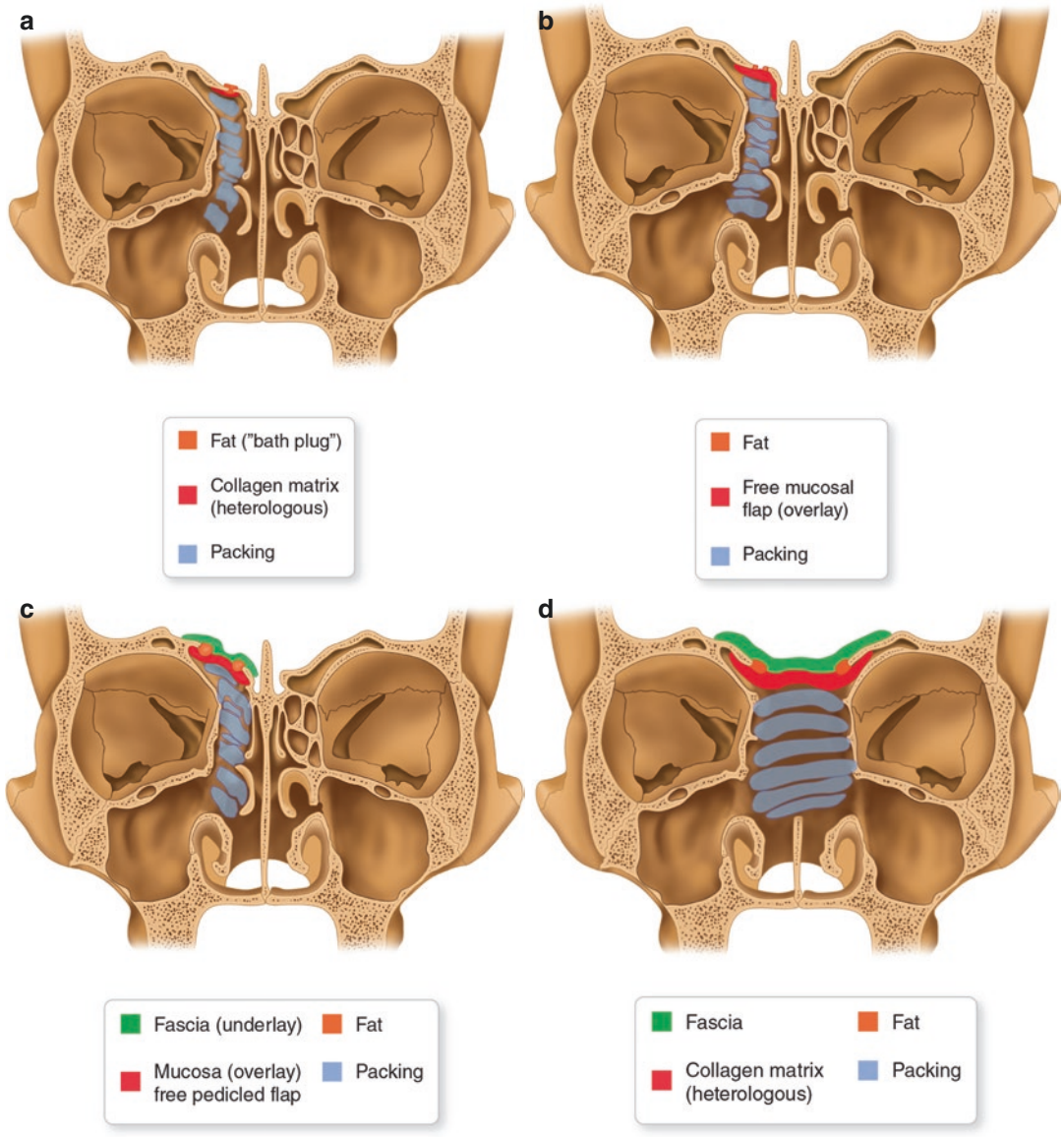


Fig. 38.6 (**a**) Reconstruction of a small CSF leak with abdominal fat as 'bath plug'. The fat is stabilised with a heterologous collagen matrix sheet and resorbable packing. (**b**) Reconstruction of a medium-sized defect with fat and a free mucosal flap as 'overlay'. The reconstruction is stabilised with fibrin glue and resorbable packing. (**c**) Reconstruction of a large defect with rectus abdominis fascia as 'underlay', fat and a free (or pedicled) mucosal flap as 'overlay'. The reconstruction is stabilised with fibrin glue and resorbable packing. (**d**) Reconstruction of a large defect with fascia lata as 'underlay' and fat. The reconstruction is stabilised with a collagen matrix sheet (heterologous) and resorbable or non-resorbable packing (see also Fig. 38.5)

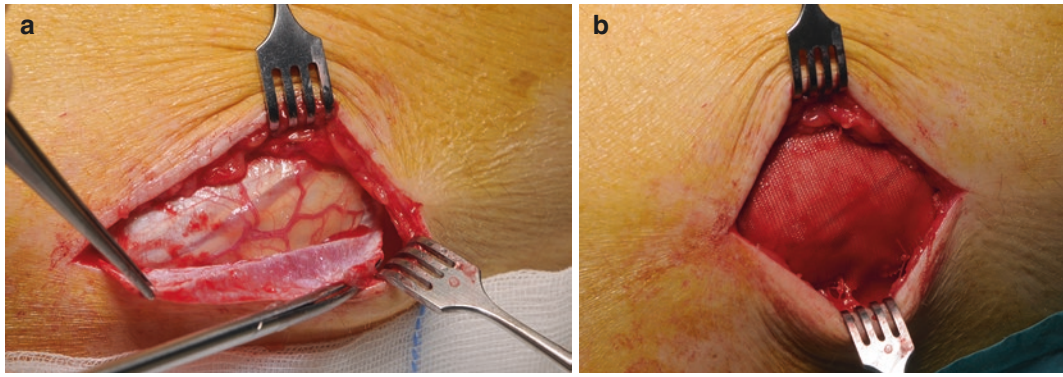


Fig. 38.7 (**a**) Harvesting fascia lata from the right thigh. (**b**) Reconstruction of the donor site defect with a resorbable 'Vicryl®' mesh

Table 38.5 Algorithm for the reconstruction of CSF leaks depending on the size and type of the defect

Defect type	Endonasal endoscopic approach	External approach	Collagen matrix (heterologous)	Mucosa free flap	Mucosa pedicled flap	Fat	Fascia	Lumbar drainage
Small (>0.5 cm)	**X**		X	**X**		**X**	X	
Medium (0,5 cm–2 cm)	**X**		X	**X**	X	**X**	**X**	
Large (>2 cm)	**X**		X	X	**X**	**X**	**X**	
Extensive skull base resection	X	**X**	X		**X**	**X**	**X**	X
High-pressure, high-volume CSF leak	X	X	X		**X**	**X**	**X**	**X**

An algorithm for the reconstruction of CSF leaks depending on the size and type of the defect is shown in Table 38.5.

Lumbar Drains

There is a consensus of opinion that a lumbar drain is not recommended in the majority of CSF leak repairs, and the potential benefit is not proven [19, 20]. However, there are occasions where a leak will be high pressure/high flow, and evidence suggests that a lumbar drain lowers the risk of a persistent CSF rhinorrhoea, as may occur when the arachnoid cistern or the third ventricle communicates directly with the leak [21].

A lumbar drainage also carries a risk of additional complications such as headaches, meningitis, pneumocephalus and subdural haemorrhage.

Antibiotics

Preoperative antibiotics: With the risk of meningitis in an active CSF leak, antibiotic cover would seem logical. However, the consensus is that, in the absence of sinusitis, the risk of meningitis is not significantly reduced, and bacterial resistance may be encouraged.

Antibiotics not only increase the risk of selecting resistant bacteria but also carry a risk of other possible adverse effects such as allergy and an

increased risk of *Clostridium difficile* enterocolitis.

Preoperative antibiotics: The evidence for prophylactic antibiotics during and after surgery is unclear [20]. Reasonable indications for antibiotic prophylaxis include CSF leak closure in a patient with a purulent sinus infection, repair with free grafts rather than vascularised flaps and prolonged graft support with absorbent nasal packing.

Miscellaneous

Acetazolamide: Acetazolamide is a diuretic drug that decreases CSF production and lowers intracranial pressure. There is evidence that the use of acetazolamide lowers the risk of recurrence in CSF leak closure in patients with idiopathic intracranial hypertension [22, 23].

Nursing care: Patients should be counselled to avoid manoeuvres that raise intracranial pressure such as forceful nose blowing, coughing, sneezing, abdominal straining and lifting, especially in the first days after CSF leak repair when the reconstruction is not yet stable. Obstipation (severe constipation) is quite common in the postoperative period and leads to abdominal pressing/straining. It should be prevented by administering stool softeners during the recovery period.

Idiopathic Intracranial Hypertension (IIH)

Spontaneous CSF leaks may sometimes occur with raised intracranial pressure from IIH. From the practical point of view, the diagnosis should always be considered, and if appropriate, the patient should see an ophthalmologist to exclude papilloedema and a neurologist/neurosurgeon for additional investigation.

IIH patients are more likely to be obese and female (body mass index >30 kg/m^2). Associated symptoms include headaches, nausea, photophobia, phonophobia, visual disturbances, papilloedema, abducens nerve palsy, diplopia, pulsatile tinnitus and neck and back pain [22, 24]. IIH combined with a CSF leak can be extremely difficult to identify as the intracranial pressure is intermittently released with each CSF leak and papilloedema may well be absent (IIH without papilloedema: IIH WOP). Reaching the diagnosis of IIH WOP often relies on more invasive diagnostics, such as ICP monitoring.

Radiological imaging, such as high-resolution CT and MRI including venogram, may reveal signs suggestive of IIH such as an empty sella turcica, transverse sinus stenosis, perioptic subarachnoid space distention and tortuous optic nerves and flattening of the posterior globe. The skull base may be thin or dehiscent.

Once recognised, IIH can then be treated, either medically by a combination of weight loss, medication such as acetazolamide or headache management, with careful monitoring of visual function. In more severe cases where vision is threatened, CSF diversion, frequently with a ventriculoperitoneal shunt or venous sinus stenting, is recommended.

Areas of Controversy

There are several areas of controversy in the management of CSF rhinorrhoea.

Surgery when the CSF leak stops spontaneously: One subject of debate is the indication for surgical exploration and repair in patients with post-traumatic CSF rhinorrhoea that stops spontaneously. Spontaneous healing of small post-traumatic defects is common. However, the risk of developing meningitis is still slightly increased and continues in a cumulative manner over many years. Patients should be counselled about this potential risk, especially if surgical exploration is not performed.

Use of antibiotics: The use of antibiotic treatment in active CSF rhinorrhoea and as prophylaxis in CSF leak repair remains controversial. There is a general recommendation against the use of antibiotics in CSF rhinorrhoea. However, the benefit of preventing meningitis must be weighed up against the risks of selecting resistant bacteria and adverse effects of antibiotics in each individual clinical situation.

Intrathecal fluorescein: The frequency of use of intrathecal fluorescein is another topic for discussion. The proponents will recommend its use in the majority of surgical cases, but others will argue to point that they can locate and repair the leak without staining the CSF.

Lumbar drainage: The use of lumbar drainage as supportive treatment in CSF leak repair is a controversial topic that always generates much debate. Significant complications may occur from lumbar drainage, and the current recommendation is to use it only in 'difficult-to-close' CSF leaks, such as recurrences and 'high-flow/high-pressure' leaks.

Key Learning Points

- In an adult human, there is a volume of 150 mL of CSF protecting the brain and the spinal cord.
- Traumatic CSF leaks are most common (95%).
- Spontaneous CSF leaks are least common (5%) but may be associated with idiopathic intracranial hypertension (IIH).
- CSF leaks can cause life-threatening complications such as meningitis and pneumocephalus and must be repaired.
- The diagnosis of a CSF leak must be established by nasal endoscopy, measurement of CSF-specific proteins (beta-2 transferrin, beta-trace protein) and imaging (HRCT, MRI). Intrathecal application of sodium fluorescein is a further diagnostic option to consider, especially in difficult-to-detect CSF leaks.
- Autologous tissue (nasal mucosa flaps, fat, fascia) is the preferred technique for repair.
- The surgical approach and technique of repair depend on the size and location of the CSF leak.

Conflicts of Interest Hans Rudolf Briner has a relationship as a Consultant for Karl Storz GmbH, Tuttlingen, Germany, and is the shareholder of the Swiss Rhinology Teaching Center GmbH Company, which gives license for a Smell Diskettes Screening Test. None of these relations pose a conflict of interest in connection with this book chapter.

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Section VII

Miscellaneous Rhinological Disorders

Epistaxis

39

Russell A. Cathcart, Rich Williams, and Andrew C. Swift

Introduction

Epistaxis (pl. epistaxes) is a bleed from the nose, although the true etymological derivation does not directly reference either blood or the nose—it simply translates as 'cover with a flow of drips'. However, the term was first phrased by the Greeks at the turn of the eighteenth century to refer to a nosebleed, and it has done so ever since.

Although nosebleeds are in no way unique to humans, it is likely that humans are the only species to experience idiopathic bleeds, as nosebleeds in animals almost always result from infections, trauma or neoplasms. Why only humans should experience idiopathic epistaxis is unclear, as humans have proportionally underdeveloped nasal cavities, but it is likely that our rapid evolution and indoor living are implicated.

Despite its prevalence over the centuries and the frequency with which patients present to the Emergency Department and ENT clinic with epistaxis, it remains a condition that is managed with great variability and inconsistency across the world. A recent multidisciplinary working group consensus document, produced under the auspices of the British Rhinological Society by the National ENT Trainee Research Collaborative, has done much to address that inconsistency by proposing an evidence-based approach to the management of epistaxis in secondary care [6].

R. A. Cathcart (✉)
ENT Department, Jersey Hospital, Jersey, UK
e-mail: r.cathcart@health.gov.je

R. Williams
University Hospitals Plymouth NHS Trust, Derriford Hospital, Plymouth, UK
e-mail: Richard.williams8@nhs.net

A. C. Swift
Liverpool Head and Neck Centre, Liverpool University Hospitals Foundation Trust, Liverpool, UK

Paediatric Epistaxis

Aetiology

The vast majority of paediatric nosebleeds arise from the anterior nasal septum. The network of prominent vessels that make up Kiesselbach's plexus within Little's area of the anterior nasal septum is effortlessly reached by small, explorative fingers (Fig. 39.1).

The mucosa is thin and easily torn in children and even an inadvertent rub of the nose in the night can be enough to shear a vessel and trigger a bleed. Although often numerous, these terminal vessels are invariably small diameter, and as such, the bleed tends to be a low-pressure flow that is self-limiting within a short period of time, typically minutes. Thus, paediatric epistaxes are, by and large, a problem of recurrent, low volume bleeds over a matter of weeks, months or even years.

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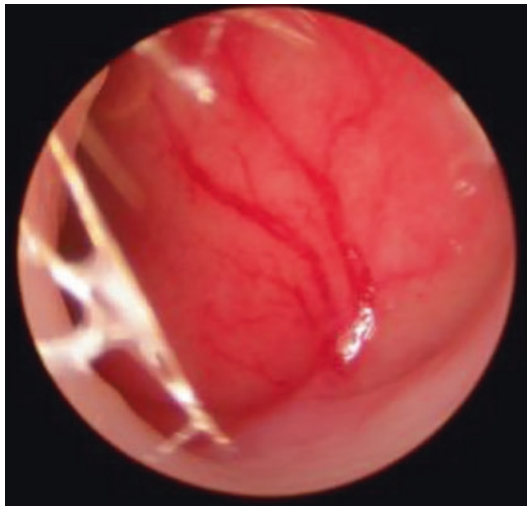

Fig. 39.1 Superficial fragile vessels of the anterior nasal septum (Little's area or Kiesselbach's plexus)

Very low-level bleeds—those manifesting only as blood staining when the child blows their nose—often indicate a localised staphylococcal infection of the nasal vestibule (vestibulitis) with consequent fissuring of the squamous epithelium around the ala, particularly in the soft tissue triangle.

Catastrophic acute bleeds are exceptionally rare in children. When they do occur, they inevitably do so as a result of a vascular neoplasm or vascular malformation within the nasal cavity.

Juvenile Angiofibroma

Juvenile angiofibroma is a rare, benign neoplasm that arises from the region of the pterygopalatine fissure and sphenopalatine foramen. Although a juvenile angiofibroma will commence as a small localised lesion, at the time of diagnosis they are often much larger and will invariably extend into nasopharynx. For reasons not yet fully elucidated, juvenile angiofibroma arises almost exclusively in teenage boys and a brisk bleed in this age group should instigate nasendoscopy to examine the nasopharynx.

Clotting Disorders

Clotting disorders do, of course, exist in the paediatric population and will predispose a child to having more frequent, more prolonged bleeds. Most disorders of clotting factors in children (e.g. haemophilia, von Willebrand disease) are hereditary, and thus there will usually be a family history of bleeding tendency known about from older relatives. Disorders with platelet dysfunction, on the other hand, are usually acquired, and one should consider thrombocytopaenia in a child with an unusual bleeding pattern or recalcitrant bleeds.

Management of Paediatric Epistaxis

Management of Acute Paediatric Epistaxis

Due to the majority of epistaxes in children being low-pressure, low-volume bleeds, it is unusual to require anything more than digital pressure to stop each bleeding episode. Given that most bleeds arise from Little's area, then it can be expected that silver nitrate cautery will terminate any bleeds not controlled with simple pressure. The use of nasal packing or balloon tamponade in children is, and always should be, a rare event.

First Aid Measures

It is surprisingly common for patients, and parents, to demonstrate pinching the bridge of the nose during bleeds. This only compresses the thin skin over the nasal pyramid and in no way serves to control the bleeding, other than by rendering the child inactive and restful. Instead, the alae/nostrils should be firmly pinched closed, thus applying pressure over Little's area on the septum, where the bleeding vessel will invariably lie. Patients should also be advised to tilt their head forwards rather than backwards during a bleed as this will prevent retrograde passage of blood into the nasopharynx and into the throat, which would otherwise result in ingested blood and the ensuing nausea that induces or, worse, aspiration of blood.

Nasal 'plugging' with tissue paper is often employed by patients and is not unreasonable as it will apply some degree of pressure on the

bleeding vessel on the anterior septum (though less so than with digital pressure).

Haemostatic Agents

On the rare occasion that a bleed is sufficiently brisk to resist pressure or anterior cautery, consideration should be given to the use of a low-pressure haemostatic agent before resorting to nasal packing. Various formulations are now manufactured, ranging from impregnated absorbable sheets to foam gels (see Management of Adult Epistaxis). These are powerful procoagulants and their insertion is relatively painless and therefore much better tolerated by patients, particularly children. They also have the advantage of not requiring removal.

Nasal Tamponade

Where bleeding proves resistant to the preceding measures, then it will be necessary to pack the child's nose. Dry compressed sponge packs are abrasive to the nasal mucosa, painful on insertion and painful on removal. Their use should be avoided unless no other option of packing is available.

Far preferable are gel-coated inflatable balloons, the insertion and removal of which are far less traumatic. They should, however, still be inserted after application of topical anaesthesia wherever possible—ideally one mixed with a decongestant such as phenylephrine (Co-phenylcaine™). Inflatable packs come in 4.5 cm lengths in their shortest form, which will still reach the nasopharynx in most children, so should be inserted with care.

Management of Recurrent Paediatric Epistaxis

History Taking

The value of a clinical history when dealing with recurrent paediatric epistaxis should not be overlooked. In addition to the self-evident questions relating to timing, frequency, duration and laterality of bleeds, it is essential to elicit any other tendency to bleeding such as easy bruising with innocuous knocks or bleeding gums whilst brushing teeth. The presence of such symptoms should raise suspicion about a clotting disorder. An enquiry should also be made regarding any bleeding disorders known to run in the family such as von Willebrand disease, haemophilia or HHT.

Investigations

Paediatric epistaxis is a ubiquitous problem and, for the vast majority, investigations are unfruitful and unnecessary. If there is suspicion of a coagulopathy, either because of family history or a description of prolonged bleeds or bleeding diathesis, the child should undergo a coagulation screen and bleeding time studies in the first instance, with further haematological investigations being guided by the results.

Any male beyond his pre-teen years presenting with brisk bleeds should undergo endoscopic examination of the sphenopalatine area on both sides, to exclude a juvenile nasopharyngeal angiofibroma. Imaging is only indicated where a JNAF or vascular malformation is observed on nasendoscopy or where nasendoscopy is unremarkable but suspicion is high as a result of the severity and frequency of bleeds. In those circumstances, a magnetic resonance angiogram (MRA) would be the investigation of choice.

First-Line Treatments

Simple Measures

Keeping the child's fingernails cut short minimises tearing of the thin nasal mucosa when fingers do inevitably make their way into the nose.

Intranasal Ointments

Randomised controlled trials have demonstrated that twice daily use of cream containing neomycin and chlorhexidine (Naseptin cream™) for 4 weeks is effective in increasing the rate of resolution of recurrent bleeds in children [4]. It is unclear whether the cream produces this effect through its antimicrobial properties or by acting as a barrier cream, but a subsequent randomised control trial using just petroleum jelly for 4 weeks did not demonstrate any significant difference in bleed resolution rate compared to no treatment

[5], suggesting that the benefit may come from reducing bacterial load in the nasal vestibule (vestibulitis), thus reducing crust formation.

Silver Nitrate Cautery

Both the antiseptic and pro-thrombotic properties of silver nitrate have served medical practitioners for centuries. Silver nitrate in its dry form is inactive, but on contact with water, a chemical reaction is catalysed, which releases free silver particles that bind with the surrounding tissue, forming an eschar that obstructs and thromboses small-calibre vessels (Fig. 39.2a, b). Cautery means, quite simply, to brand or burn (*kauterion* = branding iron). Silver nitrate cautery is generally well tolerated and effective in children, so long as the child is old enough to sit still for the time needed for the cautery to be applied. It should always be done after application of a lignocaine-soaked pledget against the area to be cauterised, for at least 20 min to obtain good anaesthesia; otherwise the chemical burn will cause distress to the child, rendering them unwilling to have the procedure repeated, as may be necessary. Interestingly, 75% silver nitrate has been shown to be more effective in resolving recurrent bleeds than 95% silver nitrate and induced less pain in the children.

The requirement for using antiseptic cream after cauterisation in children is open to debate—whilst it is thought to keep the cautery scab moist and so less prone to being picked at by the child, it is the authors' experience that it only serves to carry silver nitrate out of the nose as the cream liquifies, thus staining the nostril black for days afterwards. For this reason we have discontinued prescribing it after cautery with no increase in rebleed rate. Furthermore, a well-performed cauterisation should not result in thick eschar requiring moisturisation but rather just blanching of the nasal mucosa and thrombosis of the underlying vessels.

Silver nitrate, once activated, will react with most tissues it encounters, and so it is important to ensure that only the area to be treated is touched by the moistened silver nitrate stick. Patients or parents should also be advised post-procedure to wipe any nasal discharge away immediately with soap and water, to dilute the silver nitrate and minimise the subsequent staining of the skin of the nostril and upper lip. Any such staining will disappear after 3–4 days; they can be reassured.

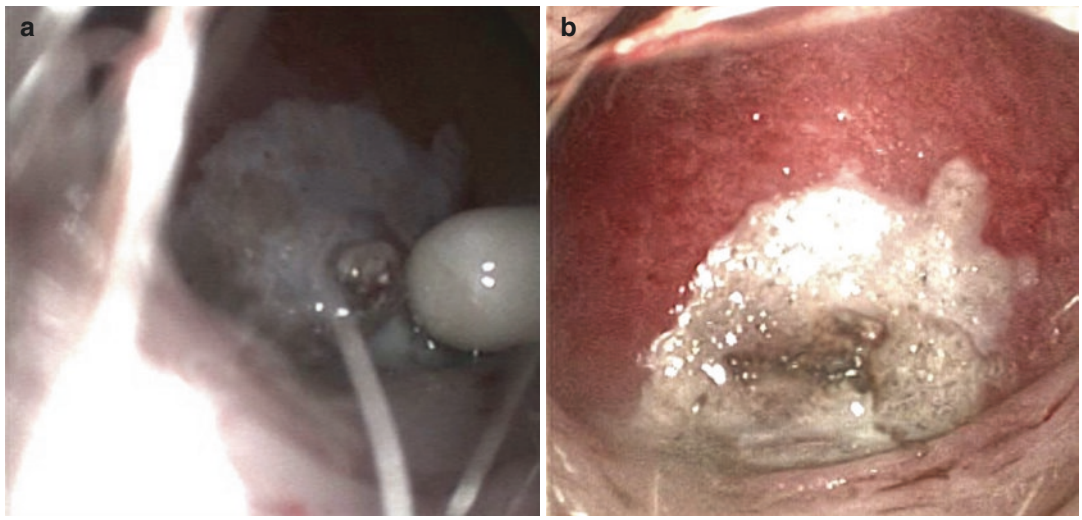

Fig. 39.2 (**a, b**) Silver nitrate cautery of anterior nasal septum (**a**). Applied as a rosette around bleeding point and then directly onto bleeding point. Resulting eschar that typically remains localised at the site of chemical cautery (**b**)

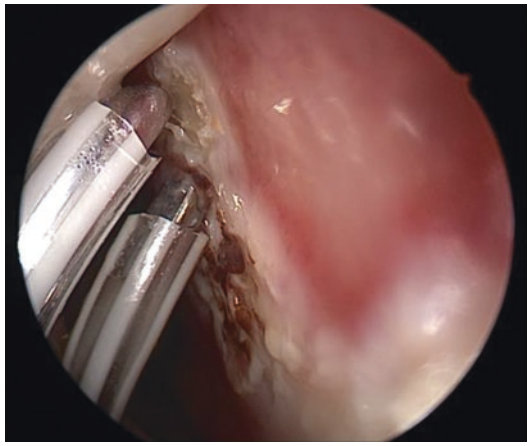

Fig. 39.3 Bipolar diathermy technique. Note the supplementary insulation added to the diathermy prongs by use of an intravenous cannula to cover the exposed tips

Second-Line Treatments

Electrocautery

If repeated attempts at silver nitrate cautery in clinic prove unsuccessful in reducing bleed rates, consideration should be given to a more substantial cauterisation using electrocautery—either bipolar, monopolar or hyfrecation (Fig. 39.3). A compliant and comprehending older child may tolerate having that done in clinic after local anaesthetic injection, but for most children, it will require a general anaesthetic. The more substantial, deeper burn resulting from electrocautery will reach the perichondrium, de-vascularising the cartilage immediately under the cauterisation on that side. For this reason, it is recommended that electrocautery should not be performed to Little's area on both sides of the septum synchronously to avoid the risk of inducing an iatrogenic septal perforation.

Surgical Treatment

Endoscopic Sphenopalatine Artery Ligation

Endoscopic ligation of the main feeding artery of the nasal cavity (the sphenopalatine artery) is rarely performed in children—not because it is contraindicated or ineffective but simply because first- and second-line treatments will be effective in adequately reducing the bleed rate in almost all cases of recurrent childhood epistaxis, and even when they don't, the small amount of blood lost during each recurrent bleed rarely results in a volume deficit and so is rarely detrimental to their health.

Endoscopic Tumour Removal

With recent advancements in endoscopic sinus surgery, the vast majority of Juvenile angiofibromas (JAs) can now be removed via the endonasal route (please refer to Chap. 33). It is not unusual for the tumour to be embolised preoperatively, to reduce the amount of bleeding at surgery, as bleeding is a major limiter of endoscopic surgery. Juvenile angiofibromas (JAs) do vary in their constitution, ranging from predominant fibroma (and thus less vascular) to predominant angioma (from which significant bleeding can be expected at the time of surgery). The preoperative contrast scan will help ascertain which variant is being operated on.

Adult Epistaxis

Epistaxis is the most common acute adult ENT presentation in the UK. Although ultimately self-limiting, adult epistaxis presenting to secondary care does carry an all-cause 30-day mortality rate of 3.4% [2], which is to say that 3 in 100 adults requiring secondary care for an acute epistaxis will not survive the next month, for whatever reason.

Aetiology

The mechanisms underlying adult epistaxis are quite different to those in children, to the extent that they can almost be considered separate clinical entities. Adult arterioles are thicker walled than those in children and, in the elderly, are also atherosclerotic. The overlying nasal mucosa is also more resilient. As a result, it takes a more concerted effort, usually through habitual nose

picking, to induce a nosebleed in adults. Most adult bleeds do, therefore, tend to be truly spontaneous. The intravascular event that occurs to result in a nasal blood vessel spontaneously rupturing its wall and adventitia to result in a bleed is still unknown and open to conjecture. Whatever that event is, it is not selective in which arterioles it ruptures, as adults can have spontaneous bleeds from the larger posterior nasal vessels as frequently as they do from the smaller anterior vessels within the mucosa of the septum. Such an intravascular event does not appear to occur in children, as posterior bleeds are thankfully seldom seen in children. Similarly, that event does not seem to happen with anything like the same frequency in the trachea or lungs, despite them being similar structures with lumen that are lined with the same columnar respiratory epithelium and subject to the same airflow stresses as the nose, suggesting there is something idiosyncratic about the nasal vessels that makes them so prone to spontaneous rupture.

Coagulopathy

The presence of a coagulopathy—whether inherited or pharmacological—is not a factor in causing spontaneous bleeds, as epistaxis is as common in adults who do not have a coagulopathy as it is in those who do. An existing coagulopathy does, however, more often result in a presentation to hospital, as the bleeds will be more protracted and more difficult to stop with first-line measures.

Pathology

There are, of course, pathologies that predispose patients to having spontaneous bleeds, such as septal perforations, vascular anomalies and neoplasms (Fig. 39.4). These are therefore considered secondary bleeds. Even in the presence of such pathologies, an intravascular event must still occur to result in the vessel rupturing.

Septal Perforation

In the case of a septal perforation, it is likely that the event is crust excursion from the edge of the perforation, as most bleeds from septal perforations arise from the posterior edge, which tends to be the most crusted edge due to the drying effects of turbulent airflow induced by the presence of the perforation.

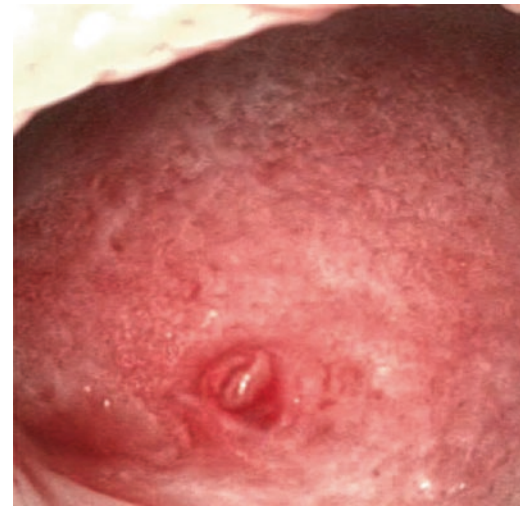

Fig. 39.4 Tiny vascular lesion from recent bleeding point of mid-nasal septum

HHT

Hereditary haemorrhagic telangiectasia (previously also known by its eponymous name Osler-Weber-Rendu syndrome) is an autosomal dominant condition in which vascular malformations replace normal capillaries between arteries and veins within the mucosal membranes of the upper aerodigestive tract, the intestines and the lungs, as well as on the skin, liver and brain. The tell-tale telangiectasia usually first appears on the skin and lips when patients are in their late 20s and 30s and become increasingly numerous over the course of their lifetime. Within the nose, the telangiectasia typically confine themselves to the anterior nasal cavity—on the septum and middle/inferior turbinates, with relative sparing of the posterior nasal cavity (Fig. 39.5). The main effect of the telangiectasia is to cause spontaneous epistaxes, but they can also result in spontaneous, and potentially catastrophic, bleeds in the gut, lungs or brain. The epistaxes associated with HHT are frequent, prolonged and profuse, and they present a particular problem to ENT surgeons, as the usual means of stopping brisk

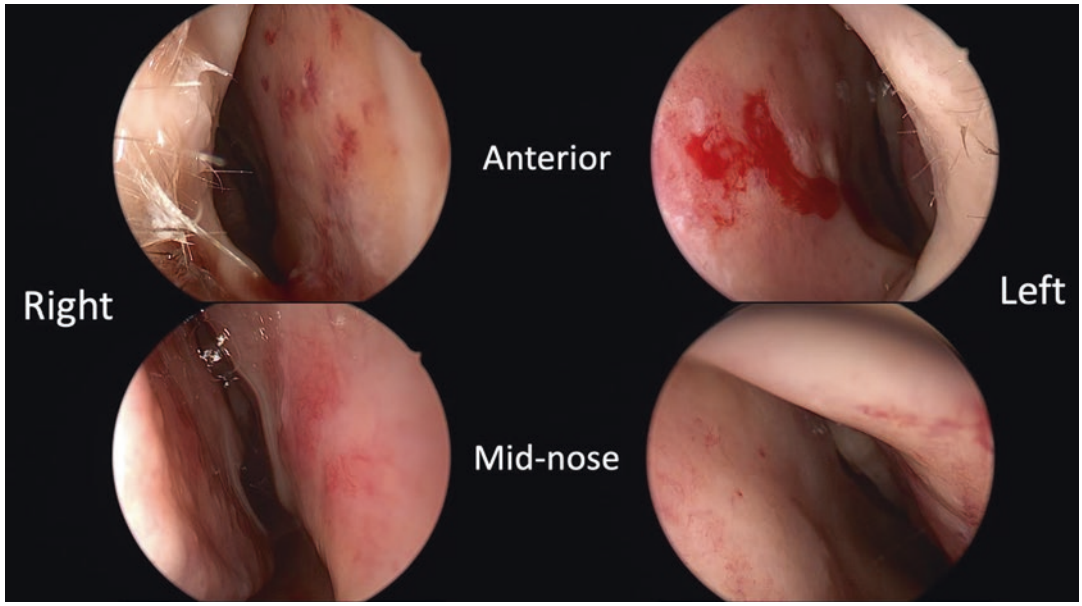

Fig. 39.5 The vascular lesions of HHT are concentrated in the anterior nasal cavities, and the posterior lesions are relatively infrequent and rarely bleed

bleeds, viz. nasal packing and tamponade only serves to precipitate the bleeding by causing other telangiectasia to rupture and bleed.

It is common for HHT patients to have chronic iron deficiency anaemia due to the frequency of their bleeds, and blood transfusions are often sadly a fact of life for them. HHT has no known cure for now, although the abnormal genetic sequences causing the condition have been identified, which allows for genetic testing of family members and provides hope for gene replacement therapy in the future.

Other Vascular Abnormalities

Other vascular abnormalities occurring in the nose will also predispose patients to spontaneous nosebleeds, such as large vessel arteriovenous malformations and inflammatory conditions such as vasculitic and granulomatous disorders. A pyogenic granuloma is a characteristic lesion of the anterior nasal cavity that is a common cause of nosebleeds during pregnancy.

Neoplasms

Intranasal neoplasms can predispose patients to epistaxis—both benign neoplasms (haemangiomas, angiofibromas) and malignant neoplasms (squamous cell carcinoma, adenocarcinoma, mucosal melanoma). It is unusual for malignant lesions to invade nasal arterioles to cause brisk bleeds. For this reason, a blood-stained unilateral nasal discharge is a far more concerning symptom than a unilateral brisk bleed.

Induced Epistaxis

Of course, not every epistaxis is spontaneous and some are clearly preceded by a trigger event.

Facial Trauma

It can be expected that trauma to the nose will result in some degree of bleeding—the degree of bleeding largely being proportional to the degree of trauma. Such trauma may induce bleeding from the anterior ethmoidal artery (Fig. 39.6). A low-velocity blow may simply rupture a septal vessel causing a transient, self-limiting bleed. Medium-velocity blows may cause tearing of the nasal mucosa, particularly if the nasal bones are displaced, causing a more persistent but low-pressure bleed. A high-velocity blow sufficient to cause fracture and displacement of the ethmoid bone may well result in rupture of the anterior

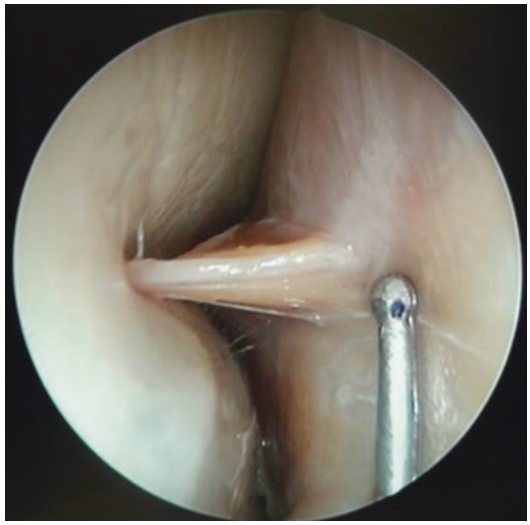

Fig. 39.6 Anterior ethmoid artery, as seen through an external incision with retraction of orbital contents. Note that the artery passes through the suture line between the frontal bone and lamina papyracea

ethmoid artery, especially if it involves the fovea ethmoidalis. The resultant bleed will be brisk and standard balloon packs will not directly tamponade it as the bleeding vessel is high in the vault of the nose. Because the bleed is arterial, the vessel will frequently spasm, giving a false perception that the bleeding has been controlled by packing, only to restart again several minutes later. A traumatic ethmoidal bleed can only properly be controlled once the nasal bones have been reduced and realigned, allowing the vessel ends to be re-approximated.

Iatrogenic

Almost all iatrogenic nosebleeds arise as a result of endonasal surgery—either endoscopic sinus surgery, septoplasty or turbinate surgery. Bleeds can happen at the time of surgery or in the postoperative period. They are often problematic, requiring nasal packing and a prolonged postoperative stay. Unfortunately, postoperative packing significantly increases the risk of intranasal adhesion formation in the healing phase, which will invariably counteract any benefit the patient may otherwise have gained from the original surgery.

Pharmacological

Recreational use of cocaine causes intense vasoconstriction and, eventually, ulceration of the nasal mucosa. The ulcerated mucosa will be prone to bleeding, sometimes quite briskly. With continued use, the ulceration will progress to a septal perforation, which, as already discussed, carries its own rate of bleeding.

Nosebleeds are a common side effect of intranasal corticosteroid sprays due to their action of thinning of the nasal mucosa, mostly notably where they are directly administered. They are generally low-level bleeds, but their frequency can render patients non-compliant with using their steroid spray. Septal crusting and bleeding can be improved by asking the patient to administer their spray with the contralateral hand for each nostril, thus directing the nozzle of the metred-dose spray towards the lateral nasal wall, rather than towards the septum, as it usually is on the side of the dominant hand.

Management of Adult Epistaxis

Management of Acute Adult Epistaxis

A national audit of management of epistaxis in secondary care conducted in the UK by INTEGRATE (National ENT Trainee Research Network) in 2016 [7] identified several factors that are associated with poorer outcomes in adult acute epistaxis. These are:

- Established hypertension
- Ischaemic heart disease
- Diabetes
- Previous epistaxes
- Antithrombotic medication

Initial First Aid

Early appropriate first aid is the most important and often neglected element of hospital-based epistaxis care. A recent RCT exploring the role of topical tranexamic acid in acute epistaxis noted incidentally that, outside of trial protocol,

95% of patients attending the Emergency Department with epistaxis went on to have nasal packs inserted. However, within the trial, the robust instigation of 10-min anterior nasal pressure followed by 10 min of intranasal topical vasoconstriction in patients who continued to bleed saw the percentage of patients packed fall to 42.5% [8].

Medical Management

Management of Concurrent Oral Antithrombotic Agents

There is a paucity of condition-specific evidence to guide the optimal management of concurrent oral anticoagulants during episodes of acute epistaxis. However, local and national generic guidelines on their general management are felt to be transferable to epistaxis patients. The post-treatment recommencement (or otherwise) of these agents should be considered via a documented risk/benefit assessment undertaken in liaison with the patients' primary care and haematology clinicians.

It is currently recommended that anti-platelet therapy should be continued during the hospital management of uncomplicated epistaxis and discussed with haematologists in cases where sustained haemostasis is not achieved. Evidence suggests that halting such agents does not shorten initial hospital stay, largely due to the extended duration of effect of these drugs. The 2016 UK national audit, however, did show a reduction in epistaxis-specific re-presentation rates where anti-platelet medication was stopped, highlighting the benefit of establishing whether such medications are truly still indicated prior to discharge, with changes documented and discussed with the patient's primary care providers.

Blood Transfusion

Blood products are administered to 4.5% of patients presenting to hospital with acute epistaxis. The 2016 INTEGRATE national audit demonstrated our threshold to transfuse is probably too low, given the associated risks from anaemia. National guidance in the UK recommends a transfusion threshold of 70 g/L in most patients/clinical scenarios, but 80 g/L in patients symptomatic from their anaemia, or in patients with cardiac comorbidity, where significant ongoing or future blood loss is predicted.

Systemic Tranexamic Acid

Emerging evidence suggests tranexamic acid should not be used in epistaxis despite previous national guidance (weakly) recommending its use in certain clinical scenarios. There are no data relating to its systemic use in acute epistaxis, but a large trial of intravenous tranexamic acid in upper gastrointestinal bleeds demonstrated no reduction in mortality, yet a slight increase in venous thromboembolic events [1].

Nasal Cautery

Intranasal cautery is strongly recommended as first-line treatment in all epistaxis patients following appropriate initial first aid and topical vasoconstriction. Cautery should be precise and targeted at a visible or potential site of bleeding as identified during anterior rhinoscopy. Evidence suggests the addition of rigid endoscopy or microscopy may lead to a greater rate of detection of bleeding points, although logistics often prevent this being available at point of initial presentation (in the Emergency Department) or being practical due to the unstemmed flow of blood. Low-quality evidence suggests that electrocautery is superior to chemical (silver nitrate) cautery, although the 2016 national epistaxis audit demonstrated this was rarely employed during first-line intervention. The prophylactic placement of dissolvable packs post-cautery is not supported by evidence.

Intranasal Agents

The placement of non-dissolvable anterior nasal packs is a highly effective treatment of epistaxis [3]. Such packs, however, should only be used when first aid, vasoconstriction and attempted cautery have failed to achieve haemostasis or in circumstances where the extent of bleeding makes the aforementioned unsafe or impractical. Their use should be limited due to significant associated patient discomfort both on insertion and removal of the packs. Many non-dissolvable

packs are licensed for domiciliary use although, in the UK, audit data shows that patients with nasal packs are traditionally admitted. National guidelines do support outpatient management in appropriately selected patients where suitable governance measures are in place. Inflatable packs and nasal tampons have been shown to be equally effective at achieving haemostasis; however inflatable packs are better tolerated by patients and therefore should be considered the non-dissolvable pack of choice (Fig. 39.7). Once placed, the pack pressure should be assessed again 20 min post-insertion and regularly thereafter to ensure the tamponade effect is maintained. Under inflated packs will be less effective (though still of some value), but over-inflated packs (or equally ribbon gauze packs inserted too tightly) run some risk of septal mucosa necrosis and subsequent perforation formation, or necrosis of the nostrils, if left in place for a duration. This should be considered in any packed patient who complains of significant pain. It is always worth remembering that nasal packing does NOT need to be inserted tightly—it just needs to be inserted completely. The optimum period for packs to remain in situ is still unclear. This represents a crucial area for future research as it is this time period that largely dictates the total length of inpatient stay in such cases. Recent further interrogation of the national audit data did suggest a packing period of 24 h may be optimal; however there are substantial limitations acknowledged when reporting this conclusion.

Fig. 39.7 Image of an inflatable nasal pack. Note correct placement of nasal pack. The pack is orientated parallel to the palate and not towards the top of the nose. The pack is inserted in its entirety as far as the balloon conduit—any pack left external to the nostril will have a tendency to expel the pack once inflated

The use of prophylactic antibiotics following extended periods of packing is common practice but is done largely on historical grounds. Nasal sponge packs could harbour intranasal organisms (largely *Staphylococcus*) and, if left for prolonged periods, could risk sepsis and even toxic shock syndrome. However, current packs are non-porous and gel-coated, so do not carry such risks. Indeed, there is now evidence confirming that prophylactic antibiotics are not beneficial; they go against the philosophy of antimicrobial stewardship; as such, they are not recommended.

Following pack removal, a further attempt to identify a potential site of bleeding has been recommended and if identified targeted cautery should be applied post-local anaesthetic vasoconstriction. This said, with or without post-pack cautery, 30-day representation rates have been demonstrated to be low and broadly similar at somewhere between 10 and 15%.

There is a wide array of dissolvable packs and haemostatic agents available for the management of acute epistaxis, many of which have high-level evidence supporting their use from generally small, single-centre studies. Despite such evidence, no single product has emerged widely into common practice. This may be due to general resistance to change, the relative high cost per intervention or due to the complexity of delivery for some of the haemostatic agents. Improved patient tolerance and reduced requirement for hospital admission have suggested that such interventions may in fact be cost-effective, resource-light and preferable to patients. It is for these reasons that such products would benefit from larger-scale research or increased use within well-constructed and monitored service-development projects.

Management of Recalcitrant Epistaxis

The general principle in managing epistaxis is to employ a logical, stepwise approach to treatment, ensuring each iterative intervention is delivered optimally. It is recommended, therefore, that if sustained haemostasis is not achieved despite a period of optimised non-dissolvable intranasal packing, then the next step should be surgical intervention with repacking only employed as a temporising measure whilst safe transfer to theatre is organised. If immediate access to the operating theatre is not possible, guidance permits the patient to be repacked, accepting that more substantial packing may be required, including postnasal packing and ribbon gauze packing anteriorly. This is the only situation when such extensive packing should be considered, nowadays, as it is extremely uncomfortable and unpleasant for the patient, even after application of local anaesthetic.

Surgery

Ipsilateral endoscopic sphenopalatine artery ligation (ESPAL) is supported as the gold standard surgical intervention for refractory acute epistaxis and should be performed by a suitably trained emergency-safe surgeon who has knowledge of the anatomy of the sphenopalatine region. It is essential that all branches of the SPA are identified and dealt with, bearing in mind that the artery may divide and give off some branches before it has exited the sphenopalatine foramen (Figs. 39.8a, b).

Some surgeons clip the individual branches; some ablate them with diathermy. No strong evidence exists to recommend one means over another, so it comes down to surgeon preference, as does the decision whether to divide the branches once clipped/ablated or not.

In experienced hands, endoscopic ligation can be performed in a matter of minutes, minimising the time required under anaesthesia. Where even a short general anaesthetic is considered too high a risk, ESPAL can be performed under local anaesthesia after good decongestion.

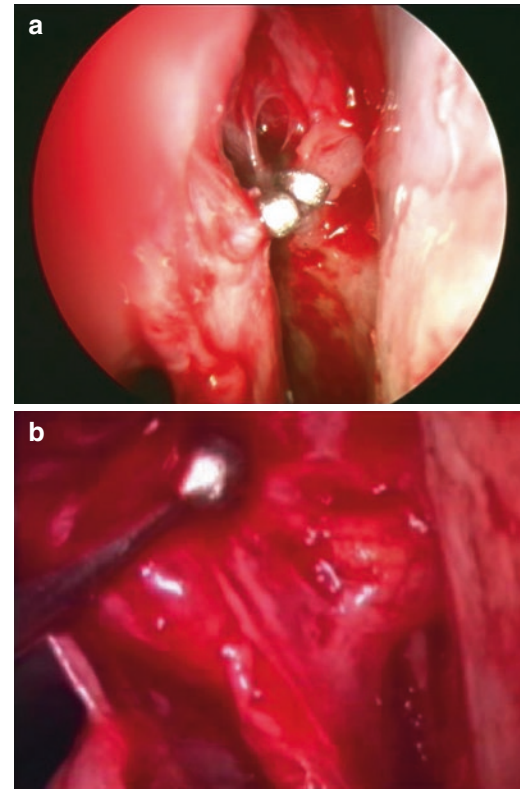

Fig. 39.8 (**a, b**) Images demonstrating ligaclips across the sphenopalatine artery. Two clips are more secure than a single clip, should the latter become detached. Note the arterial branches on figure b (Images courtesy of Sean Carrie)

Precautionary repacking after artery ligation is poor practice and should be discouraged.

Embolisation

Whilst artery embolisation by an interventional radiologist (IR) has been demonstrated to be an effective treatment in refractory epistaxis, it is considered to have a poor side-effect profile and is not widely available in UK centres (Fig. 39.9). It is very much both resource-dependent and expertise-dependent, and so is largely the domain of tertiary centres with high levels of expertise and high case numbers. In such centres, complication rates are very low. Interventional radiologists who contributed to the national consensus document were keen to dispel the misconception that embolisation is a routinely feasible option in patients otherwise

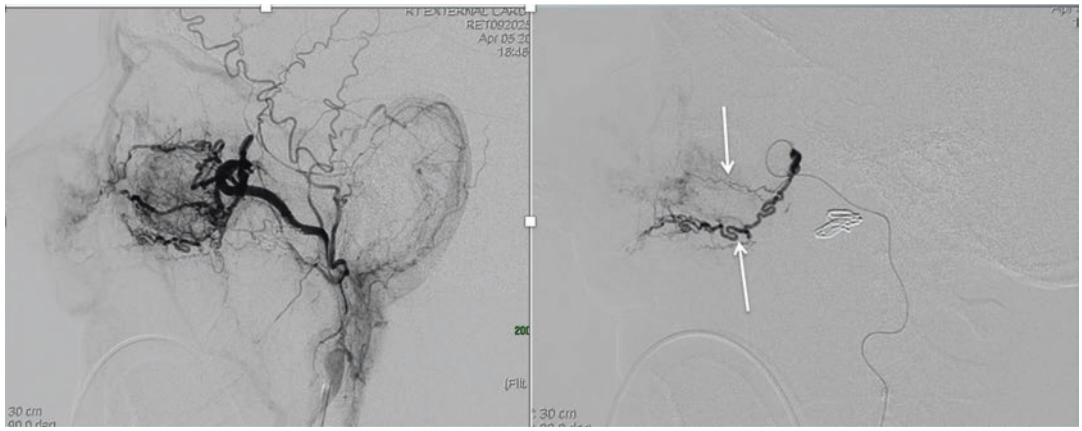

Fig. 39.9 Embolisation images: pre-embolisation vascular blush shown on left and post-embolisation image shown on the right

felt to be too high risk for general anaesthesia. It is apparent that IR procedures attempted under local anaesthetic are generally poorly tolerated by patients and likely to be associated with higher rates of complications due to the requirement to deploy less targeted embolisation.

Management of Hereditary Haemorrhagic Telangiectasia (HHT)

The management of HHT is described separately because of the difficulties and unusual problems the condition poses that demand different strategies from other causes of epistaxis. The bleeding occurs from fragile superficial telangiectatic vessels that are typically multiple, bilateral and in the anterior region of the nasal cavities. The severity of the problem ranges from mild to severe, depending on the individual genetic mutations and age. The severe bleeders will invariably present to hospitals, but it is estimated that 80% of the people affected by this familial disorder remain undiagnosed at present. Whilst it affects children and adults, the bleeding generally starts to be more frequent and profuse in adolescents and young adults and progresses with age in adulthood.

Acute bleeds: The acute situation in HHT can be a very difficult situation to control and generally lead to hospital admission. It is best managed by external pressure compressing the nasal alae to tamponade the nose with the patient sitting upright and forward whilst maintaining calm and patience. Unlike normal epistaxis, it is often impossible to see or control the bleeding point that can be on the septum or lateral nasal wall. Nasal packs are best avoided unless absolutely necessary as they will traumatise other fragile telangiectatic vessels and make the situation worse. If packs are necessary, it is best to use fragmentable material (Nasopore: Kalamazoo, MI, USA) that does not need removal which will induce recurrent bleeding. If non-absorbable packs are inserted, they are best left in situ for several days before very gentle removal. A preferable strategy is to fill the nasal cavities with a haemostatic thrombotic preparation (Floseal: Baxter, Deerfield, IL, USA). It is important to consider the systemic effects of epistaxis as patients may be anaemic from frequent bleeds could require haematological intervention.

Recurrent bleeds: Frequent recurrent nose bleeds will typically present in outpatients. Management should include a comprehensive history that includes a family history, gastrointestinal bleeding, and menorrhagia in some cases. Utilising the Epistaxis Severity Score (ESS) questionnaire is a helpful assessment and helpful to monitor progress. Consideration should be given to wider investigations that include genetic assessment, CT thorax/abdomen, and MRI brain to identify arteriovenous malformations that may need intervention.

Setting up a multidisciplinary team that includes specialists such as paediatrics, thoracic medicine, gastrointestinal disease, haematology, neurosurgery and genetics is highly beneficial to the management.

Patients should be advised to avoid local trauma to the delicate nasal mucosa and to apply topical medications to the nasal cavities such as saline, antibiotic cream/ointment or petroleum jelly. Applying oestrogen cream to the nose is sometimes helpful but lacks any evidence base. The standard outpatient nasal cautery with silver nitrate is usually ineffective and should be avoided in severe cases. Day case admission for ablation of telangiectatic vessels within the nose should be offered if epistaxis is frequent and heavy. Vascular ablation can be performed in theatre by a coagulating Laser (KTP: potassium titanyl phosphate (KTP) crystal), careful use of diathermy (bipolar or monopolar) or coblation. This often improves the situation but new telangiectatic vessels will always form and require further ablation within a few months. Daily tranexamic acid has been shown to be effective in decreasing recurrent nasal bleeds. Tamoxifen is an anti-oestrogen that has a positive impact on HHT-related epistaxis. In severe cases, thalidomide and monthly intravenous bevacizumab are both effective but should be used selectively in a controlled manner. Thalidomide enhances blood vessel stabilisation and induces vessel maturation. Bevacizumab is an expensive anti-VEGF monoclonal antibody but may cause serious side effects.

Management surgical strategies for patients with severe bleeding problems include septodermoplasty (septal mucosa is excised and replaced by a split skin graft) and total closure of both nostrils (Young's procedure). The latter is effective and evidence based but reserved for the most difficult cases.

Areas of Controversy and Research

- A greater adoption of the use of non-absorbable nasal packs in the community would prevent a significant number of hospital admissions. Such a relatively major shift in paradigm would need to be demonstrated as safe and cost-effective through large-scale studies and would have to be conducted under tight local protocol.
- The optimal timing of ESPAL surgery remains contentious. There are proponents of early surgery—even as a first-line alternative to nasal packing—although cost-benefit studies to date indicate that early surgery is only cost-effective when packing would otherwise have necessitated 3 or more days as an inpatient. Others still feel that surgery should be reserved for refractory epistaxis once all local and medical factors have been addressed.
- There is currently much interest in local anaesthetic/office-based rhinology surgery, and a move to ESPAL under LA would certainly be an attractive proposition, as it would obviate the need for nasal packing and for hospital admission. However, it would first need to be proven to be both safe and effective.

Key Learning Points

- There are very few situations where 'posterior' packing with Foley's catheters and ribbon gauze can still be justified these days.
- Repeat packing of the nose for failed haemostasis should only ever be a temporising measure to control bleeding until access to the operating theatre can be organised.
- Endoscopic sphenopalatine artery ligation is the treatment of choice for epistaxis refractory to first-line measures.
- The non-absorbent nature of the materials used to manufacture current inflatable packs means that antibiotics are not indicated for prophylactic cover for the duration of pack placement.
- Stopping oral anticoagulants during an admission for epistaxis does not shorten the length of stay, but it may reduce the likelihood of representation due to further bleeding.

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Olfaction, Taste and Its Disorders

40

Lisha McClelland and Abdul Nassimizadeh

Summary

- Smell
  - Physiology
  - Classification of smell disorders
  - Aetiology of impairment
  - History taking, clinical examination and investigations
  - Therapy and prognosis
- Taste
  - Physiology
  - Classification of taste disorders
  - Aetiology of impairment
  - Taste evaluation
  - Therapy and management

Introduction

Olfaction and gustation are both understated, yet critical physiological functions. It is through these sensory abilities that we are capable of perceiving thousands of odours, as well as the ability to detect the flavour of foods and detect hazards including natural gas, fire and spoiled food. Olfactory function is closely linked to longevity and quality of life. Individuals with anosmia and ageusia have been found to increase long-term sugar and salt intake, resulting in higher rates of chronic medical conditions such as renal disease, diabetes mellitus and hypertensive disorders [1, 2]. Smell sensation also plays a critical role in pleasure, kin recognition and pheromone detection. Impaired smell or taste should be taken seriously, due to the potential of harm to the individual and those near them, as well as the impact on physical and mental well-being.

Smell

Physiology of the Olfactory System (Fig. 40.1)

The nasal turbinates play a crucial role in the physiology of nasal airflow and can create turbulent airflow. Alteration to laminar airflow directs air superiorly towards the olfactory epithelium, a specialised covering lining the upper regions of the septum, cribriform plate, superior turbinate and several areas of middle turbinate. Velocity, air volume and direction can all alter smell perception.

The cells found superiorly are derived embryologically from both the olfactory placode and the neural crest. Innervation, and therefore chemosensation, involves the olfactory nerve, the trigeminal nerve and autonomic fibres of the superior cervical ganglion. Trigeminal chemosensory nerve endings play a role in the identifi-

L. McClelland (✉) · A. Nassimizadeh
University Hospital Birmingham, Birmingham, UK
e-mail: Lisha.mclelland@uhb.nhs.uk

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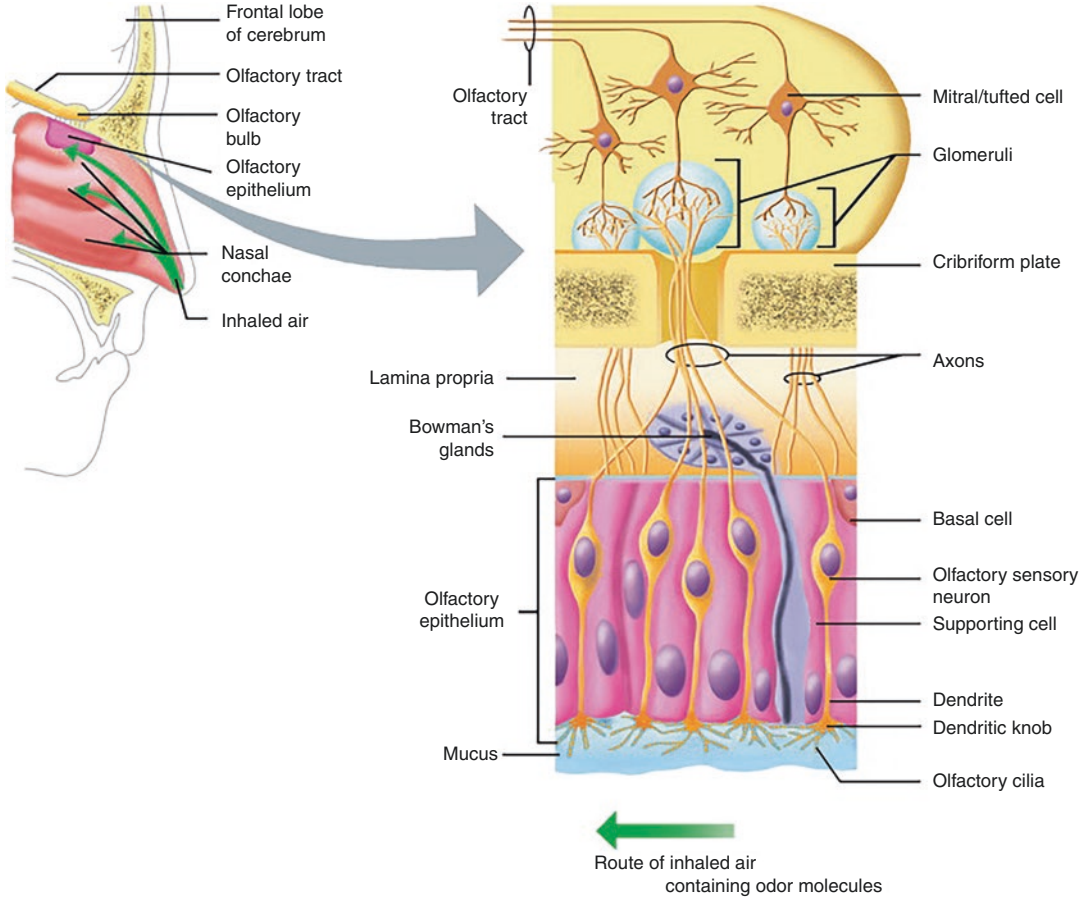

Fig. 40.1 Anatomy of nasal cavity with regard to olfaction and olfactory epithelium anatomy. (Citation: C. Moon, S. Jun Yoo, H. Soo Han. Smell. Editor(s): Michael J. Aminoff, Robert B. Daroff, Encyclopedia of the Neurological Sciences (Second Edition), Academic Press, 2014, Pages 216–220, ISBN 9780123851581, https://doi.org/10.1016/B978-0-12-385157-4.00072-5)

cation of noxious stimuli including air pollutants, ammonia, ethanol and high concentrations of carbon dioxide (sharp and acidic) [1].

Odorants are absorbed into the mucus covering the olfactory epithelium. The mucus in the olfactory cleft is derived from specialised Bowman's glands and differs in composition from the remainder of the nasal cavity. Secretions from these glands include odorant-binding proteins, growth factors, immune factors and biotransformation enzymes. The odorants bind to olfactory receptors found in the cilia. The process of transforming chemical energy into signal transduction requires a complex cascade dependant on G proteins inside cells activating the lyase enzyme and eventual opening of the ion channels to create action potentials. Olfaction changes throughout an individual's lifetime, with the process of receptor gene switching affecting the functional receptors found on neurons [1].

The axons of the olfactory receptor cells project across the cribriform plate and number approximately 10 to 20 million. Each can respond to multiple stimuli and result in billions of combinations [3]. Axons from these olfactory neurons form nerve bundles (fila olfactoria), which synapse beyond the cribriform plate with other neurons in the olfactory bulb.

There is a second method for smell perception via retronasal olfaction [4]. Odorants in this scenario rise through the nasopharynx and through the posterior choanae and ascend superiorly to

the olfactory epithelium. This form of olfaction plays a vital role in flavour perception.

Smell Impairment Classifications [4, 5]

Olfactory impairment can be classified by a variety of different methods that are not mutually exclusive. Aetiologically, there are three broad categories depending on the site:

- Conductive losses secondary to obstruction
- Sensorineural loss due to damaged neuroepithelium
- Central nervous system dysfunction

In general terms, most olfactory dysfunction due to conductive factors is treatable, but those due to sensorineural causes are not.

Smell dysfunction can also be categorised, on the basis of perception, into quantitative or qualitative disorders. Quantitative disorders include hyposmia (decreased ability to smell) and anosmia (functional inability to smell or to detect specific odours). Dysosmia (altered smell perception) is a qualitative change and can be classified as phantosmia (perception of odour without stimulus) or parosmia (altered perception of odour with stimulus).

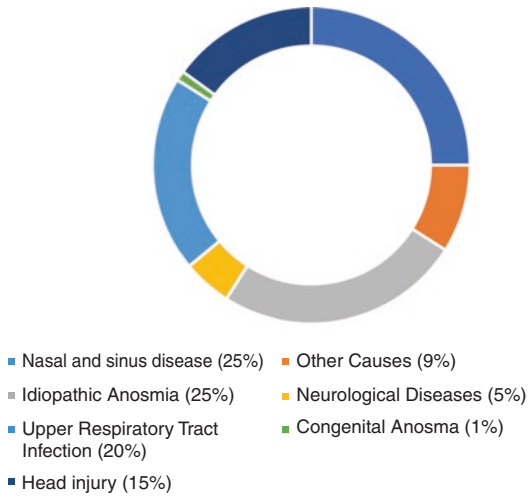

Fig. 40.2 Pie chart indicating prevalence of smell disorder aetiology [1, 4, 5, 6, 7]

Aetiology (Fig. 40.2)

Whilst sinonasal disease, respiratory tract infections and head trauma account for most causes of olfactory dysfunction, it is important to note approximately a quarter of patients have an undetermined cause. We will discuss the more frequent causes of olfactory impairment.

Nasal and Sinus Disease

Any inflammatory or obstructive process in the nose can result in disturbance of olfaction, with common examples including rhinitis and chronic rhinosinusitis (CRS). Whilst CRS has previously been viewed as a solely conductive cause of olfactory dysfunction, there now appears to be some evidence related to neural dysfunction, though this remains the most treatable cause of olfactory impairment [4].

Rhinitis and autoimmune conditions such as granulomatosis with polyangiitis (GPA) and Sjogren's syndrome can also lead to olfactory impairment. The loss of a moist receptor environment and mucosal inflammation causes deterioration in chemoreception and transduction.

Olfactory loss can also be secondary to complete obstruction of nasal airflow from neoplasms such as inverted papillomas, haemangiomas, squamous cell carcinomas and other sinonasal tumours.

Rarely anosmia can also result from intracranial tumours such as olfactory groove meningiomas, frontal lobe gliomas and pituitary adenomas. These patients often present with other cranial nerve abnormalities.

Upper Respiratory Tract Infections (URTI)

URTI continues to be one of the most frequent causes of neural olfactory loss, with a significant proportion of the population suffering temporary smell loss. This is reported more commonly in women (70–80% of cases) and is often attributed to a viral infection. This sequence of events may

be underreported in the paediatric population who suffer with significant higher bouts of URTIs [6].

Viral infection causes both conductive loss, due to mucosal inflammation, and sensorineural loss due to changes in the neuroepithelium and olfactory pathway. Common viruses include rhinovirus, human parainfluenza virus 3 and respiratory syncytial virus. Since 2020, one of the most prevalent viruses has been severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).

Over 50% of patients affected by the SARS-Cov-2 virus have reported a smell and/or taste disorder, with anosmia being the most prevalent. This is possibly due to changes in the neuroepithelial supporting cells, but the virus is neurotropic and neural dysfunction may also occur. Unlike typical URTI, olfactory dysfunction in COVID-19 was not associated with nasal obstruction or rhinorrhoea [7].

Given the plasticity of olfactory neurons and their ability to recover spontaneously, one-third of patients show improvement after 6 months [7]. Complete recovery is less likely with longer duration of symptoms.

Head Injury

Five to ten per cent of patients with head trauma experience a loss of olfactory function. Those with fractures in the frontal region are more commonly associated with olfactory loss. Occipital trauma is the second most common cause [6]. These injuries can result in a shearing injury of the olfactory axons, brain contusions or haemorrhage around the olfactory region or alterations in the sinonasal tract.

Typically, these patients have an immediate onset of olfactory dysfunction, though there can be delays in onset or reporting, often due to the important impact of other injuries. In 10% of cases with anosmia secondary to trauma, there is some degree of olfactory function that returns, though this is usually diminished.

Neurodegenerative and Neurological

Though it is difficult to quantify, ageing continues to be a predominant cause for olfactory decline, with biopsy-proven studies showing degeneration of the olfactory epithelium. >50% of individuals aged between 65 and 80 years and 62–80% of those >80 years of age show decreased olfactory function. With a reported prevalence of olfactory decline of approximately 25% in those aged over 50, and 60% in those over 80 years of age, this becomes a critical public health topic [1, 5].

There are multiple factors that contribute to this, such as age-related changes in the nasal mucosa, cumulative damage from environmental insults, decreased mucosal enzymes, sensory loss of receptor cells and changes in neuromodulator systems. It is well established that there are significant age-related changes in neurotransmitters and numerous enzymes [1]. Similarly, there may be structural and functional abnormalities that affect expression of aberrant proteins.

It is important to note that a reduction in smell may be an early warning for neurodegenerative diseases such as Parkinson's disease and Alzheimer's disease. Elderly people with lower scores in odour identification have a much higher risk of mortality.

Psychiatric disorders such as depression and schizophrenia have been associated with olfactory loss; patients with dementia and epilepsy show similar symptoms [2]. Interestingly, there are similarities in the anatomical areas of the brain associated in depression and olfactory processing.

Medication and Chemicals [8, 9]

A significant proportion of drug treatments have the potential to induce chemosensory side effects; the incidence on average is 5%. Older patients, who disproportionately use medical management, may be more vulnerable to medication-induced disorders.

Commonly used medications, which have potential olfactory consequences, include antibiotics (e.g. aminoglycosides, macrolides, tetracycline), chemotherapy drugs and opiates and antacids. Similarly, surgical patients have a risk of anosmia secondary to anaesthetic drugs with an approximate incidence of 1.8%.

Whilst most cause reduction of smell, there are several medications that report increased sen-

sitivity to odours. These include methacholine, levothyroxine and drugs that targeted α_{1A} adrenergic blockade.

There are also patients who have olfactory dysfunction following exposure to toxins or aerosols. Commonly these include formaldehyde, cyanoacrylates, herbicides, pesticides and cigarette smoke. These losses are typically permanent based on length of exposure.

Surgical Trauma

Olfactory loss is a potential risk of surgery. Local anaesthetic agents or psychological factors such as anxiety or stress may cause temporary symptoms. Postsurgical scarring or excessive crusting altering the airflow pathway, overresection of the superior or middle turbinate, avulsion or traction of the olfactory neuroepithelium, excessive use of electrocautery and vascular compromise to the olfactory epithelium may cause long-term dysfunction [3.6]. The use of through-cutting or powered instruments in areas of olfactory concern has a lower likelihood of stripping the neuroepithelium.

Childhood Aetiology

Olfactory dysfunction in a paediatric population accounts for a small percentage of all patients, though these children are susceptible to the same hazards as adults. Common causes for this symptom are similar to adults, though also include congenital failure of olfactory development alone or as part of a genetic condition such as Kallman syndrome or Bardet-Biedl syndrome [6, 10].

Kallman syndrome: anosmia with delayed or absent puberty, due to hypogonadotropic hypogonadism and failed migration of GnRH neurons from the nasal placode to the brain

Bardet-Biedl syndrome: a genetic condition that causes hyposmia/anosmia with multi-system disorders. Features include childhood obesity, visual loss, polydactyly, intellectual impairment, renal abnormalities, hypogonadism, abnormal genitals and infertility

Other Aetiology

There are various endocrine abnormalities like hypothyroidism, Addison's disease, Cushing's disease and diabetes mellitus, which may also show decreased or absent olfactory function. There are also nutritional deficiencies, most commonly vitamin A, zinc and significantly low thiamine, which have been shown to affect olfaction, as well as some renal and liver conditions [4, 6, 9].

Clinical Assessment

History

Assessment of olfactory function involves a careful history, which includes the onset, rate of improvement, decline or fluctuations and associated features. There may be an obvious causative moment such as head trauma, viral infection or occupational fume exposure.

Due to nasal inflammation accounting for most treatable forms of olfactory dysfunction, the presence of nasal symptoms such as sneezing, rhinorrhoea, pain or obstruction is important. These patients may suffer from a fluctuating sense of smell, especially those with rhinitis or CRS. Pre-existing nasal conditions, surgery or injury may be contributory. Features such as unilateral symptoms, recurrent epistaxis or crusting should raise consideration of other possible diagnoses (e.g. sinonasal tumours or vasculitis).

Focused questions surrounding pertinent neurological or psychiatric symptoms can aid with exclusion of central nervous causation. History surrounding metabolic disease, autoimmunity, occupational exposure and previous neurosurgical interventions is helpful. A dietary history should look at causes of malnourishment or deficiency both as a potential cause of symptoms and a consequence of the olfactory loss.

Some patients may present with taste disturbance, though on questioning it may be found that their perception of flavour loss is secondary to olfactory dysfunction.

Familial history of genetic diseases such as Kallman syndrome is more pertinent in paediatric patients, though presentation may be later. There

can also be clues with regard to delayed puberty or endocrine abnormalities, such as hypothyroidism, which lead to a more systemic consideration.

Medication should ideally be reviewed, and related back to symptom onset, specifically recent anaesthesia or chemotherapy, excess amino acids, antimicrobials, antithyroid, opiates and cardiovascular medications. In these scenarios medication should be discontinued if safe.

Clinical Examination

Examination focuses upon a thorough nasal examination, including nasal endoscopy. It is important to note that anterior rhinoscopy alone is insufficient, with 50% of olfactory cleft obstruction missed with this sole examination technique [5]. Attention should be paid to the space between the middle turbinate and septum, especially the superior portion, as well as any indication of polyposis, tumours, adhesions or postoperative changes. Positive findings of these features would aid confirmation of a diagnosis. A focused neurological examination and mini-mental examination may be warranted.

Investigations [9, 11]

Magnetic resonance imaging may be warranted for idiopathic, neurological or tumour presentations. Computer tomography may help with concerns of anatomical deformities, tumours or polyposis where surgery may be considered. In many patients imaging is not indicated.

The most common investigations clinically utilised are olfactory tests. The threshold for olfaction can be measured using an olfactometer.

Sniffin' Sticks test is validated internationally. The test allows a semi-objective assessment of olfactory performance through three subtests: threshold, discrimination and identification tests. These provide not only individual scores but also a combined global olfactory score, which helps both quantify and monitor olfactory performance.

Other options include the 40-item University of Pennsylvania Smell Identification Test (UPSIT-40) and a briefer 12-item Brief Smell Identification Test (BSIT-12). These tests present familiar odorants to the patient and require identification, before assessing function, whilst accounting for sex- and age-related differences. These tests have been validated in cross-cultural populations. Adapted for the UK, they have a high reliability, are single use, and are comparably costed making them an attractive option to most clinics.

Other investigations include electrophysiological tests that measure odour-induced electrical activity, functional MRI scanning used both in research and some clinical practices, psychophysiological tests measuring mainly the autonomic nervous system response to stimuli and varying neurophysiological techniques.

Therapy and Prognosis

Due to the regenerative capability of the olfactory neuroepithelium, spontaneous improvement can occur over time, as long as its stem cell layer is not significantly damaged. This has previously been reported as approximately occurring in 50% of patients, though only 10% regained normal age-matched function [5, 6].

Conductive loss: In these cases, most treatment consists of intranasal or systematic anti-inflammatory medication, antibiotics, allergy medications, allergy immunotherapy and/or saline therapy, with or without sinus surgery. Though it cannot be accurately predicted, there is likely to be improvement in these patients if the pathway for olfaction recovers. It is important to note that there is a possibility of iatrogenic injury from treatment and that there is a reduction in recovery over time with repeated surgery or medical treatment [9, 11].

Post-viral or traumatic anosmia: Patients may spontaneously recover with time, though this number is approximately only 30%. The presence of some smell function 1 year after the onset of anosmia is a positive prognostic indicator [5]. However, the longer the dysfunction is present, the worse the chances of recovery.

Sensorineural causes and central dysfunction: These patients are very challenging to treat. Unfortunately, there is no effective medical therapy or intervention for neural olfactory loss. Some evidence exists for the use of vitamins and minerals, such as zinc, vitamin A and vitamin B, though these are typically weak [9, 11]. Patients can have a trial with high-dose oral steroids, which may or may not help improve symptoms.

Olfactory training is recommended in patients with olfactory loss of different aetiologies. Although the exact underlying mechanism for improvement is unknown, there is the potential that repeated exposure helps increase the regenerative capacity of olfactory neurons [4].

Supportive care measures are vitally important for these patients. These include emphasis on food characteristics such as texture, temperature and visual appeal; counselling regarding spoiled food detection, appropriate storage and labelling; and checking installation and maintenance of smoke detectors and monitoring for gas leaks. Patients should consider living in an electric- or oil-heated residence. A balanced diet, especially in an elderly population, is important to prevent malnutrition and its subsequent sequelae, whilst flavour enhancers can enhance quality of life.

Due to the considerable effect upon quality of life, there are multiple charitable organisations including Fifth Sense and AbScent, as well as research centres targeting future management such as the Centre for Smell and Taste.

Taste

Anatomy and Physiology of Taste (Fig. 40.3)

Whilst taste buds are primarily located on the tongue, they are also present on the epithelial surface of the oropharynx and larynx. They are concentrically arranged around epithelial pores and found in three different types of papillae, which hold approximately 5000 taste buds, although this number is a rough estimate focused solely on the tongue, with little consideration for the remaining oral mucosa [3, 6].

Fungiform papillae: small red structures on the tip and anterior two-thirds of the tongue and innervated by the chorda tympani. Each contains 3–5 taste buds.

Circumvallate papillae: raised circular structures found posteriorly and innervated by the glossopharyngeal nerve (cranial nerve IX). Each contains 100 taste buds.

Foliate papillae: concentrated along the lateral borders of the tongue and innervated by the

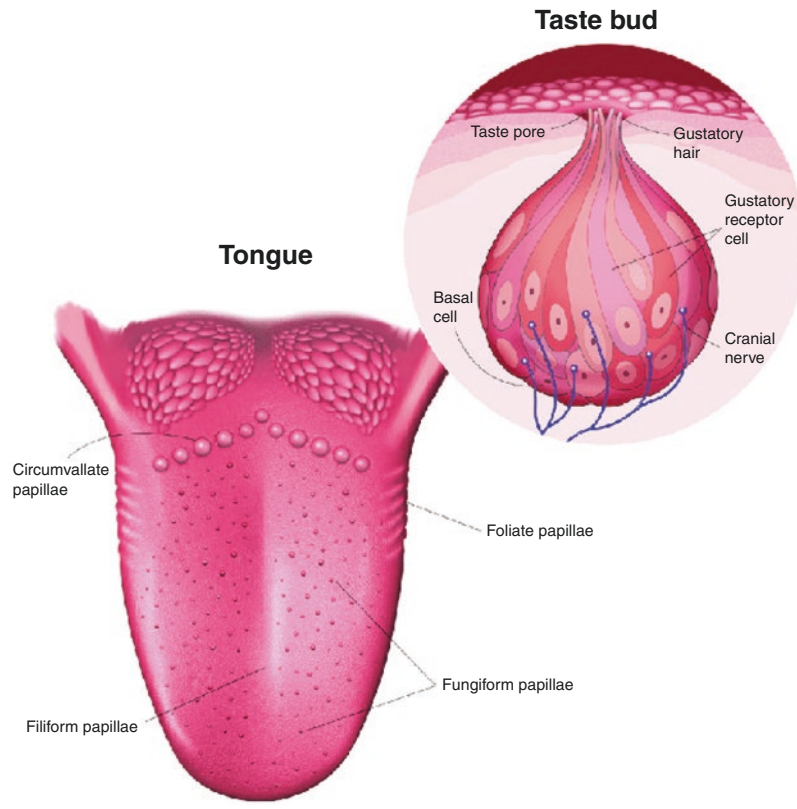

Fig. 40.3 Human tongue anatomy of papillae and taste buds. (Citation: Gravina, Stephen & Yep, Gregory & Khan, Mehmood. (2013). Human Biology of Taste. Annals of Saudi medicine. 33. 217–22. 10.5144/0256-4947.2013.217)

glossopharyngeal nerve (cranial nerve IX). Each contains over 100 taste buds.

Filiform papillae: do not contain taste buds, but are abundant, especially on the anterior two-thirds of the dorsal surface of the tongue. Filiform papillae are responsible for tongue texture, sensation of touch and abrasion. They become prominent secondary to increased keratinisation (furry tongue).

Collectively, these taste buds transmit information regarding salt, sweet, bitter and acid and umami (savoury) [4]. Whilst their patterns are established during embryogenesis, taste buds have a limited lifespan and are continuously replaced every 10 days throughout life [6]. Whilst previously considered to be specifically localised anatomical areas of the tongue, this theory has since been abandoned and quashed, with perception of different qualities equally distributed. There is also the consideration that taste bud number and size decrease throughout normal ageing, with this process becoming more apparent during the fifth and sixth decades of life.

Within these taste buds, there are three varieties of spindle-shaped cells, namely, the taste receptor cell, the edge cell and the basal cell. Saliva transports soluble molecules towards the receptor cells, before washing them away once stimulation has occurred. Taste receptor cells are similar to neurons, and an ingested taste molecule causes depolarisation or hyperpolarisation. Stimulation leads to a rise in intracellular calcium, and processing involves a combination of multiple receptors that allows simultaneous sensation of different tastes. Adaptation can occur within taste receptor cells, where prolonged stimulation of a singular taste quality leads to decreased stimulation over time [3, 4, 6].

Taste Disorder Classification [6, 12]

Taste disorders can be classified by either type or site. Site classification involves an abnormality in one of three principal locations: epithelial, neural or central dysgeusia.

With regard to the type of disorder, classification includes quantitative dysgeusia, ageusia (loss of taste), hypogeusia (reduced sensitivity to taste) and hypergeusia (increased sensitivity taste) and qualitative dysgeusia, parageusia (abnormal taste with stimulus present), pseudogeusia/phantogeusia (abnormal taste without stimulus) and gustatory agnosia (inability to interpret tastes).

Aetiology

Taste loss historically has been extremely rare, with most presenting patients actually being found to have olfactory dysfunction. The introduction of the COVID-19 virus has increased this number significantly, with patients having independent impairment in both olfactory and gustatory systems. Irrespective of this novel virus, there are other certain aetiologies specific to gustatory dysfunction [4, 12, 13]. Taste impairment is typically caused by any negative influence upon the taste buds and their cells physically, the nerve pathway or central processing. Taste is also dependant on normal salivary production, with appropriate saliva production integral to protection of the mucosa, buffering, tooth mineralisation, tissue repair and antibacterial and gustatory functions. A combination of these factors can result in significant taste disturbance.

Age

Whilst the ageing process affects taste sensation, this is far more conservative than olfaction. Specifically, bitter and sour tastes diminish with age, but this is typically only partial and the residual function is enough to avoid clinical concern [6].

Infective Causes

Viral, bacterial and fungal organisms can cause taste disturbance through infections of the oral mucosa. There is a higher risk in patients with poor oral hygiene and those with radiation-induced mucositis.

Infections elsewhere, specifically the ear, such as chronic otitis media or externa, Ramsay-Hunt syndrome or Lyme disease can induce taste disturbance through injury of the chorda tympani. These patients typically complain of phantom taste, typically metallic, more than complete loss.

Medication/Chemicals

Medication, leading to drug-induced chemosensory disorders, continues to be one of the

most common causes. Chemosensory complaints include bitter or metallic tastes, reduced acuity and distortions. Mostly, these include hypogeusia or dysgeusia. These account for a significant proportion of patients with true taste disorders. There remains debate over the mechanism. For some drugs this may be due to alterations in neurological pathways. For other drugs it may be due to their presence (post absorption), in saliva after diffusion from the lingual blood vessels where they can directly affect taste receptors [12].

Similarly, long-term smoking may affect taste sensitivity and discrimination, with only marginal improvement after cessation (depending on length of time).

Cancer

Neoplasms that involve the floor of the mouth, submandibular space, infratemporal fossa, glomus tumours affecting cranial nerves IX and X or acoustic neuromas can produce a permanent loss of taste following mass effect or infiltration of local nerves.

Iatrogenic

The lingual or pharyngeal branches of the glossopharyngeal nerve can be damaged during tonsillectomy or uvulopalatopharyngoplasty (UPPP), with either temporary or permanent gustatory changes.

Damage to the chorda tympani during otological surgery can leave patients with a metallic taste.

Incidentally, there have also been reports of ageusia postoperatively as a result of anaesthetic drugs, as well as method of intubation, such as laryngeal mask airways, though the percentage likelihood is small.

Trauma

Head injury rarely causes loss of taste, though there is an incidence of approximately 0.5% [6].

Other Causes

Systematic disease, such as renal or liver disease, can cause phantom taste, typically bitter or metallic. With regard to renal disease, this is most likely due to the build-up of uremic toxins and may improve following bouts of dialysis [12].

Taste dysfunction may occur in patients with diabetes mellitus and peripheral neuropathies that often affect other anatomical locations. This is secondary to elevated glucose taste thresholds, as well as progressive loss of taste sensitivity.

Vitamin and mineral deficiency, such as zinc deficiency, has been a proven cause of taste disorders. Mental health disorders, including depression, can affect taste sensation.

Taste Evaluation [12, 13]

The assessment of quality and intensity of taste is important when assessing these patients, with each factor individually assessed. A simple assessment of taste can be done in the clinic with four easily available substances: sodium chloride (salt), sucrose (sweet), citric acid (sour) and quinine hydrochloride or coffee (bitter).

Taste function can be measured spatially, due to the differing distribution and nerve supply of taste buds. There are standardised taste strips with specific concentrations of the stimuli, which allow different sections of the tongue and oral cavity to be evaluated.

During the evaluation it is important to differentiate a genuine stimulus from a phantom taste. This involves regularly rinsing of the patient's mouth, to determine whether the phantom taste is real (washed away) or still exists following cleansing. Local anaesthetic can also be used topically to eliminate a true taste; present from stimulus, saliva, laryngopharyngeal reflux or post-nasal drip; and thereby confirm true phantom taste.

Therapy and Management [6, 12, 13]

Treatment, as always, is directed towards the causative factor. Therefore, patients with inflammatory or infectious causes may benefit from anti-inflammatory, antifungal or antibiotic therapy. On the other hand, those with postradiotherapy mucositis seem to respond

well with artificial saliva or salivary stimulants due to its physiological properties in aiding gustation.

Whilst zinc and alpha lipoic acid are both important naturally produced properties in maintaining taste buds, the current information surrounding their use is insufficient, though there are rare papers mentioning success. This is similar with other management strategies such as acupuncture.

In general, even with an identifiable cause, most deficiencies of taste are untreatable due to the irreversible effects on nerve supply and signalling. As a result, therapy typically focuses on psychological support for patients and similar supportive care measures as olfactory dysfunction.

Conclusion

The importance of managing smell and taste disorders cannot be stated highly enough, with patients suffering from increased levels of morbidity and mortality. Whilst management may not necessarily be straightforward, emerging studies investigating treatment modalities, diagnosis and support remain the key cornerstones when protecting patients. Information and institutional support are available in abundance, allowing individuals to modify lifestyles and cope with potential changes.

Key Learning Points

- Smell and taste are both critical functions, affecting both quality and longevity of life.
- Smell dysfunction can be categorised into conductive losses, sensorineural loss or central nervous system dysfunction.
- Conductive smell losses are more responsive to treatment than sensorineural and central nervous system dysfunction.
- Taste disorders can be classified by location into epithelial, neural or central dysgeusia.
- True taste disorders have historically been extremely rare, with a majority of patients found to actually suffer with olfactory dysfunction; however with the recent introduction of the SARS virus, this has increased in frequency.

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41 Headache and Facial Pain: Diagnosis, Evaluation and Management

Bhaskar Ram, Vamsidhar Vallamkondu, and Sangeeta Maini

Introduction

Facial pain refers to any type of pain in the area bounded by the eyes and the lower mandibular margins, including the oral cavity. It is a frequent complaint that affects women more than men (female: male ratio 2:1 [1]) and has a population prevalence of around 1.9%.

Pain can be provoked by virtually all structures in the head and neck region. Whilst patients are often referred to ENT surgeons, many have already seen colleagues from other disciplines, such as dentists, ophthalmologists, psychologists, pain specialists, internal medicine physicians, neurologists and neurosurgeons. Patients may have experienced multiple consultations and treatment regimens, passing between different specialities, without perceiving any benefit.

By the time they are seen in the ENT clinic, many will have reached the firm conclusion that the cause of their facial pain lies within their sinuses, reinforced by opinions held by their primary care physician or other hospital specialists. The otolaryngologist may therefore face a significant challenge to dispel the patients' preconceived ideas that their facial pain is sinogenic, and consultations can be onerous and difficult.

Conventionally, the primary goal for the otolaryngologist was to make a distinction between sinogenic and non-sinogenic causes of headache and facial pain. However, an alternative view is for the otolaryngologist to understand pain disorders, make the correct diagnosis and instigate effective management.

Facial Pain

Facial pain can be broadly classified into primary and secondary (Table 41.1).

Primary facial pain has no obvious causative factors and includes migraine, trigeminal neuralgia, trigeminal autonomic cephalgia's, tension-type headaches, mid-facial segment pain, and atypical facial pain.

Secondary facial pain has a specific causative factor and can be subdivided into sinogenic and non-sinogenic causes.

Non-sinogenic facial pain includes pain secondary to dental pathologies, temporomandibular dysfunction and vascular disorders such as Giant cell arteritis.

B. Ram (✉) · V. Vallamkondu · S. Maini
Department of Otolaryngology, Grampian University Hospital, Aberdeen Royal Infirmary, Aberdeen, UK
e-mail: bhaskar.ram2@nhs.scot

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Table 41.1 Facial pain

Primary facial pain	Secondary facial pain
Migraine Mid-facial segment pain Tension headache Atypical facial pain Trigeminal neuralgia Trigeminal autonomic cephalgia	Sinusitis Orofacial/dental infections Temporomandibular dysfunction Giant cell arteritis

Approach to a Patient with Facial Pain

A structured approach to history taking remains an essential part to making a diagnosis. It may not be possible to reach a definitive diagnosis at the first visit and re-taking the history at a subsequent consultation with the patient's diary of their symptoms will aid in the diagnosis.

Systematic Approach to Facial Pain Diagnosis

History and Examination

One should elicit the following:

- Where is the pain?
  - Asking the patient to point with one finger to the site of the pain is often helpful.
- What is the type of pain? Is the pain superficial or deep?
  - Pain from the skin is sharp and localised. Deep-seated pain is dull and poorly localised.
- How long does the pain last?
  - Migraine-related pain lasts for a few hours, pain in trigeminal neuralgia and short-lasting unilateral neuralgiform headache (SUNCT) lasts for seconds to minutes.
- Is it unilateral or bilateral?
  - Migraine, cluster headaches and trigeminal neuralgia tend to be unilateral. Tension headaches and mid-segment facial pain tend to be central or bilateral.
- Is there any facial numbness?
  - If yes, these patients need full neurological assessment to exclude intracranial lesion. These patients often need an MRI brain/Sinus scan.
- Periodicity:
  - The periodicity of symptoms may be a pointer to the diagnosis, e.g. being woken in the early hours by severe facial pain which lasts about 45–120 min suggests cluster headache.
  - Monthly premenstrual headaches are typical of hormonal/menstrual migraine.
- Pattern of attacks:
  - The relentless progression of a headache, in particular if associated with nausea or effortless vomiting is worrying, and an intracranial lesion should be excluded.
- What precipitates the pain and what relieves the pain?
  - Ask whether hot, cold, eating, touching the face, weather, chocolates, wine, periods or stress precipitates the pain—more commonly seen in trigeminal neuralgia and migraine, respectively.
- Ask for any associated symptoms?
  - Nausea, vomiting, aura, nasal symptoms, clenching, bruxism habits, locking or clicking of jaw joint, altered sensation, eye symptoms and toothache.
- Any other pain conditions?
  - e.g. fibromyalgia
- Is there any impact of pain in daily routine?
  - e.g. sleep, mood, concentration, fatigue, beliefs and quality of life.
- A full drug history is important and what treatment has been tried before.
- Past medical history is important.
  - What treatment has patient tried before.
- Psychological history
- It is useful to use questionnaires to help in assessment and monitoring of effects of therapy.
  - Questionnaires such as the "*Pain self-efficacy questionnaire* and *EuroQol 5D*" [2] have been well validated and are sensitive.
  - SNOT 22 questionnaire—high symptom scores of psychosocial symptoms and ear and facial symptoms in absence of rhinosinusitis should raise the suspicion of Primary headache disorders [3, 4].

Examination Should Include the Following

- Nasal examination including nasal endoscopy.
- Oral examination.
- Temporomandibular joint examination—looking for tenderness, crepitus, malalignment and muscle hypertrophy.
- Examination of the muscles of mastication.
- Examination of head and neck muscles for tenderness and trigger points.
- The cranial nerves examination looking for any facial numbness, paraesthesia and weakness.

Investigations

- Laboratory investigations are of limited value except in the potential diagnosis of giant cell arteritis.
- Radiographic X-ray dental imaging or orthopantomogram (OPG) is important for dental pain.
- Magnetic resonance imaging (MRIs) is indicated for suspected cancers and cranial conditions.
- Computerised tomography (CTs) is indicated for suspected chronic sinusitis.

Sinusitis and Facial Pain

Contrary to popular belief, so-called sinus headaches are uncommon and seen mostly in acute sinusitis or acute exacerbations. Acute sinus infection typically follows a bad head cold and may present as a severe throbbing pain that refers to the teeth, in association with purulent nasal discharge and pyrexia.

As per EPOS 2020 Guidelines

Sinusitis is defined as inflammation of the nose and the paranasal sinuses characterised by two or more symptoms, one of which should be either nasal blockage/obstruction/congestion or nasal discharge (anterior/posterior nasal drip):- ± facial pain/pressure - ± reduction or loss of smell.
And/Either Endoscopic signs of: nasal polyps, and/or—mucopurulent discharge primarily from middle meatus and/or—oedema/mucosal obstruction primarily in middle meatus. And/Or
CT changes: mucosal changes within the ostiomeatal complex and/or sinuses.

Patients with facial pain secondary to sinusitis, almost invariably have coexisting symptoms of nasal obstruction, hyposmia and/or purulent nasal discharge and there are usually endoscopic signs of disease [5].

Patients with acute maxillary sinusitis complain of unilateral facial and dental pain, and endoscopy often confirms the diagnosis with findings of purulent discharge from the middle meatus. A normal nasal cavity showing no evidence of middle meatal mucopus or inflammatory changes makes a diagnosis of sinogenic pain most unlikely [6]. Key points within the medical history that are consistent with sinogenic pain are exacerbation of pain during an upper respiratory tract infection, an association with rhinological symptoms, worsening of symptoms during flying or skiing, and a good response to medical treatment.

Chronic sinusitis seldom causes facial pain except during an acute exacerbation, although this diagnosis is often made too readily. Patients with chronic rhinosinusitis will normally have endoscopic features of polypoidal mucosal change, nasal polyps or mucopurulent discharge. In a cohort of patients with suspected sinusitis, actual sinusitis was present in less than a third, and the most common cause of facial pain was migraine [8].

Whilst imaging may offer important diagnostic information interpretation must be treated with caution [7]. Approximately 30% of asymptomatic patients who undergo imaging of the head will demonstrate mucosal thickening in one or more sinuses as an incidental finding. Should patients with facial pain undergo imaging studies, mucosal thickening is not evidence of sinogenic pain or that surgery is indicated. The features should be correlated with a detailed history and endoscopic findings.

Headaches are common in the general population and care must be taken not to link headaches with unrelated nasal symptoms that lead to an erroneous diagnosis of sinusitis. Diagnostic confusion may also occur from autonomic rhinological symptoms associated with vascular pain and cephalgias.

Sinus surgery should only be considered where there is good evidence of sinogenic pain in whom

appropriate medical treatment has failed. In patients who undergo surgery for non-sinogenic pain, some experience temporary pain relief, but the pain typically recurs 2–3 months later, and a third will experience much worse pain that is difficult to manage with medical treatment [8].

Key Points

1. A careful, detailed history is pivotal.
2. Sinogenic facial pain is rarely a symptom on its own. It is most often associated with other nasal symptoms (nasal obstruction, rhinorrhoea or olfactory dysfunction).
3. A CT sinus scan is rarely indicated in the diagnosis of sinogenic facial pain.
4. Surgery should be avoided in patients with facial pain unless there are clear features of sinusitis.

Primary Facial Pain

Migraine and Facial Pain

Migraine is a common disabling primary headache disorder predominantly affecting young and middle-aged women, affecting approximately 18.9% (18.1–19.7) women, and 9.8% (9.4–10.2) men [9].

Classical migraine presents as a unilateral throbbing headache, often associated with nausea, photophobia and phonophobia. It is frequently misdiagnosed but has strict diagnostic criteria (Table 41.2). The headache may be preceded by an aura that can be visual, sensory or motor. Migraine attacks are often induced by stress, hormonal changes and dietary triggers. About 70% of migraineurs have a positive family history.

Table 41.2 The international classification of headache disorders [11]

Migraine without aura (MO) diagnostic criteria
1. *At least five headache attacks lasting 4–72 h (untreated or unsuccessfully treated), which has at least two of the four following characteristics:*
(a) Unilateral location
(b) Pulsating quality
(c) Moderate or severe intensity (inhibits or prohibits daily activities)
(d) Aggravated by walking stairs or similar routine physical activity
2. *During headache at least one of the two following symptoms occur:*
(a) Phonophobia and photophobia
(b) Nausea and/or vomiting
Migraine with aura (MA) diagnostic criteria
1. *At least two attacks fulfilling with at least three of the following:*
(a) One or more fully reversible aura symptoms indicating focal cerebral cortical and/or brain stem functions
(b) At least one aura symptom develops gradually over more than 4 min, or two or more symptoms occur in succession
(c) No aura symptom lasts more than 60 min; if more than one aura symptom is present, accepted duration is proportionally increased
(d) Headache follows aura with free interval of at least 60 min (it may also simultaneously begin with the aura
2. *At least one of the following aura features establishes a diagnosis of migraine with typical aura:*
(a) Homonymous visual disturbance
(b) Unilateral paraesthesia and/or numbness
(c) Unilateral weakness
(d) Aphasia or unclassifiable speech difficulty

There may be a significant symptom overlap between a sinogenic headache and migraine that must be appreciated by the otolaryngologist in the quest to differentiate the two. A central lesion must be excluded in patients over the age of 50 years who present with newly diagnosed migraine.

Nasal endoscopy during an acute migraine episode may display significant mucosal inflammation due to autonomic imbalance at the time. The autonomic/cortical dysfunction is believed to induce cephalgia and the associated rhinogenic symptom complex of blockage, lacrimation and rhinorrhoea.

It is thus perfectly understandable for patients who experience increased congestion, rhinorrhoea and lacrimation during migraine episodes to be treated for sinus disease. Furthermore, patients may find that some drugs that treat rhinosinusitis-like symptoms, such as pseudoephedrine, may coincidentally alleviate their 'sinus headaches'. Pseudoephedrine is a vasoconstrictor that may prevent the downstream vasodilation effects of migraine and thus alleviate migraine pain by indirectly treating the migraine. Unfortunately, the pain relief after taking such medication further reinforces the misperception that migraines are sinus headaches.

Management includes the active treatment of acute symptoms, prophylaxis and avoidance of inducing factors, in various combinations according to the frequency and severity of the episodes.

Simple treatment in the acute phase includes aspirin and antiemetics. Serotonin agonists such as rizatriptan are frequently effective in treating acute attacks. Beta-blockers are often the first-line treatment for prophylaxis, provided there are no contraindications to their use. Prophylactic treatment is considered if symptoms occur more than three times a month with a duration of more than 48 h. Local injections of Botulinum Toxin Type A are often effective in refractory cases, but neurological referral is recommended in such patients [10].

Top Tips

- Migraine headaches can often mimic sinusitis.
- Knowledge of the presentation of facial migraine will ensure appropriate investigations, correct diagnosis and effective treatment.
- Migraine headache treatment may be commenced by ENT but refractory cases need neurological referral.

Trigeminal Neuralgia

Patients typically present with paroxysms of severe, lancinating pain, induced by a specific trigger point such as the lips and nasolabial folds. Chewing, talking, drinking hot or cold fluids, touching, shaving and brushing teeth may also precipitate the attacks in these patients. Attacks typically last from seconds to 2 min. The pain occurs in both the maxillary and mandibular divisions in more than one-third of sufferers, but the pain is confined solely to the maxillary division in one-fifth. The ophthalmic division is affected in only 3% of patients.

Patients do not usually have any sensory deficits, but when present, magnetic resonance imaging (MRI) is required to exclude secondary causes such as multiple sclerosis or posterior [12] fossa tumours (present in 2% and 4% of patients, respectively). MRI imaging is also indicated in young patients presenting with unilateral or bilateral trigeminal neuralgia to exclude disseminating sclerosis (DS), as trigeminal neuralgia can be the first manifestation of DS in some patients.

Carbamazepine remains the first-line medical treatment. In cases refractory to medical treatment, referral to specialist centres for consideration of other treatment modalities such as microvascular decompression, glycerol gangliolysis, balloon compression or stereotactic radiotherapy may be appropriate.

Table 41.3 Common key features of trigeminal cranial neuralgias

- Periorbital or ocular pain
- Unilateral pain
- Excruciating severity
- Accompanied by at least one of these ipsilateral autonomic phenomena/signs:
  - Conjunctival injection/lacrimation
  - Nasal congestion/rhinorrhoea
  - Eyelid oedema
  - Forehead/facial sweating
  - Miosis and ptosis

Trigeminal Autonomic Cephalgias (TACs)

Trigeminal autonomic cephalgias (TACs) are primary headaches with a common clinical phenotype consisting of trigeminal pain with autonomic signs such as lacrimation, rhinorrhoea and miosis (Table 41.3).

Three main types are recognised. These are cluster headache, paroxysmal hemicrania, and short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing (SUNCT).

Cluster Headaches

Young adults with periodic unilateral orbital pain associated with autonomic symptoms should raise a suspicion of cluster headache, especially if precipitated by alcohol. The classical symptoms include a unilateral, severe stabbing pain over the periorbital region that disturbs sleep. Patients may have 2–3 attacks per day, lasting from 30 min to 2 h, characteristically at a similar time daily, with phases over several weeks, followed by months of remission.

In contrast to migrainous pain where patients prefer to lie down and rest in a dark room, cluster headache induces restlessness without associated nausea or vomiting.

Associated symptoms include rhinorrhoea, lacrimation and conjunctival injections, facial flushing and sometimes miosis during these episodes. As patients experience pain and nasal symptoms, they assume that they have severe sinusitis and seek ENT opinion. Clinician often finds normal Nasal endoscopy and CT scan is usually normal. In such situations, one must have a high index of suspicion to diagnose this condition.

Acute episodes respond well to nasal or subcutaneous sumatriptan or oxygen inhalation. Verapamil or topiramate provide effective prophylaxis if required. A neurological opinion should be considered.

Paroxysmal Hemicrania

Paroxysmal hemicrania is an excruciating unilateral pain occurring almost exclusively in women. It can occur at any time of day or night, with 2–40 attacks per day over several episodes.

Similar to cluster headaches, patients with this condition present with unilateral facial pain/headache, affecting the frontal, ocular, cheek or temporal regions, with associated autonomous symptoms [13]. However, in contrast to cluster headaches, where attacks last for hours, paroxysmal hemicrania headaches are shorter, lasting from 15 min to 30 min.

Patients and clinicians will often attribute symptoms to recurrent sinusitis, and some may occasionally undergo endoscopic sinus surgery, but nasal endoscopy is invariably normal.

Indomethacin, 25 mg orally thrice daily, is the drug of choice, typically inducing a dramatic response that is characteristically diagnostic. In contrast to migraine and cluster headache, paroxysmal hemicrania does not usually respond to triptans. A high index of suspicion should be maintained with a neurological referral if in doubt.

SUNCT

Short-Lasting, Unilateral, Neuralgiform Headache Attacks with Conjunctival Injection and Tearing (SUNCT)

This condition bears many similarities to trigeminal neuralgia but affects the ophthalmic division of the trigeminal nerve with associated autonomic symptoms.

Attacks of sharp, shooting periorbital pains lasts for seconds only, that may total 250 attacks per day. Lamotrigine is the drug of choice and a neurological opinion should be considered.

Table 41.4 Tips: summary points of trigeminal cephalic cephalgias

	Cluster headache	Paroxysmal hemicrania	SUNCT
Attack frequency (daily)	2–3	2–40	250
Duration of attack	30 min to 2 h	15–30 min	5–240 s
Pain quality	Sharp, throbbing	Sharp, throbbing	Stabbing, burning
Pain intensity	Very severe	Very severe	Very severe
Treatment	Sumatriptan	Indomethacin	Lamotrigine
Circadian periodicity	70%	45%	Absent

Table 41.4 summarises the key differences between these three conditions.

Tension Headache

This is another common condition which is commonly seen in young adults. It is usually stress related and anxiety, depression or agitated depression will often co-exist. Patients describe a feeling of tightness, pressure or constriction over their forehead, retro-orbital or temple and cheeks. Hyperaesthesia of the skin or muscles of the forehead often leads patients to assume they have rhinosinusitis, as they know their sinuses lie under the forehead [14]. Patients will often take large quantities of various analgesics without deriving much benefit. Patients are often convinced that their headaches are sinus related, often reinforced by family/friends and sometimes even other healthcare providers.

Treatment should involve good counselling. Low-dose amitriptyline is often effective [15], but propranolol, sodium valproate, gabapentin or a change in lifestyle may also bring successful relief of symptoms. Amitriptyline should be given for at least 6 weeks before judging its effect and should be continued for 6 months if effective. The starting dose is 10 mg/day, and gradually increased up to 50 mg/day over 6 weeks if necessary, according to the clinical response. Patients need to be warned of the sedative effects, even at this low dose, but they can be reassured that tolerance usually develops after the first few days. Symptoms will return after stopping amitriptyline in 20% of patients, and they should re-start medication should this occur.

It is good practice to inform patients that amitriptyline is also used in higher doses for other conditions such as depression, but that it is not being given for this reason. It is often reassuring for patients to know that the dose used for depression is some seven or more times the dose used in tension-type headache. Cognitive behaviour therapy is another option that could be considered.

Mid-Facial Segment Pain

Mid-facial segment pain has all the characteristics of tension-type headache with the exception that it affects the midface. Patients describe a feeling of pressure, heaviness or tightness and they often complain of a blocked stuffy nose despite a normal nasal examination. The symptoms are symmetrical and may involve the nasion, the bridge of the nose, either side of the nose, the periorbital region, retro-orbitally or across the cheeks. The forehead and occipital region may also be simultaneously affected in about 60% of patients. There are no consistent exacerbating or relieving factors. Patients often take a range of analgesics but with negligible or minimal effect, other than ibuprofen that may occasionally help to a minor extent. The symptoms are typically episodic initially but become persistent as time progresses. Whilst patients will often complain of episodic pain, it is quite common to reveal that they effectively have constant pain or discomfort with episodic exacerbations. Patients may be convinced that their symptoms are due to sinusitis as they know that their sinuses lie in the area of the pain.

Patients may have undergone treatment over long periods with antibiotics and topical nasal steroids. Some patients have a transient but inconsistent response that may be related to the placebo effect or cognitive dissonance.

Routine of physical activity and the ability to go to sleep are rarely affected. To make matters more complex, the stimulus of a genuine acute sinus infection may exacerbate symptoms, with a return to the background headache on resolution of the infection. It is therefore hardly surprising that both patients and medical practitioners will interpret their symptom complex as being related to their sinuses. Patients often describe tenderness on touching the areas of the forehead or cheeks, reinforcing the concept of underlying inflammation of the bone. Examination will often demonstrate hyperesthesia of the skin and soft tissues over the face and gently touching certain areas is enough to cause discomfort, but there is no evidence of underlying bony disease. This is similar to the tender areas over the forehead and scalp seen with tension-type headache. It appears that this is an organic disorder, in line with an increase in the pain sensitivity in the central nervous system described in tension-type headache.

Interestingly, nasal endoscopy is typically normal. A CT sinus scan may confuse the picture, as approximately 1 in 3 asymptomatic people have incidental findings. However, patients who undergo maximal nasal medical treatment with oral or nasal steroids and a broad-spectrum antibiotic with anaerobic cover fail to improve. The most effective treatment is low-dose amitriptyline as described above. If amitriptyline is not tolerated or fails, then relief may be obtained from gabapentin, pregabalin, propranolol, carbamazepine and, occasionally, sodium valproate. Cognitive behaviour therapy is another option that could be considered. It seems likely that the underlying pathophysiology in mid-facial segment pain is similar to tension-type headache. The aetiology of this type of pain is uncertain. It is of interest that if surgery is performed in the mistaken hope that pain will resolve, the pain may abate temporarily, only to return after several weeks to months.

Atypical Facial Pain

This condition is a diagnosis of exclusion after a careful clinical assessment even when backed up by previous opinions and no evidence of identifiable pathology. The history is often vague and inconsistent. Pain may be widespread, extending from the face to other areas of the head and neck and may move from one part of the face to another between different consultations. Additional odd symptoms, such as ‘mucus moving’ in the sinuses, are often described.

The patient may have a completely fixed idea about their condition and will not be convinced otherwise, whatever the weight of evidence to the contrary. Pain is often described in dramatic terms in conjunction with an excess of other unpleasant life events. Many will have a history of other pain syndromes and their extensive records show minimal progress, despite various medications. Previous sinus or dental surgery is not uncommon, and pain might be attributed to interventions, but the true onset of pain usually precedes any of these procedures, thus and differentiating it from postsurgical neurogenic pain.

Many patients with atypical facial pain exhibit significant psychological disturbance or a history of depression and are unable to function normally as a result of their pain. Some project a pessimistic view of treatment, almost giving the impression they do not wish to be rid of the pain that plays such a central role in their lives.

The management of such patients is challenging, and confrontation is easily induced but counterproductive. A comprehensive examination (including nasendoscopy) is essential to identify significant pathology before the patient is labelled as having atypical pain.

A good management strategy is to reassure the patient that you accept that their pain is genuine and maintain an empathetic persona. Reassure

them that you will continue to treat their condition and maintain a level of hope.

Medication revolves around a gradual introduction of high levels of analgesia and antidepressant with amitriptyline, 75–100 mg at night. Patients should be sympathetically counselled that psychological factors may play a role in their condition and referral to a clinical psychologist may well be helpful.

Giant Cell Arteritis (Temporal Arteritis)

This is a rare cause of facial pain that requires a rapid diagnosis to avoid disease progression affecting the ophthalmic artery leading to visual loss. Patients are typically women, aged over 50 years, who present with fever, malaise and severe temporal or retroauricular pain. On examination, the temporal artery is thickened and exquisitely tender. Investigation reveals an elevated erythrocyte sedimentation rate (ESR). The diagnosis is confirmed by histology of a temporal artery biopsy showing intimal hyperplasia and fragmentation of the internal elastic lamina.

Other causes of facial pain that can mimic temporal arteritis include dental infections and deep neck space infections involving the maxillary space/pterygoid spaces. An urgent CT scan of the sinuses and head neck will exclude these pathologies.

If there is a strong clinical suspicion that temporal arteritis is present, high-dose systemic steroid (60 mg prednisolone daily) should be rapidly commenced, prior to a diagnostic biopsy. An urgent medical referral to a rheumatologist should be arranged.

Dental and Oral Disorders Causing Facial Pain

Dental pathology is an important cause of facial pain that can be mistaken for sinusitis, but the diagnosis can be easily missed. Patients typically present with unilateral facial pain, sometimes radiating to the teeth. Examination may show bite problems. Whilst some patients may have sought a dental opinion, this does not always exclude dental pathology, and vigilance is required.

Some patients will present with unilateral facial pain associated with a purulent, dentally induced sinusitis. This is often accompanied by a foul-smelling unilateral nasal discharge and pus in the middle meatus seen on nasal endoscopy.

Pertinent investigations include an OPG and/or a CT sinus scan that should include all of the paranasal sinuses as well as the lower maxilla and dentition. Cone-beam CT is becoming more popular and is improving with time but may not provide a full assessment of the paranasal sinuses. Key radiological features include periapical lucency with unilateral maxillary sinusitis.

The patient should be referred to a dentist or maxillo-facial colleague should a dental cause be identified.

Temporomandibular (TMJ) Dysfunction

Patients usually present with unilateral dull facial pain across the face which may radiate to the temple, ear and jaw. As it radiates across the face, patients will often assume that they have sinusitis, but a careful history will elicit minimal no associated nasal symptoms. The patient may complain of pain made worse with chewing, locking of the jaw on mouth opening, bruxism or teeth clenching. Examination may show some limitation of jaw opening, tenderness over the masticatory muscles, clicking or tenderness of the TMJ and lateral deviation of the mandible. Most patients will respond to simple analgesics, moist heat and massage of the masticatory muscles and a soft dental appliance. Should the history include jaw locking and lateral deviation of the mandible, an MRI scan of

the temporomandibular joint should be requested and patient referred on to an oro-maxillo-facial colleague.

Sluder's Neuralgia

In 1908, Sluder described 'sphenopalatine neuralgia' as a cause of an ipsilateral, boring and burning facial pain beginning along the lateral side of the nose associated with lacrimation, rhinorrhoea, injected conjunctiva and sometimes involving the cheek [16]. Sluder's definition did not describe a single entity but a diverse symptom complex. The term Sluder's syndrome is often used loosely and it is best avoided as his description differs from most clinical entities.

Contact Point Pain

McAuliffe described stimulating various points within the nasal cavity and paranasal sinuses in five individuals and said that both touch and faradic current caused referred pain to areas of the face [17]. These findings have been used to support theories which state that mucosal contact points within the nasal cavity can cause facial pain. McAuliffe's work has recently been repeated in a controlled study and was found not to produce the referred pain that he described [18]. The prevalence of a contact point has been found to be the same in an asymptomatic population as in a symptomatic population and when they were present in symptomatic patients with unilateral pain, they were present in the contralateral side to the pain in 50% of these patients.

Current Developments

There have been new developments in the management of patients with refractory facial pain:

1. *Sphenopalatine ganglion: block, radiofrequency ablation and neurostimulation*

   The Sphenopalatine ganglion is a promising target for treating cluster headache using blocks, radiofrequency ablation and neurostimulation. Blocking activity in the Sphenopalatine ganglion also has some supporting evidence for use in several other conditions. However, most of the controlled studies were small and without replications. Further controlled studies are warranted to replicate and expand on these previous findings.
2. *Role of botulinum toxin type A in pain management*

   The neurotoxin, botulinum toxin type A, has been used successfully, in some patients, as an analgesic for myofascial pain syndromes, migraine, and other headache types. The toxin inhibits the release of the neurotransmitter, acetylcholine, at the neuromuscular junction thereby inhibiting striated muscle contractions. In the majority of pain syndromes where botulinum toxin type A is effective, inhibiting muscle spasms is an important component of its activity [19].
3. *An update on botulinum toxin A injections of trigger points for myofascial pain*

   Myofascial pain syndrome (MPS) is a common chronic pain condition that is characterised by distinct 'trigger points'. Despite current treatments with physical therapy, analgesics, anti-depressants and trigger-point injections, myofascial pain remains a challenging chronic pain condition in clinical practice. Botulinum toxin A (BTX-A) can cause prolonged muscle relaxation through inhibition of acetylcholine release. It may offer some advantages over the current treatments for MPS by providing a longer sustained period of pain relief [20].


Algorithm for facial pain
Facial Pain Pathway
History
Site: Unilateral/Bilateral
Nature: Sharp, dull, constant
Duration: seconds, hours, days
Any nasal/sinus symptoms?
Any facial numbness?
Autonomic symptoms: Watery eye, rhinorrhoea (Cluster headache)
Any associated symptoms: Nausea, vomiting, photophobia, tiredness (Migraine), toothache (Dental), pain on chewing, locking of jaw, mouth opening (TMJ Dysfunction)
Nasal Examination
Associated nasal /sinus symptoms >3months with abnormal nasal examination (Polyps/discharge/Oedematous mucosa)
No associated nasal/sinus symptoms with normal nasal examination
Please follow chronic rhinosinusitis guidance pathway
Bilateral pain symptoms
Unilateral pain symptoms
TMJ Dysfunction
(Bilateral periauricular pain, locking jaws, pain on chewing, mouth opening)
Treatment :
-Soft diet
-Dental opinion
Tension headaches and mid-facial segmental pain
(Forehead /mid-facial pain, sensitive skin, stress related)
Treatment :
-Weekly incremental dose of Nortriptyline 10 mg at night, can be increased upto 30 mg at night for 3/12
Could it be:
Dental: toothache
Migraine: pain, nausea, photophobia, tiredness
Cluster headache: periorbital, severe pain with autonomic symptoms
Trigeminal neuralgia: sharp, jaw pain, worse with touching/shaving
Temporal arteritis: temporal headaches, visual disturbances
If persistent symptoms
If persistent symptoms
GP to consider:
Dental opinion
Anti-migraine treatment
Nasal sumatriptan for cluster headaches
Trigeminal neuralgia- oxcarbazepine
ESR/ANA to rule out temporal arteritis
Referral to OMFS
Routine referral to ENT
RED FLAG SYMPTOMS AND SIGNS
Facial pain with facial numbness-needs Urgent ENT REFERRAL/ MRI SCAN
Temporal headaches with high ESR/positive ANA factor –Urgent REFERRAL TO RHEUMATOLOGY

Key Learning Points

- A careful structured history of facial pain, examination, supplemented in some cases by diagnostic tests, will permit a definitive diagnosis in most patients.
- Imaging should be kept to the minimum and only done for appropriate cases. Very rarely a CT scan may be indicated to reassure an extremely anxious patient and may have a positive psychological impact on him.
- Laboratory studies are indicated only when a systemic cause is suspected, such as Giant cell arteritis.
- Neuroimaging is indicated regarding the diagnosis of primary headache when the clinical features suggest a secondary cause.
- Should a precise diagnosis not be possible, a multidisciplinary approach should be considered.

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Trauma to the Nose

42

Forsan Jahshan and Yujay Ramakrishnan

Summary

The aim of this chapter is to compile the knowledge and practical management of nasal fractures which is a common ENT presentation. There are clearly subtle differences in treatment philosophies depending on the severity of injury across the world. We have distilled the wisdom from the literature and incorporated our own experience, presenting the information in a clear, concise manner. It is our ambition that both junior and experienced ENT colleagues will find this to be an easy to use and practical resource, regardless of geography.

Introduction

The nose is the most prominent anterior projecting structure of the face and is therefore susceptible to trauma. Nasal injuries occur at all ages; it is likely in children with play and sports; in adults, the predominant causes are sport, physical injury and accidents. Nasal trauma from physical abuse is less common but important to recognise, especially in young children and women [1–3].

Nasal trauma ranges from minimal soft tissue injury to severe trauma that may include soft tissue, bones and adjacent facial structures. Most injuries cause soft tissue swelling and bruising, often accompanied by a closed nasal fracture. Nasal bone fractures account for 40% of all facial bone fractures and range from simple, non-displaced fractures to severe comminuted nasal bone fractures. The more severe injuries may be accompanied by injury to the nasal septum, orbital injury, orbital rim or wall fractures, cerebrospinal fluid (CSF) leak or cervical spine trauma.

The consequences of not treating a fractured nose include significant long-term consequences such as nasal deformity, nasal obstruction, saddle nose, deviated nasal septum and septal perforation. These complications can often be avoided or minimised by effective appropriate management soon after the injury, thus avoiding the need for further surgery such as a septorhinoplasty [4].

Anatomy

The nose is divided into thirds: the upper, middle and lower vault. The upper third is a pyramid-like structure composed of a pair of nasal bones attached to the frontal bone superiorly and the frontal processes of the maxilla laterally and bilaterally. The middle third constitutes two upper lateral cartilages (ULC's) connected to the quadrangular septal cartilage in the midline while the lower third is defined by the medial and lateral crura of the lower lateral cartilages (LLC's)

F. Jahshan · Y. Ramakrishnan (✉)
Queen's Medical Centre, Nottingham, UK

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which largely define the nasal contour and tip of the nose [5].

The nasal septum is a midline structure that divides the nasal cavities into two parts, and it also supports the nasal skeleton. In children, it has a major role in the growth of the face as it continues to develop until ages 12–13, therefore septal trauma and disruption of the growth centre in the nasal septum can affect the growth of the face. The nasal septum is made up of membranous, cartilage and bony parts. Anteriorly, the membranous part is attached to the columella and the quadrangular cartilage posteriorly. The quadrangular cartilage is attached to the vomer posteriorly and superiorly to the nasal bones, upper lateral cartilage and the perpendicular plate of the ethmoid. The quadrangular cartilage and vomer are attached to the maxillary and the palatine crest inferiorly.

Generally, nasal trauma is more likely to cause more nasal bone and septal fractures rather than damage to the LLCs or ULCs as greater force is required to fracture these structures.

The nasal bone is thicker superiorly (demarcated by the intercanthal line) and thinner inferiorly. Fractures commonly occur below this line. However, a proximal nasal bone fracture that also involves the frontoethmoidal complex or the orbits is defined as a nasoorbitoethmoid (NOE) fracture. These fractures are considered more severe and require further attention for associated injuries to intracranial or orbital structures.

Internally, there are two nasal valves in each nasal cavity; the external nasal valve and the internal nasal valve:

The external nasal valve: this is an area composed of the nasal sill, nasal ala, medial and lateral crura of the lower lateral cartilage and membranous septum.

The internal nasal valve: this is a more defined structure that is defined by the nasal septum medially, the caudal part of the ULC and the anterior head of the inferior turbinate. The superior angle of this valve is formed by the relationship of the ULC with the septum and should be about 10–15 °. Physiologically, this valve plays a key role in the overall resistance of air entering the nose as it is responsible for about two-thirds of nasal airway resistance. Therefore, trauma affecting this area can lead to narrowing of the valve and nasal obstruction.

Arterial blood reaches the nose by a rich network of terminal branches of the external and the internal carotid systems, and nasal trauma is often accompanied by epistaxis. The anterior nasal septum is supplied by the superior labial artery and the anterior ethmoid artery. Branches of the greater palatine artery and the septal branch of the sphenopalatine artery also contribute to the blood supply of the anterior septum. Posteriorly, the septum is supplied mainly by the posterior ethmoid artery and the septal branches of the sphenopalatine artery [3, 6].

The nasal skin is innervated by the ophthalmic and the maxillary divisions of the trigeminal nerve. The superior aspect of the nose is supplied by supratrochlear, infratrochlear nerves and external nasal branch of anterior ethmoidal nerve. The inferior and lateral part of the nose is supplied by infraorbital nerve [1, 3, 5].

Pathogenesis and Mechanism of Injury

The characteristics and severity of a nasal fracture are determined by various parameters such as the intensity and direction of the force and the physical characteristics of the object hitting the nose.

There are two main patterns of nasal injuries:

Lateral injuries: these are the most common and result in less severe damage. They have a more favourable prognosis compared to frontal injuries. The nose is likely to be deviated away from the midline on the opposite side of the injury.

Frontal injuries: the nasal bones can be pushed up and splayed resulting in a wide flattened bony nasal bridge, saddle deformity and loss of nasal projection.

The nasal septum can be damaged in both types of injuries (Fig. 42.1).

Age plays an important part regarding the consequences of injury. Children tissues have much more elasticity, and fractures are likely to be simple and not always displaced. In contrast, adults have less tissue elasticity, and fractures are more likely to be complex [1, 2].

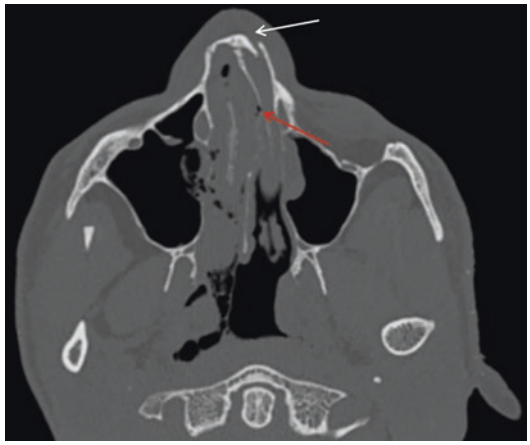

Fig. 42.1 Axial CT scan image of the head of 38-year-old patient who had a seizures and a fall, showing depressed nasal bones fracture (white arrow) and accompanying dislocated nasal septal fracture (red arrow)

Nasal bone fractures should be clearly documented and described in various ways:

- Closed or open with an overlying skin wound
- Unilateral or bilateral
- Simple, green stick or comminuted
- Undisplaced or displaced
- Depressed or open-book fracture

It is unusual for a nasal bone fracture to occur in the absence of injury to other structures of the nose, such as adjacent cartilage or the nasal septum.

Injuries such as septal hematoma, fracture of the nasal septum and cartilaginous nasal injury can all follow nasal trauma, all of which may cause nasal obstruction and a cosmetic defect. Severe trauma may even result in fractures affecting the frontoethmoidal region, maxilla, orbit or skull base [3].

Clinical Assessment

Clinical History

A detailed clinical history regarding the mechanism of injury should be obtained and details should be clearly documented. Information should include the mechanism of injury and activity at the time. Enquiry is made with regard to the force applied, the direction of the blow, the object that caused the injury and any associated injuries.

Relevant previous medical history should include pre-existing nasal deformity, nasal trauma or surgery, sinus disease and allergy [2].

The timing of presentation after injury is important and can affect the management of the patient. Following nasal injury, oedema develops in the subcutaneous soft tissues and may conceal external nasal deformities or fractures. Furthermore, it is important to differentiate between acute external deformities and pre-existing deformity that may indicate previous nasal injury. Enquiry should be made about previous nasal injury and deformity, and patients will often have images of themselves on their mobile phone/devices prior to the injury [4].

It is very important to ascertain whether the patient has previously undergone a septorhinoplasty prior to the nasal injury as surgery usually weakens the nasal bones making them more susceptible to developing an unstable nasal bone fracture and compromised airway. Nasal reconstruction may be required to obtain a positive functional and cosmetic outcome [4]. A review of possible accompanying injury related to the orbit, skull base, face or spine should be elicited [2, 4].

Physical Examination

The management of nasal fractures is based solely on the clinical assessment of function and appearance. The external nose should be carefully examined and the internal nasal structures should be assessed after internal decongestion of the nasal mucosa.

Physical examination begins with a general impression of the patient's face and nose and noting any superficial or deep cuts, oedema, deformation, deviation of the nasal axis or epistaxis. Gentle palpation of the nose is used to assess nasal deformity, loss of support or collapse, fractures, bone crepitus or movement, tenderness, depression, shortening or open book deformity.

Palpation can enhance assessment of the nasal dorsum for saddle nose deformity, deviation, upper lateral cartilage separation, nasal tip deformity or loss of caudal support [1, 2, 4].

The importance of evaluating associated injury cannot be overemphasised; decreased eye acuity, double vision, pupillary asymmetry and response as well as limited extraocular movement may suggest orbital involvement. Facial bone depression, midface numbness or crepitus may suggest a facial bone fracture related to the frontal bones, maxilla or mandible.

Assessment should include the temporomandibular joints and joint movement, mouth opening and dental injury.

Post-traumatic clear nasal discharge may indicate CSF rhinorrhea and a sample should be collected for analysis of beta-trace protein or beta2-transferrin. An increase in the intercanthal distance may indicate a naso-orbitoethmoid (NOE) fracture [2].

Careful examination of the nasal cavities with a Thudichum speculum or nasoendoscope is essential. Starting nasal examination with adequate local anaesthesia and vasoconstriction is recommended. Cotton pledges soaked with decongestants and local anaesthetic topical solution (Lidocaine hydrochloride 5% and phenylephrine hydrochloride 0.5%) are placed gently into the nasal cavities.

Septal haematoma: The internal nose is inspected, looking specifically for a septal hematoma. Should haematoma be missed and left undrained, there is a risk of infection, septal abscess, cartilage loss and saddle nose deformity [2].

Septal deviation: It is important to identify a septal fracture or septal deviation that may lead to nasal airway compromise. Severe septal deviation is considered to be an important predictor of failure following nasal bone reduction [3]. Previous septal deformity is important to recognise as this often leads to the dilemma as to whether or not the injury caused or exacerbated the deviation.

Mucosal injury: Mucosal injury, exposed cartilage and epistaxis should be documented as this can lead to future synechia between the nasal septum and lateral nasal wall, especially if the nose is packed. Consideration should be given to inserting silicon splint sheets to prevent intranasal adhesions [4].

Multiple-view photographs are beneficial for accurate documentation following injuries, both from a medicolegal perspective and to measure the effectiveness of treatment [2, 3, 7].

Imaging

Plain-film radiography: X-ray radiographs following nasal injury used to be routine, but this is no longer the case. Their low sensitivity and specificity can lead to misinterpretation between, fracture lines, sutures lines and vascular indentation lines; they cannot distinguish between acute and old fractures; cartilaginous injuries; and fractures are not displayed.

CT scans: a computed tomography scan is likely to reveal much more detail of the injury, such as comminuted nasal fractures, and injury to adjacent structures such as the face, orbit or skull base, will also be demonstrated. CT scans are therefore likely to be indicated in patients with severe injury rather than more simple nasal injuries.

Management

The diagnosis of a nasal bone fracture is mainly clinical and the decision regarding the need for a nasal bone reduction is based on the changes in the external appearance of the nose and the patient's wishes and concerns.

As with any trauma patient, the ABCDE trauma protocol should be implemented. Once the patient has a safe airway, proper ventilation and is haemodynamically stable, the nose and extra-nasal injuries can be evaluated. Patients with associated injuries such as cerebrospinal fluid rhinorrhea, malocclusion or extraocular movement deficits should be referred to the relevant subspecialist [2].

Treatment of the nose begins with external soft tissue and bony injuries, followed by management of the internal nasal injuries.

Simple, non-displaced fractures where the bones and cartilages are still aligned with no cosmetic deformity or airway compromise do not require reduction, and conservative management with analgesics and rest may be sufficient.

The aim of nasal fracture reduction is to realign the bony and cartilaginous parts of the nose to their former place pre-injury so as to restore cosmetic and functional outcome.

Other features of trauma that may require intervention include epistaxis, skin laceration, foreign bodies contamination or necrotic tissue. Laceration should be irrigated and repaired, epistaxis controlled and foreign bodies removed. Balanced debridement may be necessary for necrotic soft tissue.

In patients with open nasal fractures, the tetanus status should be managed appropriately and prophylactic antibiotics prescribed to minimise infection risk [2].

Should a septal haematoma or abscess be identified, this will require exploration and drainage immediately under local or general anaesthetic.

If the patient is seen within 2–4 h of injury, before nasal oedema sets in, clinical assessment of external nasal deformity is still possible and nasal bone reduction can be performed without delay. Once oedema develops, it will obscure nasal deformity and the adequacy in nasal reduction if performed. Such patients should be re-evaluated three to 5 days later after the oedema has subsided [2].

The optimal timing of nasal fracture reduction is between 3 and 10 days post-trauma. If more than 2 weeks have passed since the trauma, fracture reduction outcome may be suboptimal as the fractured bones may become fixed by the accumulation of fibrotic tissue, and reduction may be difficult. Moreover, in every case of nasal reduction, the patient should be clearly aware that there is a possibility that the functional and the cosmetic outcome may not be satisfactory and that they may need a future nasal reconstruction surgery [4].

Several classification systems of nasal bone fractures have been introduced in order to determine the optimal management plan [8–11]. These classification systems aim to categorise the trauma according to the extent of injury to the nasal bones and septum. The authors find that the modified Murray classification system that heavily relies on clinical findings rather than pathological ones is effective, easy to recall and simple to implement (Table 42.1).

Table 42.1 Modified Murray classification [9] of nasal bone fractures

Nasal trauma classification	Type of injury
Type I	Injury restricted to soft tissue
Type IIA	Simple, unilateral nondisplaced fracture
Type IIB	Simple, bilateral nondisplaced fracture
Type III	Simple, displaced fracture
Type IV	Closed comminuted fracture
Type V	Open comminuted fracture or complicated fracture, i.e. types II–IV fracture with CSF rhinorrhea, airway obstruction, septal hematoma, crush injury, numbness, severe displacement, or NOE midface involvement

The decision to perform nasal fracture reduction under general or local anaesthesia should take into account the patient's age, type of fracture, cooperation, safety, availability of general anaesthesia and the patient's desire. In general, we find that uncomplicated fractures (types II–IV) in adults can be managed by closed reduction under local anaesthesia. Depressed nasal fractures (Fig. 42.1) are best reduced under general anaesthetic due to the need for instrumentation and risk of bleeding. Children usually require a short general anaesthetic.

Open reduction under general anaesthetic is indicated for patients with more complex (type V) fractures [1, 12–14].

Local Anaesthesia Technique

Adequate local anaesthesia, if properly performed, can reduce operative pain and improve patient cooperativeness. A good understanding of sensory innervation of the external nose and nasal cavity is essential for effective administration of

local anaesthesia. The key sensory nerves are the infratrochlear nerve, the anterior ethmoidal nerve and the infraorbital nerve.

We recommend applying surgical patties soaked with local anaesthetic and decongestant solution (such as lidocaine hydrochloride 5% and phenylephrine hydrochloride 0.5%) inside the nasal cavities for about 10 min. This will minimise pain, reduce nasal bleeding and facilitate evaluation the nasal airway. These patties should be properly placed along the nasal dorsum and bones around the anterior ethmoid artery and nerve. Some practices also advocate an infiltrative pterygopalatine block to reduce pain as a result of internal instrumentation and possible mucosal bleeding.

We typically use lidocaine hydrochloride mixed with adrenaline (Lidocaine hydrochloride/Adrenaline 20 mg/L + 12.5 mg/) for infiltrative local anaesthesia, injected with a dental syringe and fine needle. We begin by infiltrating the submucosa of the nasal septum followed by the nasal bones and dorsum, thereby blocking the external branch of the anterior ethmoid nerve and the infratrochlear nerve. If necessary, the sidewalls of the nasal bones can also be blocked by infiltrating the infraorbital nerves [1, 2].

Nasal Bone Reduction Technique

The patient should be consented before the procedure. Consent should include the possible outcomes, the objectives of minimising nasal deformity and alleviation of nasal obstruction, and the possibility of residual or recurrent deformity.

The need for further nasal reconstruction surgery/septorhinoplasty after closed reduction is between 9 and 17% [1].

Closed reduction is adequate for simple nasal fractures where there are no complicated or comminuted nasal fractures. One of the easiest and most common methods in simple nasal bone fractures is a bimanual nasal bone reduction by applying digital pressure over the deviated part of the nasal fracture and opposite to the vector injury. The nasal bones may need to be disimpacted by exacerbating the deviation prior to realigning it to its original position.

There should be no hesitation to use instruments in a closed reduction in order to improve outcome. The set that we use for nasal bone reduction is composed of headlight, rhinoscope, suction, bayonet forceps, Boies elevator, Asch and Walsham forceps. The Boies elevator should be used when an internal pressure is needed to elevate the depressed bones. This elevator should be used with outward force and bimanually to stabilise the bone and feel when the bones have realigned. Another instrument that can be used to elevate depressed nasal bones is the Walsham forceps which has two lips, one inserted and placed below the nasal bones and the other one externally overlapping with the internal lip.

A fracture or deviated nasal septum should be carefully addressed, as leaving these conditions untreated may lead to a poor cosmetic result after fracture reduction and airway compromise. The basic principle is to apply force on the deviated part of the septum to reposition it to the midline or its former place. The Asch forceps is recommended for septal repositioning [1–4] (Fig. 42.2).

In cases of complicated or open comminuted nasal fractures with loss of nasal support and accompanying severe facial and soft tissue injury, an open reduction may be needed. The advantages of this open approach include wide exposure and more accurate reapproximating of the fractured cartilage and bony parts including the use of bone and cartilage grafts. As with closed reduction surgery, an open approach should be done early before the accumulation of fibrous tissue, ideally within 3–10 days when oedema has subsided. It is the author's opinion that extensive nasal reconstruction is not recommended because of the unpredictable healing process, risk of septal perforation and the possible need for future secondary nasal reconstruction.

We do recommend the routine application of external nasal splints to stabilise the reduced nasal fractures.

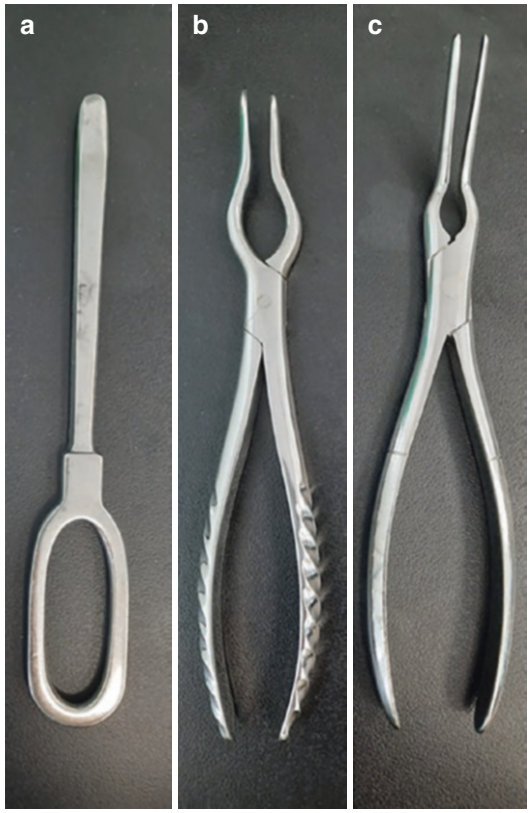

Fig. 42.2 Reduction instruments: (**a**) Boies elevator. (**b**) Walsham forceps. (**c**) Asch forceps

Special Consideration

Paediatric Nasal Fracture

Overall, pediatric nasal fractures are less common as the nasal dorsum and bones are more elastic and less prominent than in adults as they are protected by the projected forehead and the supraorbital rims. However, septal dislocation and hematoma are more common in children [4]. Nasal injuries in children should be carefully assessed for a septal hematoma. Should a haematoma be present, it should be quickly drained to avoid the formation of septal abscess, septal cartilage necrosis and saddle nose deformity. The hematoma can be evacuated via a mucosal incision; a nasal drain or a through-and-through septal suture can be inserted to prevent recollection. Despite there being no clear consensus on antibiotic choice or duration, broad-spectrum antibiotic treatment, e.g., co-amoxiclav is recommended [3, 4].

If an abscess is suspected, coverage for MRSA should be considered until culture results are available.

It is well known that the nasal septum plays a key role in the development of the midface as it continues to grow until the age 12–13 and therefore a closed (rather than open) reduction should be the treatment of choice.

An open septorhinoplasty approach for nasal fracture reduction is rarely needed and should be delayed until the nose and the midface have developed. As healing is much faster in children and fibrosis increases the difficulty of nasal fracture reduction in children, a planned nasal fracture reduction should be performed within a week of the injury. The adequacy of reduction relies on visual assessment as the sensation of bone snapping back into place is not evident in children.

It is crucial to educate the parents that even though the nose has been properly reduced, there is a chance of possible future nasal airway narrowing or suboptimal nasal appearance as the healing of the nose is unpredictable [1, 3, 4].

Conclusion

In conclusion, nasal trauma is common across all age groups. The cause and mechanisms vary. Physical abuse should be ruled out, particularly in infants, young children and women. The diagnosis of a fractured nose is mainly clinical and relies on a detailed history and examination. Radiological images have a limited role in the overall clinical management of a fractured nose. A nasal fracture may have undesired long-term consequences for the nasal airway and appearance if left untreated or undiagnosed, as may occur with other serious injuries. It is important to exclude accompanying injuries in patients with severe multiple traumatic injury. Closed reduction by manipulation is generally recommended if the nose is displaced and open reduction should be considered in selected cases.

Key Learning Points The objective of the assessment is to accurately diagnose nasal fracture and co-existent injuries such as orbital fracture.

- It is important to counsel patients that fractured noses may not always be returned to its pre-injury state despite manipulation.
- There is a window of opportunity within 2 weeks of injury to manipulate the nasal fracture. Late deformities may require surgery.
- There are medicolegal consequences of nasal fractures particularly in assaults and septal abscess.

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Septoplasty

43

Richard Green and Sean Carrie

Introduction

The nasal septum is an integral part of the nasal airway and plays a major role in both the aesthetics and function of the nose. Around 70–80% of the adult population will have an element of septal deviation but not all of these patients will be symptomatic [1, 2]. The majority of surgical procedures on the septum will be performed with a desire to improve the function of the nose.

There are approximately 250,000 septoplasties performed in the USA annually, with 22,000 in the United Kingdom [3, 4] There are several indications for septoplasty, the most common is to improve symptoms of nasal blockage, although it may also be performed to facilitate access to the nasal cavity, paranasal sinuses and skull base.

There are three established approaches to operating on the nasal septum, the traditional endonasal approach, the external open approach and the endoscopic approach, each will be systemically described.

A Brief History of Septal Surgery

Freer and Killian first described the traditional endonasal approach in the early twentieth century (1902, 1904) [5, 6]. Septal surgery was originally performed under local anaesthesia, induced by topical cocaine with the patient sitting upright. The operation was known as 'submucosal resection', or SMR, and included elevation of mucosal flaps and resection of the deviated part of the cartilaginous and bony septum.

Considerable advances in septal surgery were made by Cottle (1947), who developed a conservative cartilage-sparing technique, utilising various mucosal tunnels [7]. The concept of SMR versus the more sophisticated cartilage-sparing operation of septoplasty was still being debated as recently as the 1980s.

The endoscopic approach described by Lanza and Stammberger in the late twentieth century has become increasingly popular due to improvements in endoscopic skills and the rise of minimally invasive techniques [8, 9].

Anatomy

The nasal septum is composed of three key parts: the membranous, the cartilaginous and the bony septum (Fig. 43.1). The membranous septum is comprised of fibrofatty tissue and is positioned between the medial crura of the lower lateral car-

R. Green (✉) · S. Carrie
ENT Department, Ninewells Hospital, Dundee, UK
e-mail: Richard.green4@nhs.scot

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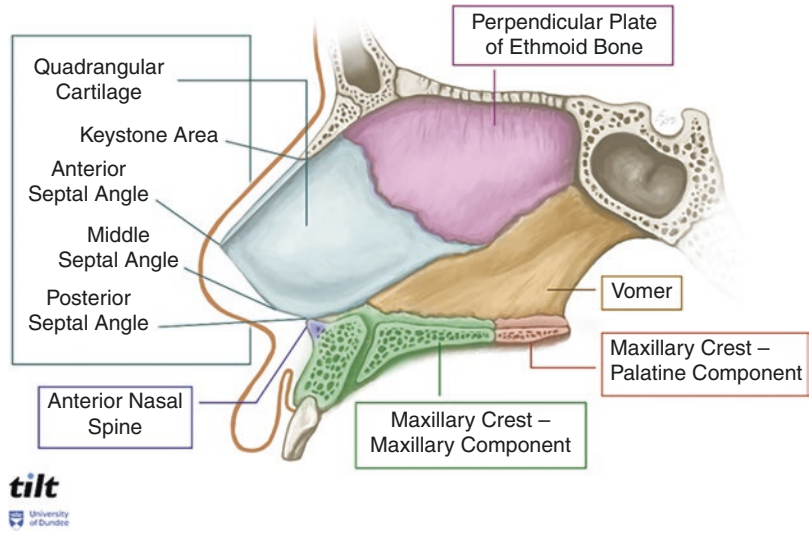

Fig. 43.1 Cartilaginous and bony septal anatomy

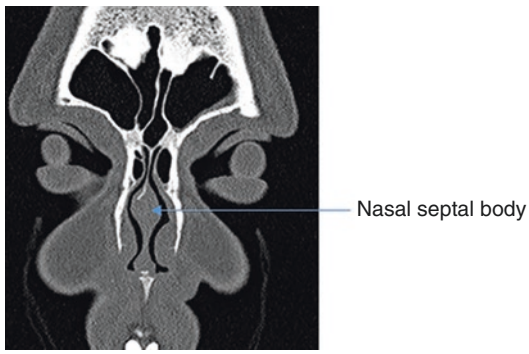

Fig. 43.2 Septal body on coronal CT

tilages (LLC) anteriorly and the cartilaginous septum posteriorly. The anterior part of the septum is formed of the hyaline cartilage, named the quadrilateral cartilage due to its shape and four sides.

The caudal edge is important for nasal support and the tip projection and shape. The superior caudal edge forms the anterior septal angle, and this sits posterior to the intermediate crura of the lower lateral cartilages (LLC). The inferior caudal edge of the cartilage sits on the most anterior part of the maxilla (the anterior nasal spine) and is termed the posterior septal angle. This forms one of the key attachments of the septum in relation to the support of the external nose.

Superiorly, the septal quadrilateral cartilage attaches to the nasal bones to form the keystone area that is also crucial for nasal shape and support.

Inferiorly, the quadrilateral cartilage abuts onto the maxillary crest. Posteriorly, it is fixed by a fibrous chondro-osseus joint, to the bony vomer and the perpendicular plate of ethmoid (PPE).

Superiorly, the PPE attaches to the skull base care must be taken when manipulating this bone during surgery to prevent a fracture extending into the anterior skull base inducing a CSF leak.

The cartilaginous nasal septum forms a continuous unit superiorly with the upper lateral cartilages. The junction of the septum with caudal end of the upper later cartilages (ULCs) forms the internal nasal valve which is responsible for a significant proportion of nasal resistance [10].

The nasal septal body is a mucosal swelling that can often be seen during anterior rhinoscopy (Fig. 43.2). It is situated anterior to the middle turbinate and superior to the inferior turbinate. This mucosal swelling is thought to play a role in the regulation of nasal flow and is especially apparent on coronal CT images of the septum [11].

Mucoperichondrium and mucoperiosteum invest the septum bilaterally. The collagen fibres thicken and decussate in the region of the posterior septal angle, thus fixing the cartilage to the bony nasal spine.

The perichondrium over the anterior caudal end of the septum is firmly attached to the carti-

lage making the initial dissection in this area more difficult.

Assessment of the Nasal Septum

Measurements of Septal Deviation

There is no gold standard for the measurement of nasal septal deviation. Studies suggest anterior septal deviation is more likely to be associated with nasal block than posterior nasal deviation [12]. The narrowest part of the nasal cavity is the internal nasal valve area just anterior to the inferior turbinate and is normally at an angle of 10–15 ° (see Figs. 43.3 and 43.4). Cole et al. simulated nasal septal deviations in healthy adults and found mid to posterior deviations made little difference to the sense of obstruction, but the anterior septum was sensitive to changes as little as 1 mm thickness [13].

In reality, the management of septal deviation lacks a good evidence base and the decision for surgery is currently based on the clinician's subjective expert assessment and nasal endoscopy to exclude alternative causes of nasal blockage. Relying solely on a patient's self-reported symptoms lacks sensitivity and specificity. In a recent UK survey, the most commonly used test to determine nasal blockage was the nasal misting pattern (73%), followed by peak nasal inspiratory flow (19%) [14].

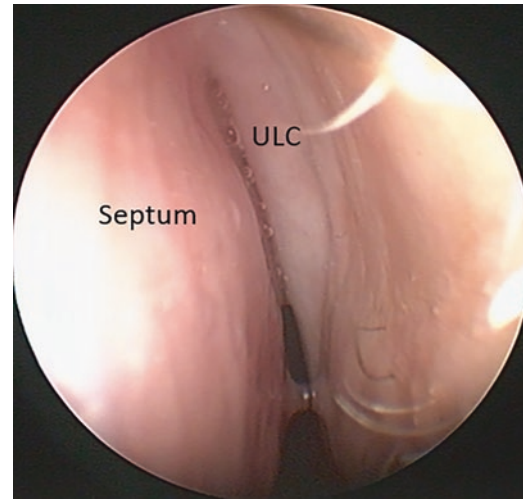

Fig. 43.3 Endoscopic photo demonstrating narrowing of the internal valve on the left side of the nose. (ULC—Upper lateral cartilage)

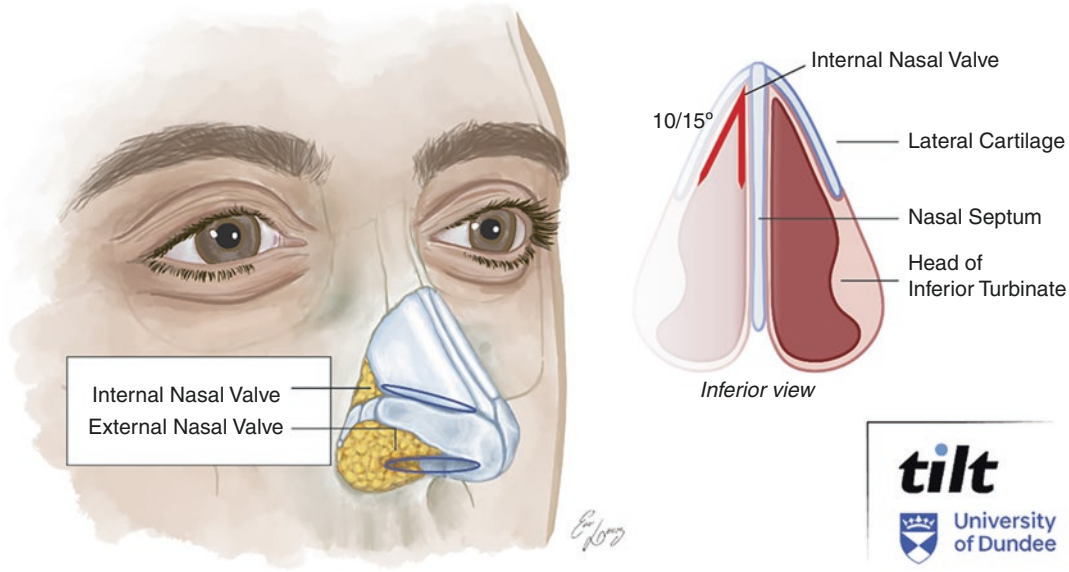

Fig. 43.4 Illustration demonstrating the internal and external nasal valve position

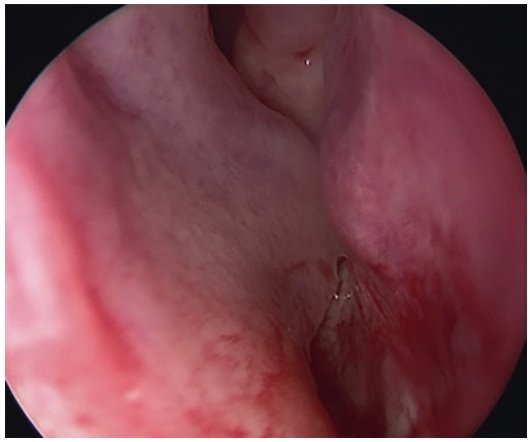

Fig. 43.5 Endoscopic image of a left-sided nasal septal deviation touching the lateral nasal wall

Clinician Judgement

In practice, most clinicians assess the degree of deviation and subjective requirement for septal surgery based on a headlight assessment of the nasal passages (Fig. 43.5). This subjective assessment is best done before and after good mucosal decongestion to facilitate an accurate assessment of a septal deformity and its effects.

In the only randomised controlled trial (RCT) to date, the authors required their investigators to use anterior rhinoscopy to quantify the level of septal deviation as mild if it obstructed less than half of the nasal passage, moderate if it obstructed at least 50% of the nasal passage, severe if the deviation was in contact with the lateral nasal wall [15].

Patient Reported Outcome Measures (PROMS)

The SinoNasal Outcome Test (SNOT22): this is an internationally recognised patient-reported outcome tool in rhinological symptom assessment. It has been used to report outcomes in septal surgery [16]. It is the primary outcome measure being assessed in the first UK multicentre RCT of septoplasty: NAIROS (Nasal AIRway Obstruction Study) [17].

The Nasal Obstruction Symptom Evaluation (NOSE) scale: this PROM is specifically designed and validated for patients undergoing septoplasty for nasal obstruction [18]. The NOSE scores are categorised into three groups according to severity: 30–50 = Moderate, 55–75 = Severe and 80–100 = Extreme. The minimal change in NOSE score associated with a detectable symptom change after septoplasty is reported to be 19.4 [18].

The Double Ordinal Scale: this measure uses a ten-point ordinal scale to subjectively assess each side of the nose [19]. The Double Ordinal Scale correlates well with *the Nasal Partitioning Ratio(NPR)* ($r = 0.8$) with a sensitivity of 81% and a specificity of 60%, the latter being considerably better compared to a simple visual analogue score (VAS) of nasal blockage.

Tests of Nasal Airflow

The readers are directed to for a more comprehensive discussion on nasal airflow measurement (please refer to Chap. 13). A number of tools have been developed to assess nasal airflow. Rhinomanometry has been described as the gold standard of assessment measuring nasal airway resistance as a function of nasal airflow and the pressure required to create that flow [20]. However, it is both cumbersome and time-consuming to use and impractical from a routine clinical perspective. Acoustic Rhinometry calculates the cross-sectional area of the nasal cavity by measuring the reflection of acoustic pulses introduced into the nostril. Although straightforward to use it has significant limitations related to the inherent challenges of assessing physical properties of sound transmission through air in a complex chamber such as the nasal cavity (Fig. 43.6) [21].

Rhinospirometry measures the fractions of the slow vital capacity volume of air expired through the right and left nasal passage in turn [22]. Asymmetry of nasal airflow is expressed as a nasal partitioning ratio (NPR) that ranges from −1 (left nasal cavity obstruction) to +1 (right nasal cavity obstruction) with 0 indicating

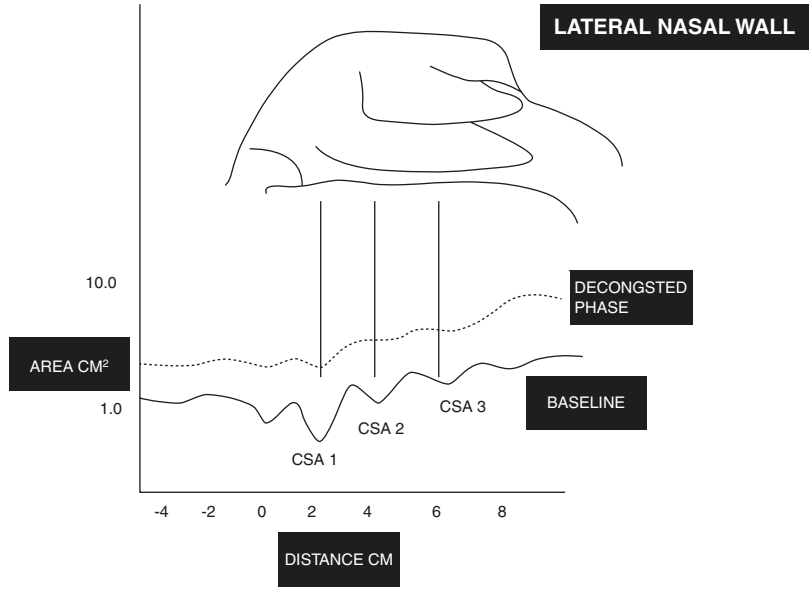

Fig. 43.6 Acoustic rhinometry graph with the lateral nasal wall showing points of reduced cross-sectional area (CSA)

symmetry of airflow [23]. In a UK study on 31 patients before and after corrective surgery for nasal septal deviation, the patients whose NPR was beyond the normal range reported a greater improvement in subjective nasal blockage.

Zones of the Septum

The different areas or zones of the septum, first described by Cottle (1961), are helpful in documentation in clinic/theatre or to orientate pathology [24]. Cottle suggested dividing the internal nose into five areas (Fig. 43.7):

- Area 1, the external ostium or naris.
- Area 2, the valve area.
- Area 3, the area underneath the bony and cartilaginous vault, also called the attic.
- Area 4, the anterior part of the nasal cavity, including the heads of the turbinates, the infundibulum or ostiomeatal complex.
- Area 5: the dorsal part of the nasal cavity, including the tails of the turbinates.

More recently, in 2008, Mladina described a schematic depiction of the seven types of septal deformities [25]. Like the zones of the septum,

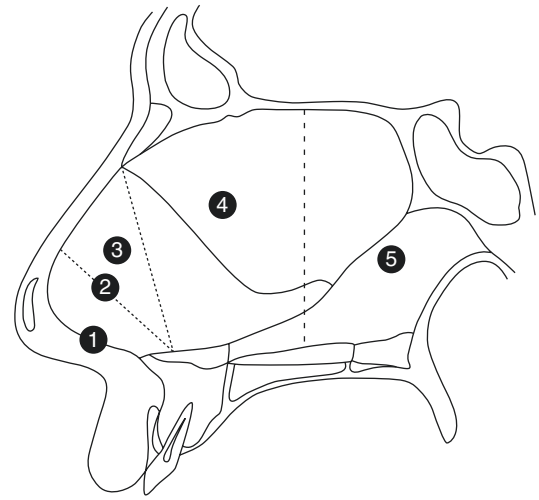

Fig. 43.7 Illustration demonstrating the septal areas as described by Cottle

this can be useful in describing this to colleagues or in reference to documentation.

Surgical Techniques

When originally described, a traditional 'septoplasty' was also known as a submucosal resection (SMR). This technique removed the bulk of

the nasal septal cartilage and bone, leaving a 1 cm strip of the caudal and dorsal septum in the keystone area. However, this was much more likely to cause complications such as perforation, haematoma and saddle deformity. The more conservative cartilage-sparing techniques are therefore strongly advised [26].

A thorough understanding of the inherent problem and a clear plan to achieve a successful outcome is required at the outset of surgery. Careful dissection in the correct plane, preserving the mucosal flaps with limited cartilage and bone removal and being mindful of the dorsal and caudal struts are the cornerstones of any technique.

There are many variations and modifications of the technique of septoplasty, and the following will aim to provide a basic practical description of the procedure.

Standard Septoplasty Technique

It is always best to carefully assess the septal deformity after vasoconstriction and decongestion, this enables the evaluation of structural anomalies contributing to the obstruction.

It is essential to minimise bleeding during septal surgery. Whilst this can be obtained with topical vasoconstrictor solutions, local mucosal injection with 2% lidocaine combined with 1/80,000 adrenailine (epinephrine) (Lignospan©) is recommended.

When injecting the nasal septum, it is important to enter the correct subperichondrial plane. This is facilitated in the mid-septum by hydrodissection. However, the mucoperichondrium around the hemitransfixtion incision is tightly bound to the cartilage and requires careful sharp dissection as described below.

The Incision

There are two types of incisions and depending on where the anatomical defect is will often determine which one is used. The caudal septal incision, often referred to as a hemi-transfixion incision (not strictly correct, but a firmly established term), is made directly along the caudal end of the cartilage; this is recommended if the septal deviation is anterior and/or involving the caudal part of the septum. The Killian incision is made 1 to 2 cm back from the caudal end of the septum and is still used by some surgeons in more posterior deviations.

Mucosal Elevation

A caudal/hemi-transfixion incision is recommended when addressing more caudal/inferior septal defects. However, identifying the correct mucoperiosteal plane is generally more difficult in the anterior septum, particularly in the presence of post-traumatic scarring, Loupes may be used to enhance vision during dissection. Entering the correct subperichondrial plane reveals the underlying 'pearly white' cartilage (Fig. 43.8). The use of a Freer elevator, sharp iris scissors or scalpel can assist the surgeon in creating access into the correct plane.

Depending on the level of septal deviation, a 'front to back' or 'back to front' approach can be employed to access the deviation and minimise the risk of mucosal tears.

Bilateral flaps can be elevated through the caudal/ hemi-transfixion incision to allow elevation of the mucosa on both sides of the deviated segment. Elevation of the mucosa on the contralateral side is needed if removing a piece of cartilage or bone to minimise the risk of tearing.

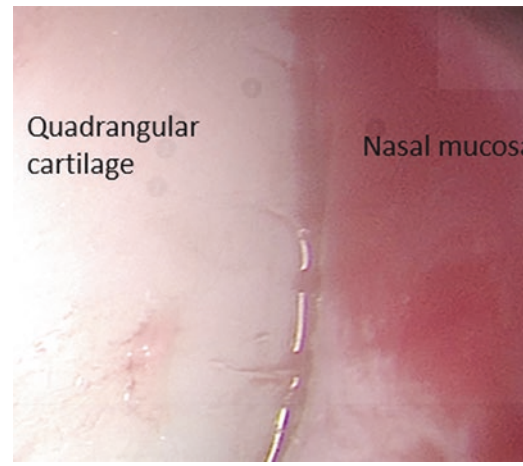

Fig. 43.8 Endoscopic appearance of the quadrilateral (quadrangular) cartilage and left mucosal flap

Septal Spurs

Once the mucosa is elevated, the spur can be dissected. The 'back to front' technique commences caudal to the spur/deviation; the plane of dissection remains deep to the mucoperichondrium/mucoperiosteum; the surgeon should dissect posteriorly to the spur and then mobilise the displaced segment from posterior towards the caudal septum, whilst remaining in the correct surgical plane.

Significant septal spurs are best addressed by a 'front to back' approach. Two tunnels can be created; one superior and one inferior to the spur. Elevating the tunnels prior to dissection over the spur can reduce the tension on the mucosa at this vital point (Fig. 43.9).

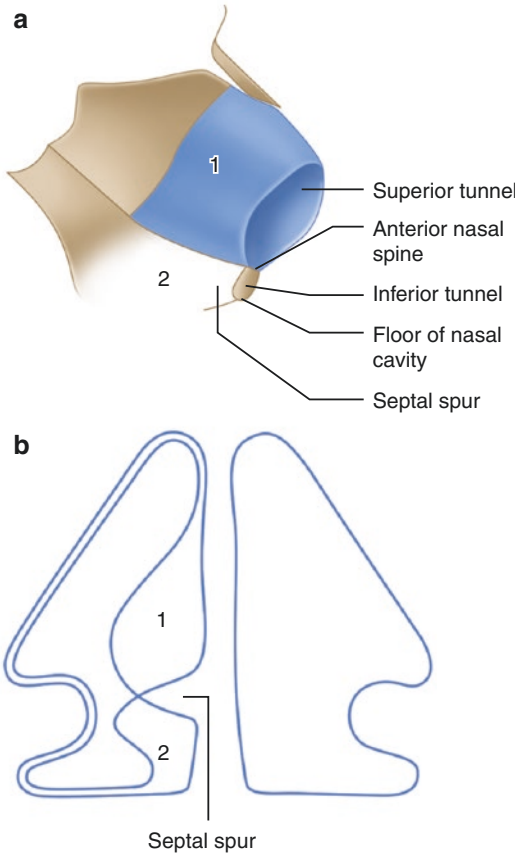

Fig. 43.9 Sagittal and coronal view of the nasal septum demonstrating elevation of superior (1) and inferior (2) mucosal tunnels over a septal spur

Septal Deviation

The next step is to determine whether the deviation is cartilaginous, bony or both. If the main cause is cartilaginous then the surgeon should make an incision anterior to the deformity such as a hemi-transfixion incision. Care should be taken to avoid disrupting the anterior 1 cm of the L-strut.

Septal Cartilage Mobilisation

The osseocartilaginous junction can then be addressed. The junction between cartilage and the perpendicular plate of ethmoid (PPE) can be disarticulated to allow the anterior cartilage to be moved towards the midline and also give access to the bony septum. The osseocartilaginous junction is identified using a Freer or similar elevator: the palpably smooth cartilage contrasts to the hard, coarse sensation of the bony septum. The cartilage can be separated from the bone by applying medial pressure over the cartilage adjacent to the cartilage-bony junction. Alternatively, a cartilaginous chondrotomy can be made in the quadrilateral cartilage just anterior to the junction.

The quadrilateral cartilage will still be attached inferiorly and medial pressure at the junction between the cartilage and the maxillary crest can then be applied to perform an inferior chondrotomy.

The Bony Septum

Should the bony septum be significantly deviated, this will need to be mobilised and segments will need to be removed. However, mobilising the superior region must be done with care as the excess movement of the perpendicular plate of ethmoid (PPE) can fracture the skull base and cause a CSF leak. Using sharp instruments to make the initial cartilaginous incision is useful but the anterior section of the PPE is often too robust and quite thick. It is important to recognise this and avoid using excess pressure, but to revert to sharp instruments. Robust turbinectomy scissors are recommended to make the initial cuts.

Once the cartilaginous deformity is isolated it can be removed and assessed for reconstitution. Flat segments of cartilage salvaged from the deviated segment can then be repositioned into the space that has been created and subsequently secured if necessary. The ultimate aim is to preserve cartilage wherever possible.

Closure

The anterior incision is then closed with an absorbable suture 3–0 or 4–0 Vicryl (90% Glycolide and 10% L0_latcide; Ethicon Inc. Johnson & Johnson, New Brunswick, NJ, USA) on a round body or reverse cutting needle to minimise mucosal trauma. A quilting suture with several passes through the mucosal flaps is used to secure the mucosal flaps, thus preventing the development of a septal haematoma. Septal tears can be repaired by this technique to reduce the risk of perforation.

Endoscopic Techniques

The authors favour using a 4 mm zero degree (0°) endoscope to maximise visualisation during this technique. The surgeon should appreciate the altered perception of distance and image magnification of endoscopic vision.

In general, the surgical principles are similar to steps taken in the traditional approach. The septal deformity should be assessed after vasoconstriction and decongestion.

The initial incision should be tailored to the location of the deformity. Although a modified Killian incision may be most commonly used, if there is a specific focal deviation then an incision immediately anterior to it should suffice.

A limitation of the endoscopic approach is the difficulty in managing anterior or caudal deviations. Such defects are therefore often considered as relative contraindications to this approach.

Whilst the conventional landmarks for identifying the L-strut are not as well defined, the head of the inferior turbinate is an excellent caudal landmark and the axilla of the middle turbinate forms the dorsal landmark [27]. Extending dissection/resection beyond these landmarks increases the risk of weakening of the L-strut.

Septal spurs can be approached much more directly, either via an incision placed just anterior to the spur or by incising the mucosa along the length of the spur (The incision is placed just above the peak of the spur, elevating limited mucosal flaps above and below the spur, excising the exposed spur and replacing the mucosa edge to edge). Significant deflections, especially affecting the vomer, can be removed with great precision with the aid of a specialised septal burr.

Studies that compare endoscopic and traditional approaches show similar operative times and patient outcomes [28, 29, 30]

The concepts of the endoscopic and traditional approaches are often seen as separate techniques. However, the excellent images provided by the endoscope can also be combined with the traditional approach to facilitate the optimum operative results. The endoscope is perfect for enhancing teaching and training and greatly improves the experience for the whole operative team.

L-Strut Deviations

There are several options available to correct deviations of the L-Strut. These range in complexity from scoring of the cartilage through to an extracorporeal septoplasty.

Scoring the concave side of the cartilage sufficiently should relieve tension and correct the deviation. Cartilage scoring does lack reliability, especially with regard to long-term outlook. The authors therefore recommend the use of batten grafts onto the concave side to support and help maintain a straightened concave segment. These grafts can also be used to strengthen the L-Strut if weakened following the removal of deviated segments or fracture lines (Fig. 43.10).

The best options for batten grafts are septal cartilage or bone from the posterior ethmoid plate (PPE). Bone grafts are more solid, they need to be secured by sutures passed through previously drilled holes.

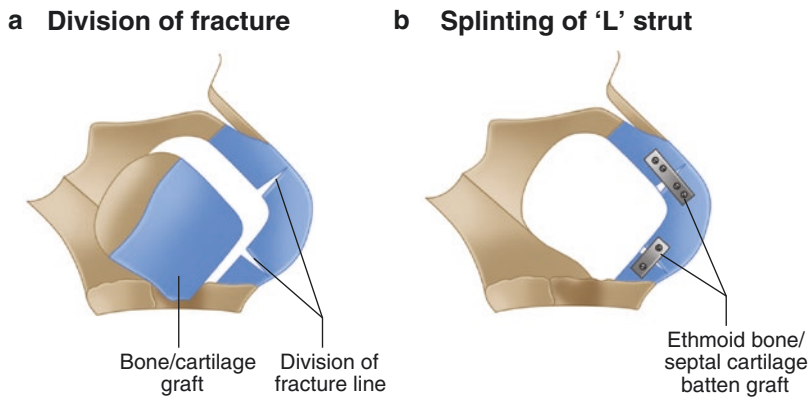

Fig. 43.10 Using batten grafts to support the L-Strut

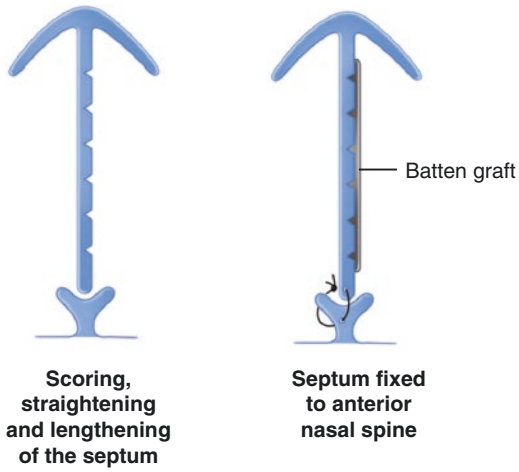

Fig. 43.11 Illustrations demonstrating the different techniques described to straighten and secure the septum

Care should be taken to avoid placing grafts too close to the caudal or dorsal edge that may become palpable. Mattress sutures are an alternative to batten grafts, but the authors find these less successful in reducing deviation in the long term [31].

If excess caudal cartilage has been removed, or the inferior part of the cartilage has been released from the spine, the septum will need to be secured back in a central position. A 'door step' technique can be used to secure the inferior caudal end onto the opposite side of the nasal spine in cases where the septum is excessively long. This acts as a 'door stop' securing the septum into the midline position. The cartilage can be secured either by suturing onto the periosteum or to the bone itself (Fig. 43.11). A fissure burr drill or straight hypodermic needle can be used to create a bony canal through the nasal spine to facilitate the placement of the suture. The authors' preference is a 4–0 PDS as it is slowly absorbable.

External Open Approach Techniques

The majority of septal deviations can be addressed using either the traditional endonasal approach, the endoscopic approach, or a combination of the two.

An external open approach is a technique that will improve access and the surgeon's ability to manage specific or complex deformities, especially where major reconstruction is anticipated. A significant deviation in the L-strut area of the caudal or dorsal septum is best approached by an open technique. The authors would generally recommend the use of an open approach should the caudal end of the cartilaginous septum be deviated >50% into the nasal cavity.

Extracorporeal Septoplasty

Extracorporeal septoplasty is another option available when there is a significant deviation of the dorsal or caudal septum. In this approach, the septum is mobilised as previously described by making posterior and superior chondrotomies and releasing it from the 'keystone' area, upper lateral cartilages and the anterior nasal spine.

There are many options available to reconstruct a remodelled anterior nasal septum. The most straightforward option is to remove and then reorientate the existing septal cartilage, provided there is a sufficient portion straight enough to provide both a satisfactory airway and dorsal support. Alternatively, the cartilage can be reshaped or augmented with nasal cartilage or bony grafts. Finally, when there is limited autograft material, a scaffold of polydioxanone (PDS) (Ethicon Inc. Johnson & Johnson, New Brunswick, NJ, USA) sheet can be used to support the graft tissue [32].

A modified extracorporeal septoplasty has been described in which a small section of the dorsal cartilage is preserved at the 'keystone' area to which the repair can be secured. This method provides increased stability and support when suturing the septum back into place [33].

Loss of projection and rotation of the nasal tip, affecting the cosmetic appearance, is a significant risk of extracorporeal septoplasty. In order to minimise this risk, the septum should be sutured to both the anterior nasal spine as well as to the upper lateral cartilages or septal remnant, if the latter remains.

Finally, suturing is then completed with a quilting suture through the septum and both mucoperichondrial flaps to provide a third means of supporting the repair.

The extracorporeal septoplasty is an advanced technique that carries significant risk and requires an experienced surgeon who can deal with the potential complications.

Iatrogenic Tears in the Mucosal Flaps

Mucosal tears are common occurrences during septal surgery, and it is important to understand the possible consequences and how to manage them.

- An isolated small mucosal tear on one side of the mucosa is very unlikely to cause a septal perforation.
- A large mucosal tear may lead to infection and later adhesions.
- Bilateral tears should be repaired intraoperatively to reduce the risk of septal perforation.
- Posterior tears are best assessed and managed endoscopically. Initially assess the integrity of the contralateral mucosa, then remove bone or cartilage that may prevent spontaneous closure.

Quilting absorbable sutures are used to repair the defect. Large anterior tears or significant mucosal loss may rarely require a mucosal rotational flap to close the defect.

Finally, the authors recommend using silastic splits to help support the mucosa following repair of any significant tears.

Nasal packing and postoperative antibiotics are not routinely used after septal surgery with mucosal tear repair.

Local Anaesthetic Septoplasty

Local anaesthetic rhinology has been performed around the world for decades and is increasing in popularity. Patient assessment and selection are crucial before surgery. There are limitations according to patient tolerance and surgical technique and some patients may require perioperative sedation.

The popularity of septal surgery under local anaesthesia has increased and may continue to do so in the COVID era, with increased competition for operating theatre facilities. In the USA, there has been a reported increase in office-based septoplasties of 423% between 2012 and 2016 [34].

Complications of Septoplasty

The complications of septoplasty have been reported in 2018 by a systematic review in which only three studies considered complications (see Table 43.1) [35]. Nasal septal perforation and nasal adhesions were reported in 3% and 2.6%, respectively, with less than 0.5% of patients having a haematoma or secondary haemorrhage. All three studies reported higher complication rates with concomitant septal surgery and turbinate surgery. External nasal deformities have been reported in the literature from 0.4 to 3.4% [36, 37].

Table 43.1 Complications of septoplasty [35]

Complications of septoplasty	Bleeding Infection Septal perforation Adhesions Change in the external appearance of the nose CSF leak Failure; need for revision surgery

An RCT on septoplasty and concomitant turbinate surgery in 2019 showed complications in 18% of patients undergoing surgery [15]. The majority of these were minor (e.g. bleeding, infection) but 2% notably had septal perforations. The reported rate of revision surgery is variable and has been quoted at 6–20% [38, 39].

Surgical Outcomes of Septoplasty

A comprehensive systematic review of septoplasty was reported in 2018 prior to a national RCT into the effectiveness of septoplasty in the Netherlands [35]. A total of 11 articles were included but there were no studies comparing surgical to non-surgical management. Five RCTs and six controlled before-and-after studies were included. Eight out of nine studies reported subjective benefit after treatment, irrespective of whether septoplasty had been performed with or without concurrent turbinate surgery. Only Kumar et al. reported that septoplasty with concurrent turbinate surgery resulted in significantly greater improvement than septoplasty alone [40].

Van Egmond et al. published an RCT of 203 patients in the Netherlands randomised to either surgery or standard non-surgical management [15]. A combination of subjective and objective assessments was used and the surgical arm was sub-divided into those undergoing turbinate reduction as an adjacent procedure.

The main findings were that septoplasty is more effective than non-surgical management in adults with nasal obstruction and a deviated septum. Patients in the septoplasty+/− turbinate reduction arm showed significant improvements in quality of life scores and an improvement in nasal airflow measured with PNIF [15]. The subgroup analysis of septoplasty compared to septoplasty and turbinate reduction did not show clinically relevant differences.

The same group in 2020 has also published data on the cost of septoplasty demonstrating the operation being more cost-effective over a 2-year period [41]. They reported a quality-adjusted life year (QALY) of 0.05 over 2 years and an incremental cost-effectiveness ratio (ICER) of €17,374.

At the time of writing, the NAIROS study (NIHR HTA 14/226 RCT: Nasal AIRway Obstruction Study) has now completed a RCT across 17 UK centres and publication of the results is awaited [17]. This study of 378 patients compares septoplasty with or without turbinate reduction to steroid nasal spray and nasal saline rinse.

Areas of Controversy

1. The Indications for septoplasty are currently practice based rather than evidence based and the place of surgery in the management of septal deviation remains to be defined.
2. The optimal preoperative assessment remains unclear, particularly the place of objective nasal airflow assessment and CT imaging of the nasal septum.
3. The indications for endoscopic, open and extracorporeal septoplasty have yet to be clearly defined.
4. Further studies are required to define the additional benefit of turbinate surgery.

Conclusion

Septoplasty continues to be one of the most common nasal operations performed and recent studies validate its efficacy and safety. Patient selection is key to achieving a good outcome. This remains a key area for further research. The trainee surgeon should ensure a good understanding of structural nasal anatomy and the potential impact of each surgical step on both the functional and cosmetic outcome of the procedure.

Key Learning Points

- A sound nasal anatomical knowledge, particularly of the nasal valve region is essential.
- Patient selection is key with a combination of subjective and objective tests available to help decision making on potential surgical benefit.
- Careful preoperative assessment will determine which surgical approach is indicated.
- Each approach requires careful dissection in the correct plane, preserving the mucosal flaps, judicious cartilage and bone removal and care to ensure maintenance of the dorsal and caudal struts.

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Nasal Obstruction: The Role and Management of the Nasal Valve and Inferior Turbinates

44

A. Simon Carney and Tim Woolford

Introduction

Nasal obstruction is an extremely common symptom in patients presenting to the rhinologist. It may be due to a variety of factors, but inflammatory mucosal disease is by far the most common and is dealt with elsewhere in this textbook. Structural problems to the nose can be either congenital or acquired and are another common cause of nasal obstruction. Management of the nasal septum is also dealt with separately and this chapter will concentrate on the nasal valve and inferior turbinate. We will outline principles of management and different types of surgical approaches and aim to provide guidance on who to consider operating on, and then which procedure to offer for a variety of different clinical scenarios.

The Nasal Valve

Applied Anatomy

The literature surrounding the description and anatomy of the nasal valve is extremely confusing. There is no universally approved nomenclature, but it is commonly described that the nasal valve consists of the external valve, where the medial wall and floor are consisting of the septum, non-cartilaginous columella and the bony nasal floor. The lateral wall of the external valve consists of the fibrofatty nasal lobule and the lateral crus of the lower lateral cartilage (LLC).

The medial and inferior components of the internal valve are essentially the same, but the lateral wall is at the caudal end of the upper lateral cartilage (ULC) extending down over the head of the inferior turbinate. Because of the varying support in the lateral wall of both of the external nasal valves, dynamic collapse can occur on inspiration and this can result in collapse of the valve and complete nasal obstruction. In many patients, this occurs at night and is a serious contributing factor to sleep-disordered

A. S. Carney (✉)
College of Medicine and Public Health, Flinders University, Adelaide, Australia

Adelaide Sinus Centre, Adelaide, Australia

T. Woolford
Manchester Royal Infirmary, Manchester, UK

Edge Hill University, Ormskirk, UK

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breathing and obstructive sleep apnoea. Increasingly, iatrogenic damage to the nasal valves is seen following excessive resection of the ULC and LLC during rhinoplasty.

Nasal Valve Assessment

Narrowing of the nasal valve causing nasal obstruction is either static due to anatomical narrowing, dynamic caused by inspiration or a combination of the two. When examining a patient with nasal valve collapse, it is important to observe the behaviour of the nasal valves during normal inspiration. The collapse of the nasal valve with forced inspiration is common and should be treated with caution as an indication of the benefit of surgery. The use of a Thudicums speculum or probe of some kind to hold open the nasal valve is a valuable tool in assessing the nasal valves and correcting the degree of collapse. Almost all patients experience an improved airway if they perform the traditional Cottle's manoeuvre, and this is of little use in the assessment of the nasal valve.

Principles of Nasal Valve Management

If the collapse is simply occurring at night, the use of some form of nasal dilator can suffice and is often all that is required for patients who are struggling with CPAP compliance because of nasal valve collapse. Nasal dilators can be purchased at pharmacies and on the Internet and are a safe alternative to potentially complex nasal surgery.

Case selection with correct anatomical diagnosis is key if surgery is planned. With experience, it becomes apparent that there is a poor correlation between clinical findings and the severity of patient symptoms. Whilst many patients with nasal valve dysfunction benefit from appropriate surgery, the results can be rather unpredictable even in expert hands. There is no doubt that there are some patients who are extremely concerned with a minor degree of nasal valve collapse. It is important that the surgeon recognises this significant psychological overlay as these patients are often extremely difficult to treat, surgical outcomes disappointing and on occasion patients resort to litigation. The use of objective testing such as peak nasal flow and rhinomanometry may have a useful role in convincing such patients to refrain from surgery.

In managing nasal valve collapse, it is important to assess whether the problem is due to a minor degree of ptosis of the fibro-fatty tissue in the lateral wall, a narrow nasal mid-third or a lack of support in the caudal ULC or lateral crus of LLC.

There are a number of surgical techniques described to correct the static narrowing of the nasal valves or to improve dynamic collapse. Those techniques which have been widely adopted by surgeons in this field are outlined below.

Surgical Treatment of the External Nasal Valve

The Lateral Crural J-Flap

Minor degrees of fibro-fatty collapse can be addressed using a lateral crural J-flap [1]. This is essentially a procedure where a 'boomerang' area of internal nasal skin is excised and then the posterior part of the flap is dissected free from the fibrofatty tissue then advanced into the defect. This has an effect of "tightening the guy ropes" of the lateral nasal wall and tensioning the lateral part of the external valve. It is only really effective for minor degrees of collapse but can be easily performed at the same time as turbinate and septal surgery in patients with sleep-disordered breathing.

In cases with more significant external valve dysfunction, more complex procedure is required. The repositioning and grafting techniques described below are generally performed via an open rhinoplasty approach to facilitate the dissection required and precise placement and fixation of grafts.

Repositioning of the Lower Lateral Cartilages

The lateral nasal wall and external valve may be weak in cases where the LLCs have a cephalic orientation. Mobilisation and repositioning of the cartilages caudally can add support to the valve and reduce collapse. In order to secure the LLCs in the correct position, it is often necessary to use lateral crural strut grafts (Fig. 44.1) in addition as described in the next section [2].

Lateral Crural Strut Grafts and Alar Rim Grafts (Fig. 44.2)

In cases where the LLCs are weak causing collapse of the external valve, the cartilage can be strengthened using a lateral crural strut graft [3]. In most cases, this problem is caused by over resection if the LLC during rhinoplastic surgery. These grafts are ideally harvested from septal cartilage and are placed between the lateral crus and the underlying vestibular skin. To increase support, they can be extended to rest on the bony pyriform aperture.

Alar rim grafts are thin strips of cartilage positioned in a subcutaneous pocket at close to the alar margin. Although they have some functional benefit in strengthening the alar, their main benefit is aesthetic and if used alone this technique is rarely sufficient to correct significant weaknesses.

Surgical Treatment of the Internal Nasal Valve

Batten Grafts (Fig. 44.2)

In cases where an area of weakness is identified on the nasal sidewall in the region of the alar crease batten grafts may be used to reinforce this area [4]. The grafts area generally elliptical in shape harvested from the septum (or pinna in a cartilage-depleted patient). They are positioned over the point of maximum weakness, often at the junction of the ULC & LLC in the scroll region. In a similar fashion to lateral crural strut grafts, they can extend onto the bony pyriform aperture to increase support and stability. These grafts may be placed via an open or endonasal approach.

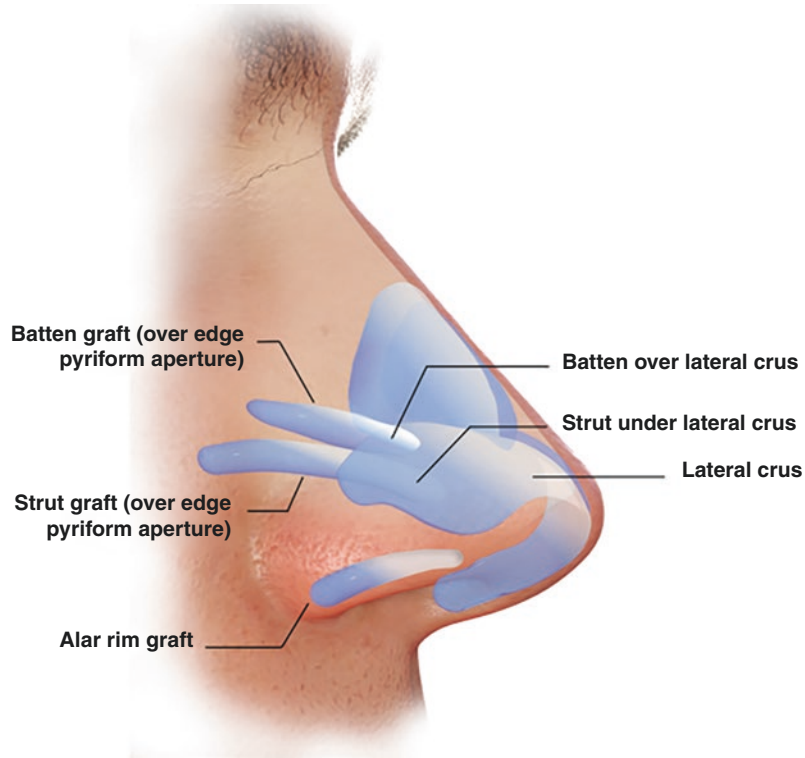

Fig. 44.1 Repositioning of the lower lateral cartilage from cephalic to caudal to increase support of the external nasal valve. The use of a lateral crural strut graft assists in the fixation of the cartilage to the correct position

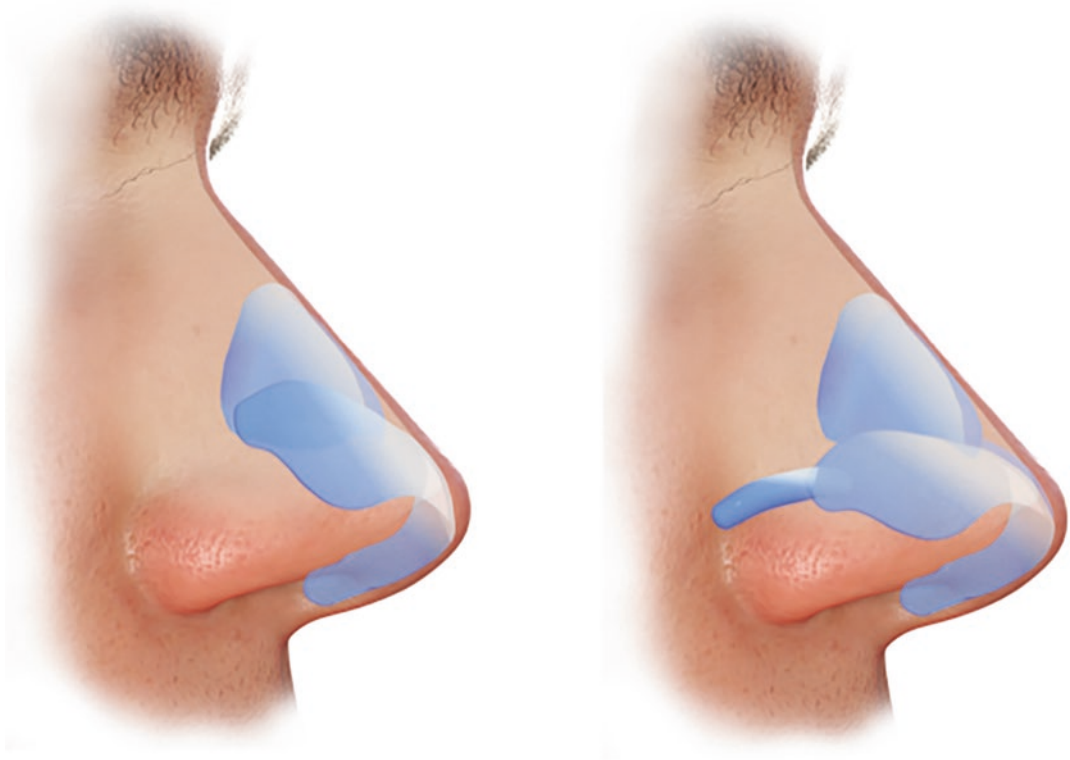

Fig. 44.2 The position of the lateral crural strut graft, the alar rim graft and the batten graft to correct weakness of the external and internal nasal valve

Spreader Grafts

Spreader grafts are thin strips of cartilage (Fig. 44.3) positioned between the septum and the ULCs to prevent or correct narrowing of the mid-third of the nose and the internal nasal valve [5]. Spreader grafts undoubtedly have an aesthetic effect on the mid-third of the nose, although their effect on nasal function is less clear. Although spreader grafts can certainly improve function by improving internal nasal valve function, it is notable that a number of patients who have a so-called 'inverted V' deformity following a rhinoplasty with a narrowed mid-third are concerned about the appearance of their nose with little in the way of functional concerns.

The grafts are ideally harvested from the septum, with pinna or rib cartilage used in cartilage-depleted patients. Spreader grafts can be inserted through an open or endonasal approach, with an

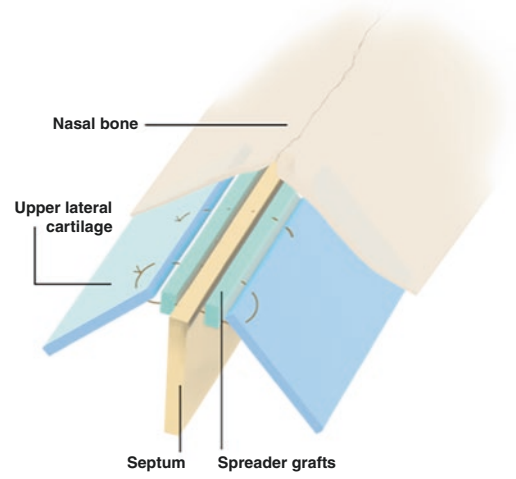

Fig. 44.3 Spreader grafts positioned between the septum and upper lateral cartilages to widen the internal nasal valve

open approach usually employed in revision functional cases allowing greater exposure, facilitating precise placement and fixation.

Auto-spreader grafts or spreader flaps [6] are a technique where the ULCs are folded medially to reconstruct the mid-third. This technique is generally employed to maintain aesthetic mid-third width following a dorsal hump reduction, rather than to improve nasal valve function.

Other Nasal Valve Surgical Techniques

Other techniques include suspension sutures to support the LLC or ULC [7] and flaring sutures to splay the ULC and open the internal nasal valve [8]. Where external valve collapse is due to marked concavity of LLC these can be excised and rotated to create convexity – a procedure which is technically demanding [9].

Butterfly cartilage grafts, generally from the pinna and bridging the ULC to widen the internal valve, have been described. The main issue with these grafts is that can result in an unaesthetic fullness of the supratip [10]. A modified Z-plasty technique has been described to open a narrowed internal valve to good effect [11].

The Inferior Nasal Turbinate

The inferior nasal turbinate is a separate nasal bone which attaches to the medial wall of the maxilla. It extends from the interior nasal valve to just anterior to the eustachian tube. The cancellous bone is covered by mucosa with an extensive submucosal complex of erectile tissue. The autonomic nervous supply to the inferior turbinate controls blood flow into the submucosa, increasing or decreasing its size and obstructive component. In severe inflammation, the mucosa swells and then eventually becomes polypoidal. In prolonged inflammation, the turbinate can then develop a ‘mulberry end’ on the posterior part which can obstruct the eustachian tube orifice or even the posterior choana of the nose. It is important to realise that the nasal cycle is a normal part of human physiology. This leads to alternate obstruction and patency of the nostrils which often occurs 2–3 times per day and is exacerbated in patients with rhinitis and other forms of inflammatory nasal pathology. After decongestion of the inferior turbinate, the appearance of the mucosa can exhibit a “cobblestone” appearance. This is a good sign of chronic nasal disease and if excessive, nasal vasculitis or recreational drug use needs to be considered in the differential diagnoses, especially if associated with crusting and dryness of the nasal mucosa.

Investigation of Inferior Turbinate Hyperplasia

The whole of the nasal cavity needs to be examined with a nasendoscope, ideally after decongestion of some kind. This allows the surgeon to examine not only the head and body of the inferior turbinate but also the frequently neglected tail and its relationship to the eustachian tube and posterior choana. Any associated septal or sinus pathology can also be identified. Adenoidal hyperplasia also needs to be ruled out by nasendoscopy as this can occasionally be the source of nasal obstruction, even in adults, which presents under the guise of an inferior turbinate problem. The degree to which the turbinate responds to decongestion is also important. This gives the surgeon some idea of the anatomical areas of the turbinate which are contributing to the obstructive pathology.

Whilst peak nasal flow and rhinomanometry are not commonly used, they are useful adjuncts to clinical examination and play an important role in complex medicolegal assessments and in patients where the surgeon is concerned about possible psychological factors which are exaggerating the patient’s perception of their nasal obstruction.

Management of Inferior Turbinate Hyperplasia

Medical management remains the mainstay of an enlarged inferior turbinate [12]. Topical nasal steroids are a safe intervention which is well tolerated in most patients and have no long-term

adverse advents if the patient is advised on the potential complications of dryness and epistaxis. It is important to use second- or third-generation nasal steroids to minimise the potential risk of any systemic absorption and to reassure the patients regarding their long-term safety. The use of large-volume saline irrigation devices to act as a delivery vehicle for nasal steroids is increasingly common and has been demonstrated to be superior to simple nasal sprays [12]. Budesonide, Fluticasone and Mometasone are frequently used in large-volume devices but may need to be compounded into a gel or concentrated solution, depending on commercial availability in various jurisdictions. It is important to remember that Budesonide does carry a much higher systemic absorption rate and there have been reports of patient's diabetic and glaucoma control being affected by Budesonide irrigation although none, to our knowledge, from Fluticasone or Mometasone irrigations.

Surgical Management of the Inferior Turbinate

There are a large number of procedures that have been described for the management of the inferior turbinate. The increasing use of in-office procedures, especially in the USA, has driven this to a certain degree. Whilst in-office procedures have their attraction, it is important to remember that convenience is not a replacement for efficacy and the patient may get an inferior result for having an office procedure which was simply not as aggressive as one which could be performed in the operating room. Turbinate procedures can largely be divided into a number of categories (Fig. 44.4):

1. *Surface cautery/diathermy/laser/ plasma* (Fig. 44.4a). These are largely historical procedures as it is now well recognised that damage to the medial mucosa of the inferior turbinate causes permanent loss of cilia, increased crusting, lack of proprioception and only short-term benefits with regard to nasal obstruction. These procedures should be avoided in the current surgical climate and would not be regarded as gold-standard practice.
2. *Submucosal channelling* (Fig. 44.4b). A variety of devices with a sharp point on the end can be inserted into the head of the inferior turbinate and passed through the submucosa to the posterior part of the structure. Using monopolar diathermy, radiofrequency or plasma, these can shrink or even remove columns of tissue within the submucosa which then produce scar tissue which limits the ability for regrowth to some degree. Trials looking at inferior turbinate channelling have produced variable results but meta-analyses have essentially shown that the more radical the technique the greater the effect size but the length of treatment benefit remains relatively short and few studies have shown benefit that extends more than 2 years.
3. *Aggressive submucosal soft tissue removal* (Fig. 44.4c). These larger devices generally involve an incision in the head of the inferior turbinate and then the introduction of a larger device which can physically remove more of the submucosa and erectile tissue. Both powered microdebriders and the coblation 'turbinator' fit in this category. Randomised trials have shown that these more aggressive techniques have a better effect size than simple channelling and provide longer relief but still not as good a long-term benefit as procedures where bone is removed.
4. *Partial or total turbinate reduction* (Fig. 44.4d). Whilst these have largely been the mainstay of turbinate treatment from a historical perspective, they are being performed less frequently owing to the increased availability of technology which allows more preservation of the anterior part of the inferior turbinate with its very important proprioceptive structures. Despite this trend, a partial turbinectomy is still an extremely effective procedure in patients who have got an isolated problem at the internal nasal valve. A total turbinate resection is probably less frequently performed due to the risks of nasal crusting

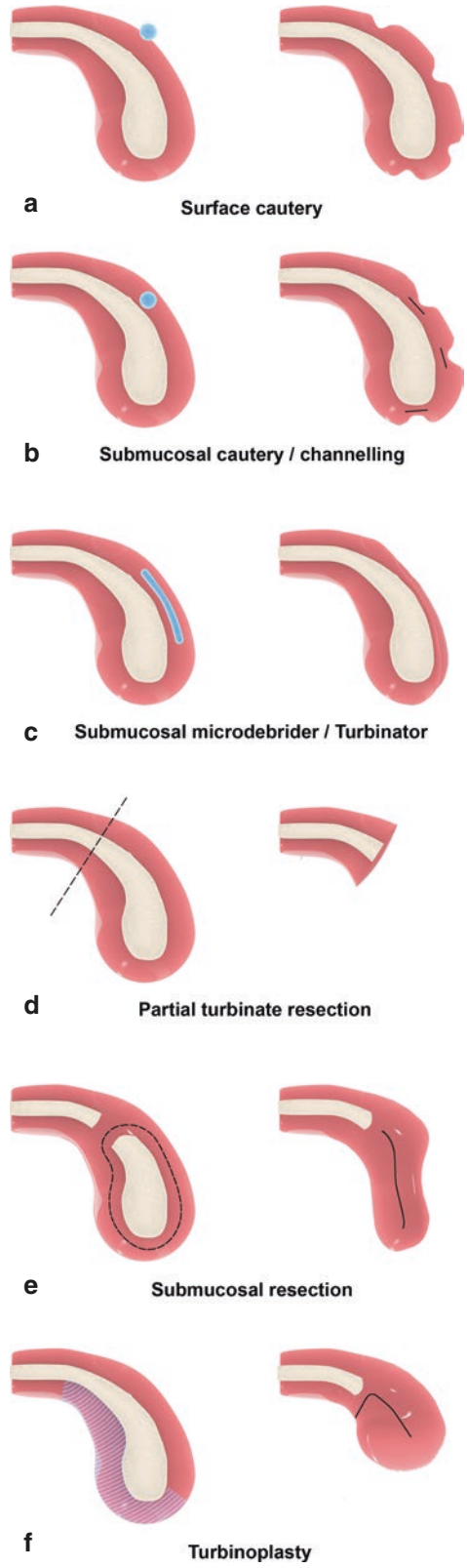

Fig. 44.4 Options for surgery of the inferior turbinate: (**a**) surface reduction, (**b**) submucosal channelling, (**c**) submucosal soft tissue resection, (**d**) partial turbinectomy, (**e**) submucosal bony resection, (**f**) turbinoplasty

and 'empty nose syndrome' in the current medicolegal environment.

5. *Submucosal bony resection* (Fig. 44.4e). An incision is placed on the head of the inferior turbinate, the soft tissue is separated from the interior turbinate bone using an elevator of some sort then the bone is removed through the anterior incision. A variable proportion of submucosal tissue can also be removed at the same time. This has been established as an extremely effective inferior turbinate surgical technique. The disadvantages are the blind nature of the procedure and inability to control haemostasis in the submucosal space.
6. *Inferior turbinoplasty* (Fig. 44.4f). The inferior turbinoplasty was first described by Dr. Richard Mabry in the 1980s [13] and has been modified over the years, most recently by Professor Raymond Sacks in Sydney [14]. Using a microdebrider (or more recently a coblation device), the mucosa on the lateral surface of the inferior turbinate is removed along with a variable proportion of soft tissue on the inferior and lower medial aspects. The inferior turbinate bone is then visible and can be fractured and completely removed exposing the inferior turbinate vessels at the posterior end. These can then be managed with bipolar diathermy as the inferior turbinate bone is removed. A 'mulberry' posterior end can also be managed extremely effectively by this technique. Once haemostasis is obtained, the bone-free mucosal flap can be turned inwards on itself. Whilst many surgeons use some form of haemostatic agent (PuraStat, Surgicel, etc.) to hold the flap in place, if there is a couple of drops of blood, these often are enough to hold the flap in place using surface tension without the use of agents which can require more debridement in the postoperative period.

Randomised controlled trials have continued to show that powered inferior turbinoplasty provides benefits as long as 10 years post-operatively [15]. The disadvantages are the need for a disposable instrument, a longer operative time and a documented increased risk of post-operative epistaxis although this can be minimised to a certain degree with meticulous surgical technique.

Key Learning Points

- Clinical examination can distinguish between nasal valve and/or inferior turbinate obstruction.
- Nasal valve dysfunction can be static, dynamic or a combination of the two.
- Correct anatomical diagnosis is key to planning nasal valve surgery.
- The most widely adopted procedures for significant valve dysfunction involve cartilage grafting to strengthen or widen the external or internal valve.
- Even in experienced hands, the results of nasal valve surgery can be unpredictable, and patient selection is key.
- The mainstay of management for inferior turbinate hyperplasia is medical therapy.
- There is a huge spectrum of interior turbinate surgical therapies available from simple in-office procedures to more lengthy procedures requiring an operating theatre.
- In general, more aggressive and complex turbinate surgery has a higher risk of epistaxis but a better and more sustainable clinical result.

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Nasal Septal Perforation

45

Alfonso Santamaría-Gadea, Juan Carlos Ceballos, Cristobal Langdon, and Isam Alobid

Introduction

Nasal septal perforation (NSP) is described as a full-thickness defect of the three septal layers (mucosa, osteocartilaginous plate and mucosa), which originates a communication between both nasal fossae. The NSP prevalence is estimated in between 1 and 2% in the general population [1, 2].

Although most septal perforations are asymptomatic or cause mild symptoms, some can originate bothersome symptoms such as crusting, nasal obstruction, epistaxis, inspiration whistling or nasal discharge. These symptoms are due to the disturbance of the airflow through the nose and the disruption of normal nasal physiology. These clinical manifestations are especially common in large or anteriorly located NSPs [3].

A. Santamaría-Gadea
Department of Otorhinolaryngology, Rhinology and Skull Base Surgery Unit, Ramón y Cajal University Hospital, Madrid, Spain

J. C. Ceballos · C. Langdon
Department of Otorhinolaryngology, Rhinology and Skull Base Unit, Hospital Clinic, Universitat de Barcelona, Barcelona, Spain

I. Alobid (✉)
Department of Otorhinolaryngology, Rhinology and Skull Base Unit, Hospital Clinic, Universitat de Barcelona, Barcelona, Spain

Centro Médico Teknon, Barcelona, Spain

Pathology

Aetiology: There are multiple causes of septal perforation described in the literature; however, the incidence of each cause is not clear, with only retrospective case series supporting the data in most cases. Furthermore, in most cases, the cause is unknown or idiopathic.

The most commonly known causes for NSPs are previous sinonasal surgery, especially to the nasal septum (iatrogenic), intranasal drug abuse or facial/nasal trauma. The incidence varies by region and country depending on cocaine consumption, street violence and other factors.

Cocaine-related perforations tend to have severe septal destruction with skin, nasal or palatal necrosis, due to the rapidly destructive process of a drug-induced vasculitis (see Chap. 45). Moreover, NSPs can arise from occupational exposure to chemical agents, or they can even be the first manifestation of a systemic disease, such as inflammatory diseases (granulomatosis with polyangiitis (GPA), sarcoidosis, systemic lupus erythematosus), septal infections or neoplasms. It is, therefore, important to exclude systemic diseases in all patients with a NSP [4, 5].

Digital trauma from nose picking is common and may set up perichondritis and loss of blood flow to the septal cartilage. However, other common causes of perforation should be considered before attributing nose picking as the true cause. Inevitably, the ensuing crust formation will

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encourage patients to clear this with their fingers. The association between nose picking and septal perforation is based on the reported case series, but the evidence base for nose picking is weak [6].

Similarly, perforations have been attributed to intranasal corticosteroid sprays, but again there is no supporting evidence. Septal perforation can be iatrogenic, traumatic, inflammatory, neoplastic, infectious or inhaled irritants. A comprehensive list of causes of septal perforation is shown in Table 45.1.

Table 45.1 Nasal septal perforation etiologies [4]

Idiopathic	
Traumatic/iatrogenic	Septal surgery Nasal fracture Self-inflicted/digital trauma Foreign body (button batteries in children) Chemical cautery Nasal packing Nasal intubation Nasogastric probe
Topical nasal medication and drug abuse	Cocaine (frequent) Vasoconstrictive nasal spray (rare) Intranasal steroids (very rare)
Systemic drug	Bevacizumab
Occupational exposure	Chemical irritants Physical irritants Heavy metal
Inflammatory	Granulomatosis with polyangiitis Eosinophilic granulomatosis with polyangiitis Systemic lupus erythematosus Rheumatoid arthritis Crohn's disease Dermatomyositis Sarcoidosis
Infectious	Septal abscess Syphilis HIV Invasive fungal infections Leprosy Tuberculosis
Neoplasms	Non-Hodgkin lymphoma Squamous cell carcinoma Adenoid cystic carcinoma Basal cell carcinoma Esthesioneuroblastoma Rhabdomyosarcoma

Pathogenesis

Necrosis and perforation of the septal quadrangular cartilage will occur if the cartilaginous blood flow is disrupted by the loss of integrity of the covering mucoperichondrium.

Clinical Features and Diagnosis

The assessment of a patient with a septal perforation requires a detailed medical history, a meticulous physical examination and sometimes additional investigations.

Medical History

It is important to address every patient's condition in a thorough manner; knowledge of the aetiology is key to deciding the specific treatment, timing and prognosis. Sinonasal or systemic symptoms, medication use, history of drug abuse, smoking and work environment history must be investigated in every patient.

Clinical Examination

Firstly, the external nose is assessed and external nasal support is considered. A saddle deformity changes the magnitude of the approach. In this situation, open rhinoplasty with a costal cartilage graft is likely to be necessary, should the patient request esthetic change.

Assessment of the remaining osteocartilaginous support is supplemented by nasal endoscopy. Endoscopy also facilitates assessment of the perforation size (as measured with a plastic disposable ruler in-office) and location. The health and integrity of the nasal mucosal lining and inferior turbinate status are considered within the assessment process. This helps the surgeon to judge the best surgical technique and predict the likely surgical outcome.

Clinical Assessment

Symptoms are determined by the location, perforation size and mucosal health in patients with septal perforation. Large and anterior perforations are associated with greater symptoms. There is no established accepted classification, but most series define large perforations as being greater than 2 cm in diameter [5].

Whilst patient-related outcome measures (PROMS) are established and validated in sinonasal disorders, a specific validated questionnaire for septal perforation has not been described in the literature. However, the Sino-Nasal Outcome Test-22 (SNOT-22) and/or Nasal Obstruction Symptom Evaluation (NOSE) are reasonable means of assessing the effects on quality of life and of any intervention.

Investigation

Each patient is managed on an individual basis and investigations are requested to confirm or exclude specific diagnoses. Basic preoperative investigations are arranged in patients due to undergo surgery, but these are supplemented by further diagnostic tests when the aetiology is in doubt. These investigations may include blood tests, urinary drug detection test, imaging and biopsy.

Blood Tests

Full blood count, biochemical profile, renal function, erythrocyte sedimentation rate and autoimmune markers such as antinuclear antibodies and anti-neutrophil cytoplasmic antibodies (ANCA). Anti-elastase antibodies should be considered if there is a high suspicion of cocaine abuse.

Should an autoimmune condition be suspected, a specialist opinion from a rheumatologist/autoimmune physician should be sought.

Urinary Drug Detection Test

Cocaine abuse is prevalent amongst this group of patients, and cocaine metabolites may be detected in urine or hair. Such analysis is strongly recommended if surgery is contemplated.

Imaging

Chest radiograph is done during the preoperative workup. However, a computed tomography (CT) of the septum and sinuses will display key features of a NSP (osteocartilaginous support, size and exact location) prior to surgery. The CT scan will also demonstrate the relationship between the vascular structures, the NSP and assist with plans for different endonasal flaps.

Biopsy

A mucosal biopsy adjacent to the edges of the NSP should be considered either to exclude malignant pathology or to assist with the diagnosis when the aetiology is uncertain. Ideally, a substantial biopsy of mucosa that looks abnormal should be sampled to aid with diagnostic accuracy. In our centre, we normally biopsy every patient preoperatively to exclude other pathologies before surgery.

Clinical Management

Most patients are asymptomatic or have mild symptoms. The clinical priority is to identify any underlying disorder, to try to prevent enlargement of the perforation and to limit future symptoms.

Medical Treatment

Septal perforations may cause several symptoms such as crusting, nasal obstruction, epistaxis, inspiration whistling or nasal discharge [3].

Saline nasal douches and nasal ointments are helpful in diminishing the local symptoms in patients with mild symptoms or for those awaiting surgical repair. Anxiety and depression, or drug abuse, should be addressed and managed appropriately prior to surgical intervention.

Comprehensive investigation is recommended in many symptomatic patients to identify or exclude systemic disease as the cause of the perforation. Understanding the aetiological cause of the perforation is important before considering the surgical repair, the approach and the technique.

An underlying systemic disease should be controlled and treated prior to further intervention for a septal perforation.

Septal Obturators

Closure of the perforation by a silastic septal obturator is an old concept that was not always very effective. Obturators can induce crust formation or become displaced, or increase sinonasal symptoms and even enlarge the septal perforation. They may, however, be useful in patients who cannot undergo surgery, or patients with chronic uncontrolled causes (e.g. systemic inflammatory diseases).

New innovations have improved matters and include a magnetic/silastic septal button with a strong magnet to hold the flanges together (Blom Singer™). These devices are circular or oval and come in a variety of sizes to facilitate a more precise fit. Another alternative is a custom-made button that is made to measure the actual individual perforation. This requires a CT scan to enable the perforation to be demonstrated accurately by the prosthetist. They are effective and helpful in moderately large perforations.

An obturator can often be inserted into small to medium perforations in the outpatient clinic, but a general anaesthetic is necessary for larger perforations. Once in situ, they generally require periodic replacement at infrequent intervals.

The decision between inserting a septal obturator and septal repair is determined by several factors, including patient choice, access to theatre facilities and operating time. In the authors' practice, septal obturators' have largely been superseded by new endoscopic techniques.

Surgery

Indications

Surgery is indicated when conservative treatment fails or symptoms, such as nasal obstruction, crusting, nasal bleeding and facial pain, become severe [4].

There is no standard technique for NSPs endoscopic repair. Different endoscopic techniques are indicated according to the remaining osteocartilaginous support, location and size of the NSP.

Some therapeutic algorithms, based on the characteristics of the perforation, have been described, but there is no accepted gold standard protocol. An in-depth knowledge of the described techniques allows the use of the most suitable technique in each case [1].

Should the NSP be accompanied by septal deviation, septoplasty can be combined with NSP surgical repair to optimise the anticipated improvement of symptoms. Should the perforation be associated with an aesthetic deformity, such as a saddle nose, an open rhinoplasty with a cartilage graft may be necessary.

Surgical Techniques

Mucosal Advancement Flaps (Fig. 45.1)

Description

Unilateral or bilateral advancement flaps can be raised. The mucosal flaps can be 'superior', based on the anterior ethmoidal artery (AEA) branches or 'inferior', supplied by septal branches of the posterior nasal artery and greater palatine artery.

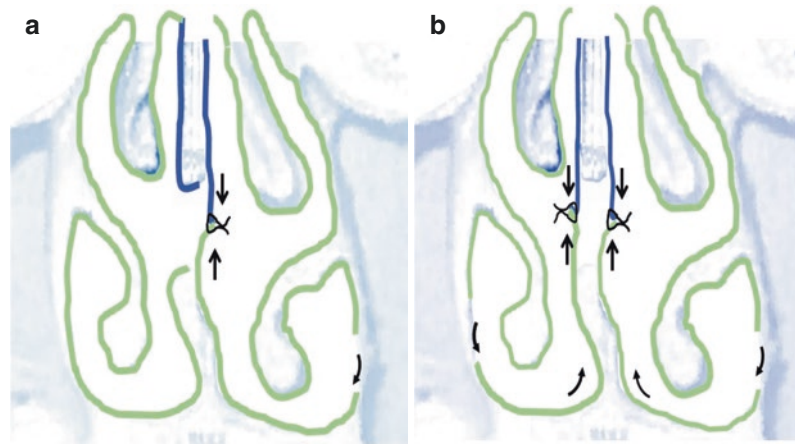

Fig. 45.1 (**a**) Unilateral mucosal advancement flap. (**b**) Bilateral mucosal advancement flap

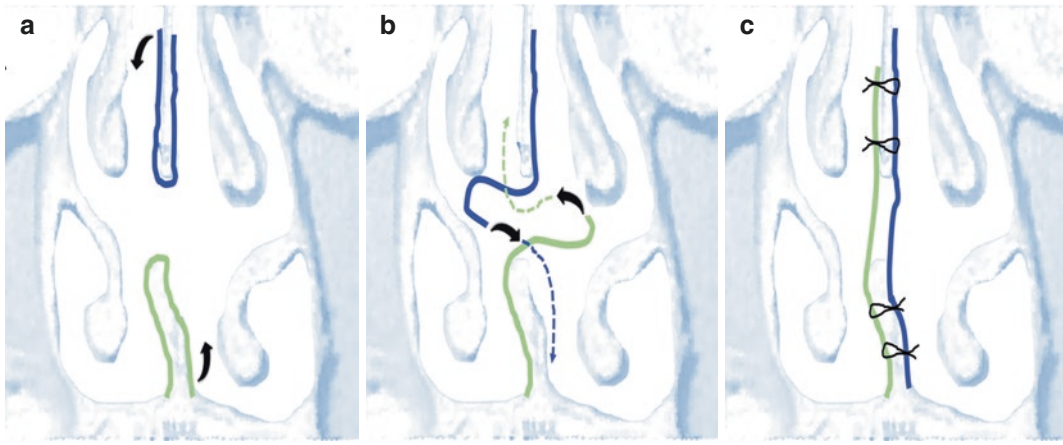

Fig. 45.2 (**a–c**) Bilateral crossover flap

Indications

This flap indicated an anterior small < 2 cm septal perforations, especially in long but not high in diameter.

Surgical Technique [6, 7]

- The NSP edges are initially trimmed to obtain fresh margins.
- A hemitransfixation incision is made along the caudal edge of the quadrangular cartilage.
- Septal mucosa is raised on both sides of the septum creating superior and inferior tunnels, surrounding the NPS, extending to the nasal roof and inferior meatus.
- The superior and inferior flaps are advanced to close the NSP. The flaps are sutured without tension using absorbable sutures.
- An interposition graft (cartilage, temporal fascia, etc.) may be placed between both flaps to avoid opposing suture lines and improve the likelihood of successful closure.

Cross-Over Flaps (Fig. 45.2)

Description

A cross-over flap consists of contralateral mucosal flaps that include a superior flap on one side of the septum and an inferior flap on the contralateral side.

Indications

The technique is suitable for small anterior perforations but contraindicated in NSP > 2 cm diameter, especially when osteocartilaginous support is missing.

Surgical Technique

In contrast to the other techniques, the edges of the perforation should not be excised or refreshed [8]:

- A quadrangular or circular flap is elevated on one side of the nose superior to the upper margin of the NSP. A similar mucosal flap is elevated inferior to the lower edge of the perforation on the contralateral side.
- Each flap is passed through the perforation to the contralateral side of the septum. The defect is closed by attaching the flaps to the septum by absorbable sutures.

Bilateral Hadad Flap

Description

This technique large nasoseptal flaps from both sides of the nasal septum, as described by Hadad et al. [9]. The mucosal flaps are sutured over an autologous fascial graft. Both flaps are supplied by the posterior septal branch of sphenopalatine artery.

Indications

Indicated in 2–3 cm NSP.

Surgical Technique [10]

- A hemi-superior nasoseptal flap is performed on one side above the NSP from the choana to the middle point of the posterior border of the NSP.
- On the other side, a hemi-inferior nasoseptal flap is harvested from the choana to the midpoint of the posterior border of the NSP including the nasal floor and inferior meatus mucosa and reaching the nasal vestibule.
- The superior flap is rotated downwards and in the contralateral side, the inferior flap is rotated to upwards cover the NSP. An interposition graft of fascia is positioned between both flaps. Both flaps are fixed with absorbable sutures.

Anterior Ethmoidal Artery (AEA) Flap

Description

The anterior ethmoidal artery (AEA) flap is a mucosal flap, initially described by Castelnuovo et al. in 2011 [11]. It has become one of the most widespread endoscopic techniques.

The vascularised mucosal flap is unilateral and based on the septal branches of the anterior ethmoidal artery (AEA).

Indications

This mucosal flap is indicated in NSPs up to *2.5 cm anteroposterior diameter in anterior placed perforations. As this flap can be extended way lateral up to the inferior meatus having finally part of the flap out of the nostril when completely dissected and rotated.*

It is however contraindicated in NSPs without osteocartilaginous support.

Surgical Technique [11, 12]

- The anterior incision starts vertically in the septal projection of the middle turbinate axilla. It is extended inferiorly along the posterior edge of the NSP to the anterior limit of the inferior meatus.
- The posterior incision originates at the level of the septal projection of the superior turbinate and descends vertically along the septum to reach the posterior limit of the inferior meatus. A lateral incision connects both incisions along the lateral margin of the inferior meatus (Fig. 45.3a.).
- The edges of the NSP are refreshed. Then, the unilateral flap is raised and rotated anterosuperiorly to cover the entire NSP. The flap is anchored to the remnant septal mucosa with absorbable sutures. Usually, one superior and one anterior stitches are enough; in cases of larger NSP, supplementary stitches could be necessary (Fig. 45.3b).

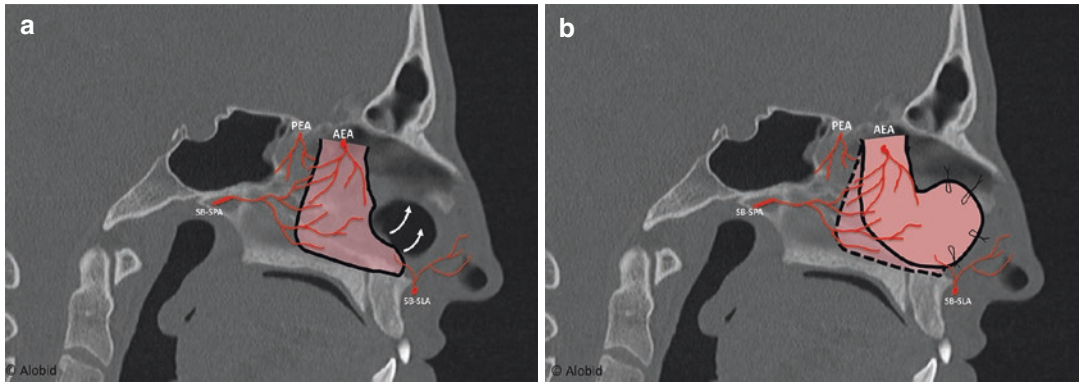

Fig. 45.3 (**a**) Anterior ethmoidal artery flap. *PEA* posterior ethmoidal artery, *AEA* anterior ethmoidal artery, *SB-SPA* septal branch of the sphenopalatine artery, *SB-SLA* septal branch of the superior labial artery. (**b**) *PEA* posterior ethmoidal artery, *AEA* anterior ethmoidal artery, *SB-SPA* septal branch of the sphenopalatine artery, *SB-SLA* septal branch of the superior labial artery

Greater Palatine Artery (GPA) Flap

Description

A unilateral rotation mucosal flap is based on the greater palatine artery (GPA). This flap includes the mucosa from the septum, nasal floor and inferior meatus.

Indications

This technique is specially indicated in very anterior septal perforations (NSP). The perforation must be located anterior to the incisive canal. There is no contraindication related to the size of the perforation.

A pre-operative CT scan may be helpful to locate the incisive canal during surgery.

Surgical Technique [13, 14]

- The greater palatine artery (GPA) should be identified at the beginning of surgery to avoid damage to the pedicle.
- The posterior incision is made vertically from an area at the back of the nasal septum to the posterior aspect of the inferior meatus.
- The anterior incision is performed from the posterior edge of the NSP to the anterior aspect of the inferior meatus, including the incisive canal.
- The inferior incision connects the anterior and posterior incisions in the lateral aspect of the inferior meatus.
- The superior incision connects the anterior and posterior incisions in the roof of the nasal fossa, 1 cm inferior to the olfactory sulcus.
- Once all incisions are made, the flap is raised and rotated anteriorly to cover the entire NSP. The flap is fixed with absorbable sutures in the anterior and superior edge of the NSP.

Middle Turbinate Flap (Fig. 45.4)

Description

The middle turbinate flap is a unilateral, posterior pedicled flap of the middle turbinate mucosa.

Indications

It is indicated in nasal septal perforations (NSPs) of the middle or superior part of the nose.

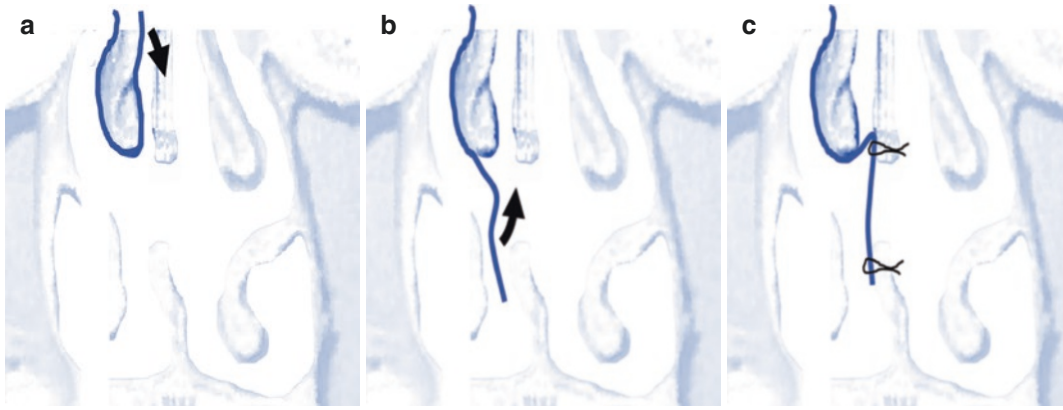

Fig. 45.4 (**a–c**) Middle turbinate flap

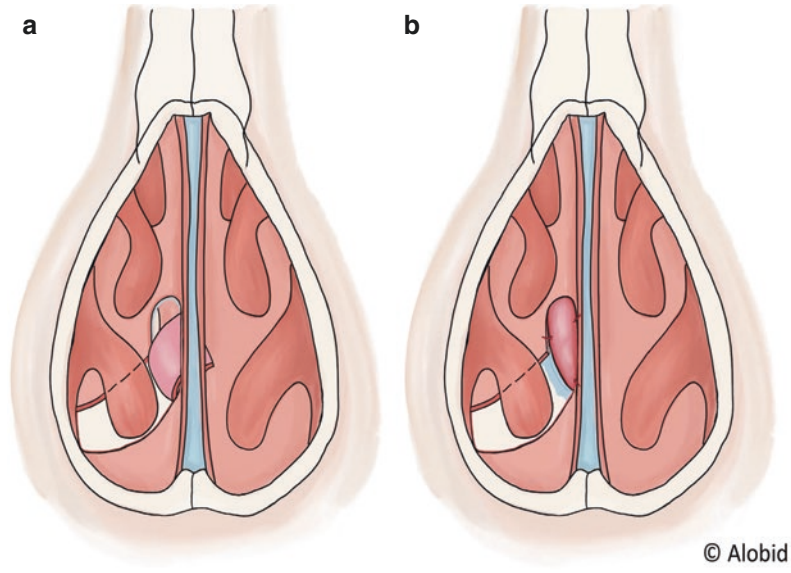

Fig. 45.5 Nasal floor and inferior meatus flap. (**a**) Flap design and elevation. (**b**) The flap is passed through the perforation to the contralateral nasal cavity

In contrast to other techniques, it is not contraindicated if osteocartilaginous support is missing.

Surgical Technique [15]

- Initially, the middle turbinate is out fractured to improve turbinate mobility and to facilitate dissection.
- A vertical incision is made from the head to the axilla of the middle turbinate.
- The medial surface of the middle turbinate mucosa is dissected, exposing the underlying bone.
- The loose turbinate mucosa is rotated to cover the entire perforation (NSP).
- The periosteal surface of the flap should face the contralateral nasal cavity.
- The flap is sutured with absorbable stitches to the septal mucosa that remains around the perforation.

Nasal Floor and Inferior Meatus Flap (Fig. 45.5)

Description

A unilateral flap based on the mucosa of the nasal floor and inferior meatus. Where the perforation is large, the flap can be extended to include the inferior turbinate mucosa.

Indications

This endonasal flap is generally indicated in medium-sized NSPs located in the lower or middle area of the nasal septum. Minimal osteocartilaginous support is required.

The lower edge of the NSP should not be excised or refreshed.

Surgical Technique [16, 17, 18]

- This flap utilises mucosa from the nasal floor and inferior meatus.
- Anterior and posterior incisions are required: Two parallel incisions are made in the coronal plane on the floor of the nose. One incision passes antero-laterally and the other postero-laterally in the inferior meatus.
- A lateral incision passing along the lateral limit of the inferior meatus connects the anterior and posterior incision.
- Once all incisions are complete, the mucosa is elevated. The flap should extend to within 5 mm, of the inferior edge of the septal perforation in the anterior and posterior plain (NSP).
- The flap is passed through the perforation to the contralateral nasal cavity.
- Absorbable sutures are used to fix the flap to the remaining mucosa of the nasal septum. A minimum of two sutures are recommended, one superior and one anterior.

The Extended Flap

- In large septal perforations (NSPs), an extended flap is recommended. The anterior and posterior incisions should be extended, and a lateral incision is made in the superior edge of the inferior turbinate.
- The naso-lacrimal duct must be divided to utilise this flap.

Lateral Nasal Wall Flap (Fig. 45.6.)

Description

A unilateral mucosal flap of the lateral nasal wall includes nasal floor, inferior meatus, inferior turbinate and maxillary process mucosa. This flap has two pedicles, an anterior pedicle based on the anterior ethmoidal artery and a posterior pedicle perfused by the sphenopalatine artery.

Indications

This technique is indicated in large septal perforations (NSPs), even those >2 cm in diameter. The flap has the disadvantage of requiring a second operation to divide the pedicle.

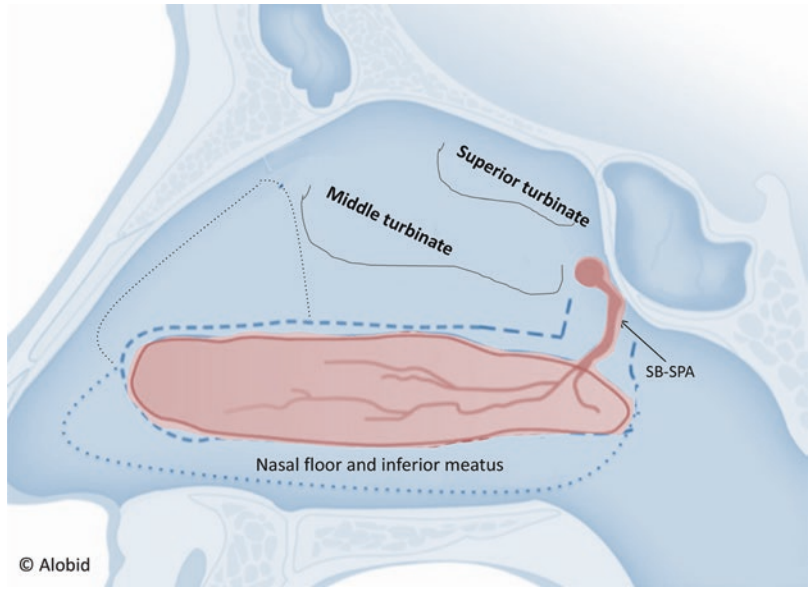

Fig. 45.6 Lateral nasal wall flap *SB-SPA* posterior septal branch of the sphenopalatine artery

However, it does have an advantage of not requiring osteocartilaginous support.

Surgical Technique [19]

- The anterior incision commences from the maxillary ostium and passes anteriorly and superiorly along the lateral nasal wall overlying the ascending process of the maxilla. The incision continues inferiorly towards the head of the inferior turbinate.
- The inferior incision passes from the posterior area of the palatine bone, descending behind the posterior edge of the inferior turbinate, before extending to the posterior part of the nasal septum.
- The incision then continues anteriorly along the junction between the septum and the nasal floor, until it reaches a point level with the start of the anterior incision.
- Once all incisions are made, the flap is dissected from anterior to posterior, based on the posterior pedicle carrying the sphenopalatine artery.
- The nasolacrimal duct is divided, and the conchal bone of the inferior turbinate is removed.
- The flap is raised and rotated to cover the entire septal perforation (NSP). The flap is sutured with an absorbable stitch to the anterior remnant septal mucosa.

- *The second procedure*

  – The posterior pedicle is divided after a period of 3 months from the initial surgery. The posterior part of the flap is also sutured to the posterior margin of the NSP.

Modification for large anterior perforations

  – In large anterior perforations (NSP), an anterior pedicled nasal wall flap is recommended. The mucosa of the ascending process of the maxilla is preserved, protecting the branches of the anterior ethmoidal artery. In contrast to the posterior pedicle flap, the sphenopalatine artery should be cauterised, and the anterior and posterior incisions are joined over the palatine bone.
  – The anterior pedicle will need division 3 months after the initial surgery.

Pericranial Flap

Description

This is a unique technique that utilises a vascularised pericranial flap from the forehead and anterior skull. The flap is introduced into the nasal cavity through a frontal sinus osteotomy and frontal sinuplasty (Draf Type III).

Indications

The pericranial flap is indicated in the repair of a total/subtotal septal perforation but it is associated with a greater comorbidity.

Surgical Technique (Fig. 45.7) [20–22]

- The nasal cavity is cleaned and prepared for the introduction of the flap.
- The remnant septal mucosa is elevated on both sides so that the pericranial flap can be placed between both layers.
- The sphenoid rostrum is dissected and exposed to create a posterior anchor for the flap.
- A complete Draf III midline sinusotomy is performed to create a corridor for the flap as it passes through the frontal sinus into the nasal cavity.
- A classic pericranial flap is harvested via a coronal incision that extends from the upper limit of the pinna to the other side. Superficial layers of the scalp (skin, subcutaneous tissue and aponeurotic galea) are raised anteriorly.

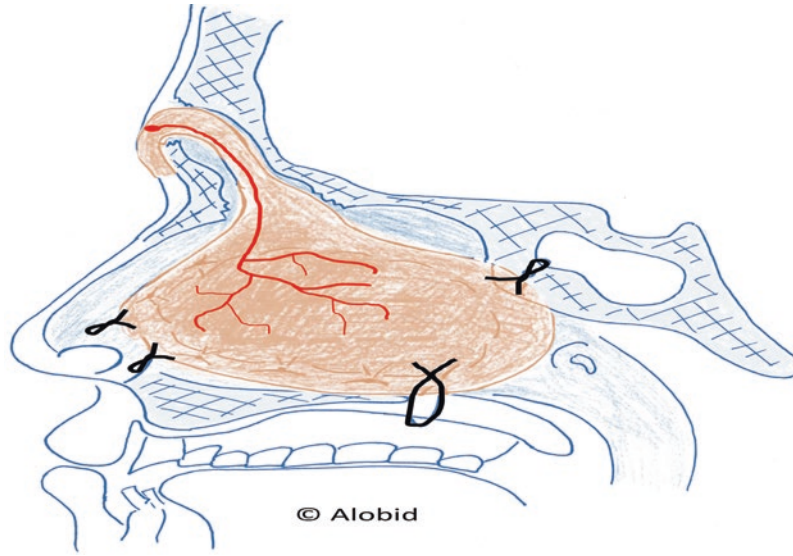

Fig. 45.7 Pericranial flap

- The pericranial flap is preserved 1 cm above the orbital rim to prevent injury to the vascular pedicle.
- The pericranial flap is incised laterally at the level of the temporal lines, and posteriorly at the level of the vertical projection of the posterior wall of the external auditory canal on the skull. Then, the flap is raised from the skull.
- The limits of the frontal sinus are located and marked by using endonasal transillumination.
- Access into superior area of the frontal sinus is gained through an osteotomy. The pericranial flap is passed through the osteotomy into the frontal sinus with the aid of an endoscope.
- Once the pericranial flap is in the nasal cavity, the posterior edge is fixed either to the sphenoid rostrum of the posterior edge of the NSP if an edge is present.
- The pericranial flap is fixed anteriorly to the columella or the anterior edge of the perforation.
- Inferior fixation may be achieved by a trans palatal suture if considered necessary. Absorbable sutures are used in all fixation areas.

Areas of Controversy

Investigation

There continues to be a range of opinions with regard to the need for investigation. This is likely to be due to many factors, such as the country, region, local facilities, patient cohort, access to operating theatres and healthcare economy.

There is also controversy over the requirement for a biopsy and how useful this is in determining the diagnosis and patient outcome.

The Indication for Surgery

There is still no objective parameter that defines whether a patient will benefit from surgical closure, how much they will benefit, or which technique is most suitable.

Nowadays, surgical experience and the patients' symptom complex and disability determine the management decision and case for surgery. However, there are sometimes significantly high failures, particularly should the surgeon be inexperienced or if there is poor patient selection.

Some surgical techniques are highly versatile (AEA flap) but are accompanied by a slow but clear learning curve. However, once mastered, the success rate is high.

Key Learning Points

1. A nasal septal perforation (NSP) is a full-thickness defect between both nasal cavities, due to the loss of the three septal layers (mucosa, osteocartilaginous plate and mucosa).
2. The main known causes include idiopathic previous nasal surgery, nasal trauma or intranasal drug abuse.
3. Most of the patients with NSPs remain asymptomatic or suffer mild symptoms and can be treated conservatively.
4. Obliteration with a septal obturator can alleviate symptoms in some patients.
5. Surgery should be offered to patients with persistent troublesome symptoms (nasal obstruction, crusting, nasal leading or facial pain).
6. There are several techniques of surgical repair, all based on the use of vascularised flaps.
7. The endoscope provides an excellent means of raising pedicled vascular mucosal flaps with precision.
8. There is no standard technique of repair.
9. The most appropriate surgical technique is chosen according to the characteristics of the perforation, such as the osteocartilaginous support, location and size.
10. The mucosal flap based on the AEA is the most often used endoscopic technique due to its versatility and that often facilitates the repair of perforations up to 2.5 cm in diameter.
11. The novel greater palatine artery (GPA) flap is recommended for very anterior septal perforations (NSPs).
12. The nasal floor and inferior meatus mucosal flap is especially recommended for inferior septal perforations.
13. The lateral nasal wall flap is advisable for large septal perforations (NSPs), especially where osteocartilaginous support is missing.
14. In complex cases of total or near-total perforations, the only available reconstructive option is the pericranial flap.

Compliance with Ethics Guidelines

Conflict of Interest: The authors declare no conflicts of interest relevant to this manuscript.

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46 Granulomatous Disease, Vasculitides and the Cocaine Nose

Andrew C. Swift and Peter Andrews

Introduction

Granulomatous disease and vasculitides are uncommon chronic inflammatory conditions that can specifically affect the nose and sinuses. Their clinical features may not initially suggest a definitive diagnosis, and this can result in diagnostic delay, especially when they present to colleagues who may not have a specialist interest in the nose.

Whilst these conditions have been recognised for many years, it is likely that there has been a significant change in the likelihood of certain conditions occurring, and some conditions are becoming highly unusual whilst other are increasing. The most likely condition within this group of disorders is now granulomatosis with polyangiitis (GPA) but this is closely followed by cocaine-induced vasculitis.

The disorders are typically associated with an antibody known as anti-neutrophil cytoplasmic antibody (ANCA). Three types of ANCA-associated vasculitis (AAV) affect the nose; granulomatosis with polyangiitis (GPA), eosinophilic granulomatosis with polyangiitis (eGPA) and cocaine-induced vasculitis (CIV), recently referred to as levamisole-associated vasculitis (LAV) or levamisole-induced vasculitis (LIV). Levamisole-associated/induced vasculitis (LAV/LIV) is an emerging entity which is directly associated with cocaine abuse.

Whilst this chapter will briefly describe the less common chronic inflammatory disorders for completeness, the main focus will be on GPA and cocaine-induced vasculitis.

Types of Chronic Inflammatory Disorders

Whilst modern-day rhinology focuses on GPA (previously known as Wegener's granulomatosis), cocaine-induced vasculitis, and eosinophilic GPA (previously known as Churge-Strauss syndrome), the specific granulomatous conditions described in older textbooks may still occur in certain parts of the world and are therefore included with a brief description.

These chronic inflammatory conditions may be primary or secondary and can be categorised into specific and non-specific diseases (Table 46.1). All are chronic inflammations, but characteristic histological features include granulomatous tissue, vasculitis, and in some cases necrosis. A granuloma is a characteristic histological lesion where granulo-

A. C. Swift (✉)
Liverpool Head and Neck Centre, Liverpool University Hospitals Foundation Trust, Liverpool, UK

P. Andrews
Royal National Throat Nose and Ear Hospital and National Hospital of Neurology and Neurosurgery, London, UK
e-mail: peterandrews@nhs.net

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Table 46.1 Types of chronic granulomatous disease and vasculitis

Specific disorders	Non-specific disorders
Tuberculosis	Granulomatosis with polyangiitis (GPA)
Syphilis	Drug-induced vasculitis (DIV)
Rhinoscleroma	Eosinophilic granulomatosis with polyangiitis (eGPA)
Leprosy	Sarcoidosis

cytes form a mass of cells that is easily recognisable microscopically. In infective conditions, the granulocytes occur around the infecting bacteria. In non-infective inflammatory disorders, the granulomas form because of an autoimmune reaction.

In addition to the granulomas, chronic inflammatory infiltrates can also occur around and within blood vessels, known as vasculitis. These autoimmune disorders are known as vasculitides. Inflammation and cellular infiltrate affect vessels of various sizes, according to the specific disorder, and conditions are classified according to the size of the vessel that is targeted. In otolaryngology, the likely disorders that may be encountered include temporal arteritis (large vessel), polymyalgia rheumatica (moderate vessels), and granulomatosis with polyangiitis (small to medium vessel disease).

Whilst there is a wide range of specific chronic inflammatory disorders, many are rarely seen in modern-day otolaryngology unless practising in certain parts of the world. Brief descriptions of the more prominent ones are included to ensure that knowledge does not disappear into obscurity.

Specific Granulomatous Disease

There are several chronic inflammatory diseases associated with granuloma formation that are caused by infection by specific bacteria. The diagnosis of each condition is confirmed by histological biopsy and microbiological culture, sometimes combined with serology. All respond to specific antibiotic regimes.

Tuberculosis

This can present as an inflammatory disorder of the skin around the nostrils, known as lupus vulgaris, or a wet ulcerative condition of the nasal mucosa in the anterior nasal cavity. It usually accompanies pulmonary tuberculosis and is caused by *Mycobacterium tuberculosis*.

Syphilis

There has been a recent resurgence of syphilis. Classically, it was a recognised cause of saddle deformity due to the destruction of the bony skeletal structures in the late stage 4 phase of the disease. The early disease presents with a chancre or sore (stage 1), followed by flu-like symptoms with a rash (stage 2). After a couple of years, the presentation changes to painful gummatous infiltration of the nose with foul crusts, secretions, well-demarcated ulceration, and lymphadenopathy (stage 3). The cause is chronic *Treponema pallidum* infection.

Rhinoscleroma

Rhinoscleroma, or scleroma, starts with purulent secretions, crusts and inflamed nodular nasal mucosa, but progresses to affect the skin, which becomes coarse, eventually healing by extensive scarring. The cause is *Klebsiella rhinoscleromatis*.

Leprosy

This is a chronic inflammatory disorder caused by *Mycobacterium leprae*, which presents with thickened skin around the vestibules, crusts, and fetid secretions.

Non-specific Chronic Inflammatory Disease

Whilst this group of disorders is uncommon, they are by far the most likely disorders to be seen in most modern-day clinics. The most likely disorder to present is GPA, whilst eGPA and sarcoidosis affecting the nose are still relatively rare. However, the newcomer on the scene that seems to be gaining in frequency is drug-induced vasculitis following cocaine abuse.

Sarcoidosis

Sarcoidosis is a multisystem chronic inflammatory disorder of unknown aetiology that occasionally affects the nose, causing a painful tender nose with nodular nasal mucosa. Disease progression may cause crusting, septal perforation, and saddle deformity. It may be accompanied by lesions in the lungs, skin disease, and ocular disorders. Diagnosis is confirmed by biopsy of affected tissues, blood tests for inflammatory factors, and detecting high serum angiotensin-converting enzyme, although the latter is non-specific. Biopsy typically shows non-caseating granulomata. Once diagnosed, the inflammatory reaction should be suppressed by medication with systemic steroids, and immunomodulating drugs such as methotrexate, under the auspices of a rheumatologist. The key point about nasal sarcoidosis is to maintain a high index of suspicion, especially if the nose is tender, as being lured into nasal surgery to alleviate obstruction may exacerbate the condition.

Eosinophilic Granulomatosis with Polyangiitis (eGPA)

This is a chronic multisystem vasculitic disorder, previously known as Churge–Strauss Syndrome, that is occasionally seen in rhinological practice but very easy to miss. The EPOS 2020 guidelines refer to eGPA and nasal GPA as secondary chronic rhinosinusitis (CRS), driven by underlying autoimmune inflammation.

eGPA presents with chronic nasal obstruction and nasal polyps, typically accompanied by asthma. However, diagnostic clues occur when other systems become actively involved such as the cardiovascular system, skin, or odd peripheral neurological disorders, especially when these features occur in relatively young adults. Diagnosis can be elusive but relies on the clinical picture, accompanied by evidence of an active vasculitis on blood tests, and histological diagnosis from affected tissue, particularly from bronchial biopsy samples. Blood tests include the detection of raised inflammatory factors and ANCA. Once diagnosed, the condition is controlled by immunosuppression and immunomodulation, again with the intervention by rheumatologist, often in highly specialist units.

ANCA-Associated Vasculitis (AAV)

ANCA-associated vasculitis primarily includes granulomatosis with polyangiitis (GPA) and a drug-induced vasculitis (DIV) that is typically caused by cocaine abuse and known as cocaine-induced vasculitis (CIV). There are strong similarities between GPA and CIV, and they will therefore be discussed in close sequence.

In clinical practice, the diagnosis of GPA and CIV can be challenging. The diagnosis of both conditions is dependent on the combination of clinical features and investigations. The range of presentation includes a clear diagnosis of either GPA or CIV, and a less certain group where a

clear differentiation is unclear. An example of the latter would be a patient with GPA who also has a history of cocaine abuse. The other issue that confounds the diagnosis is that patients with CIV will often conceal their true history of cocaine abuse.

The importance of this differentiation is that in GPA there is a risk of spontaneous flare-ups and of the renal or pulmonary systems being involved. In contrast, the renal and pulmonary disease is highly unlikely in CIV and spontaneous acute flair-ups are unlikely as long as the offending cocaine abuse is avoided [1].

Granulomatosis with Polyangiitis (GPA)

Until recently, GPA was the most likely chronic inflammatory condition to be seen in ENT clinics. It is a multisystem idiopathic vasculitis of small to medium sized vessels, which typically presents with features in the nose and sinuses or other areas within the head and neck, but may also affect the lungs and kidneys, and cause rapid failure of either system during an acute flare-up.

GPA has a slight female-to-male preponderance with an incidence of 10–20 cases per million per year in populations of Northern European extraction. In 2001, it had an estimated incidence of 5–10 cases per one million person-years in Europe [2] and approximately 12.8 cases per one million person-years in the United States in 2018 [3].

The initial symptoms of GPA affect the head and neck in 80–95% of patients, often preceding lung disease by several months. The condition can be limited to the head and neck in about 25% of patients and is referred to as a 'limited GPA' phenotype, but this can transform into a multisystem disease at a later stage in some patients [4]. The nose is the only affected site in about 30% of GPA patients. However, about 90% of patients with GPA experience sinonasal problems at some point in their disease history [5–8].

Clinical features: The features in the head and neck include nasal obstruction with excessive crusts, secretions and mucositis, septal perforation, and saddle deformity (Figs. 46.1, 46.2). It can occasionally affect the temporal bones, middle ear, the pharynx, larynx, subglottis, and trachea, sometimes causing ulceration and stenotic lesions. Hearing loss may be conductive or sensorineural, and symptoms may include tinnitus and dizziness [6, 7, 9–13]. Facial ulceration

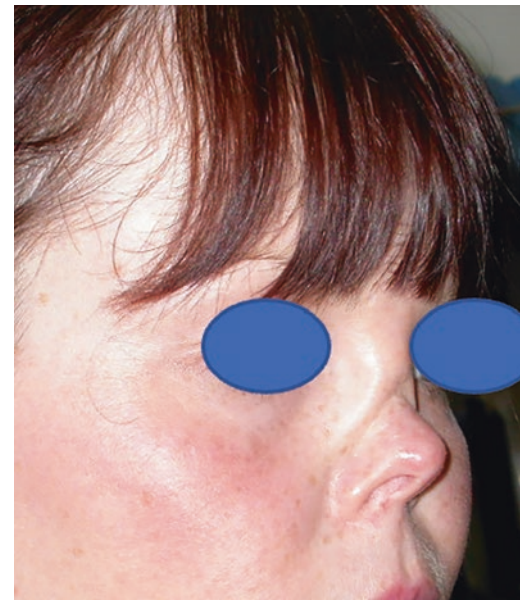

Fig. 46.1 Saddle deformity in a patient with GPA

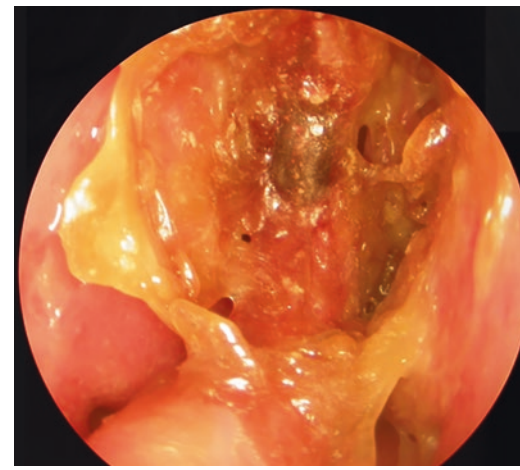

Fig. 46.2 Endoscopic appearance of nasal cavity in GPA. Note the crusting, loss of nasal architecture, and large septal perforation

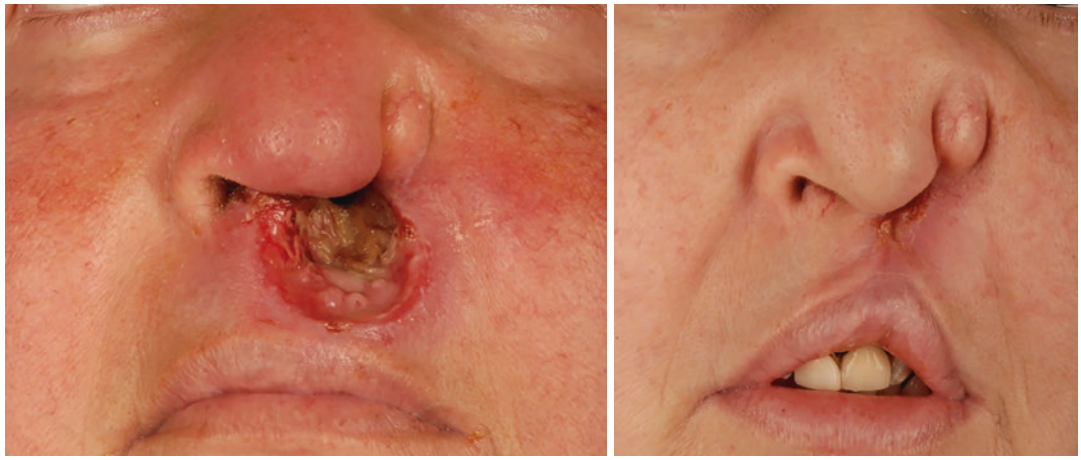

Fig. 46.3 Recurrent ulceration of upper lip and nostril floor in a patient with an acute flare-up of GPA and subtotal septal perforation. The ulcer had formed a fistula into the gingival sulcus. Once healing occurs, scar contraction shortens the upper lip

affecting the nostrils and upper lip may cause severe deformity and subsequent scarring and contracture (Fig. 46.3).

Clinical examination should include a review of all systems within the head and neck, and endoscopy of the upper respiratory tract. Characteristic findings within the nose include a subtotal septal perforation, loss of ethmoid architecture, and destruction of the bony lateral nasal walls. Sinonasal involvement typically affects the anterior cartilaginous septum initially before extending to the paranasal sinuses [14]. Large anterior septal perforations are estimated to occur in 33% of cases [15].

Whilst GPA typically presents in the head and neck, the lungs and kidneys must be thoroughly assessed and reviewed (Fig. 46.4).

The nose and paranasal sinuses are the most frequently affected sites in the head and neck with 64–80% of the cases presenting with sinonasal disease [16].

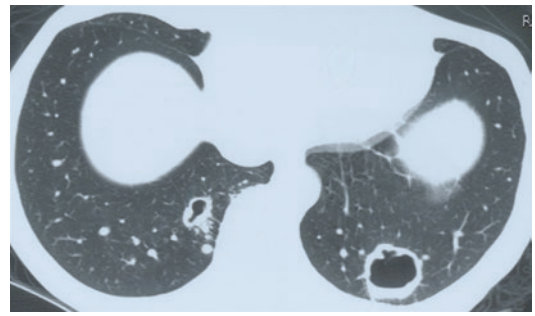

Fig. 46.4 Axial chest CT scan showing cavitating granulomatous lesions in a patient with GPA

Cocaine-Induced Vasculitis

Cocaine abuse is now a prominent activity on a global scale. The European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) estimates that approximately 4.7% of young adults in the UK, between the ages of 16 and 34 years, used cocaine in 2017 [17]. The drug is either snorted into the nose as a white powder mixed with a filler or the fumes of crack cocaine are inhaled. In general, CIV affects a younger age group and is unlikely to be associated with disease in the lungs or kidneys.

Differentiating CIV from GPA may be challenging, especially if GPA is limited to just the head and neck. As previously stated, it is easy to assume that vasculitis is cocaine-induced rather than GPA, but this could lead to a risk of missing

spontaneous flare-ups, lung disease, and the renal failure.

Clinical features: The clinical features of CIV are generally similar to those of GPA. The nasal cavity is typically blocked by excessive moist crusts with mucus secretions. Localised pain is a characteristic feature of CIV, not often seen in GPA. Sometimes, features are noted mainly in the anterior nasal cavity, but subsequent tissue destruction may cause subtotal septal perforation and significant saddle deformities (Figs. 46.5, 46.6). The nasal tip, nostrils and columella are more likely to be affected in CIV, and tissue destruction can result in loss of the columella and perforation of the hard palate, that can progress at an alarming speed (Figs. 46.7, 46.8, and 46.9). CIV occasionally affects the ear, eye, pharynx, and larynx. Endoscopic examination may show generalised atrophic rhinitis with loss of ethmoid architecture and erosion of the lateral bony nasal wall.

Pathogenesis of Cocaine-Induced Vasculitis

Cocaine-induced vasculitis is a relatively new condition that was previously named cocaine-induced midline destructive lesion (CIMDL) [18]. The tissue destruction that accompanies cocaine abuse is recognised now as being a local-

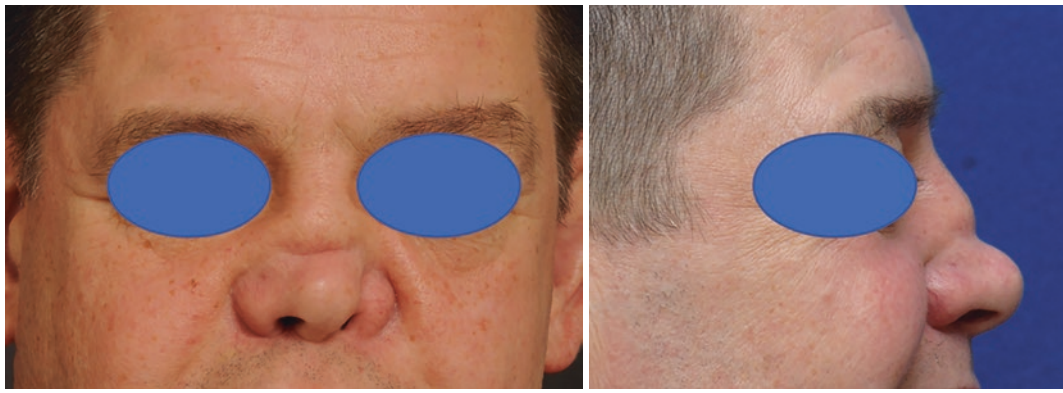

Fig. 46.5 Saddle deformity due to cocaine-induced vasculitis

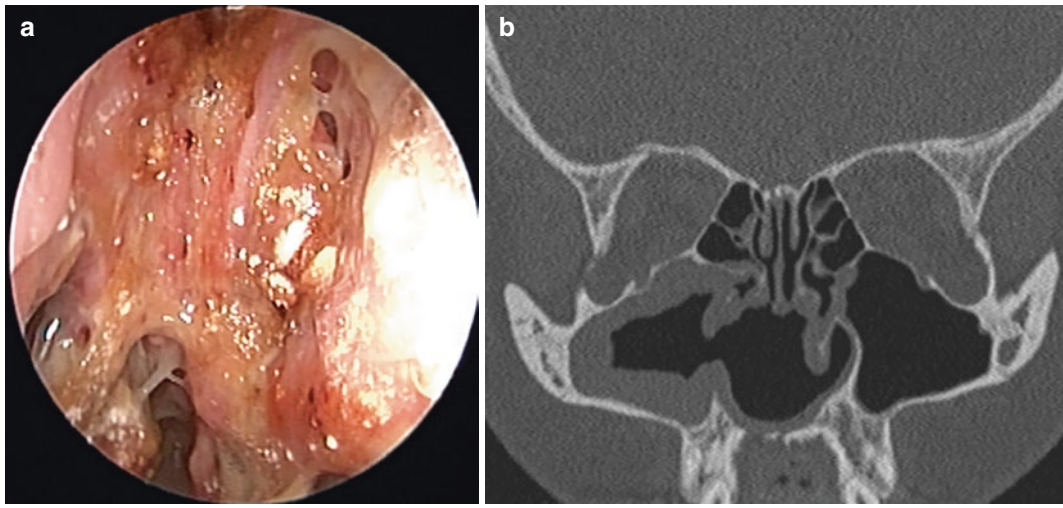

Fig. 46.6 Cocaine-induced vasculitis. (**a**) Endoscopic appearance. Note crusting, loss of nasal architecture and subtotal perforation. (**b**) Coronal CT scan showing destruction of septum, lateral nasal wall and bone of hard palate

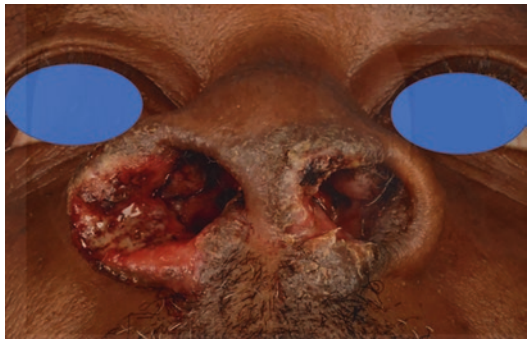

Fig. 46.7 Unusual slowly progressive nodular lesions extending far back into both nasal cavities, due to cocaine-induced vasculitis. Appearance similar to lupus vulgaris but tuberculosis excluded

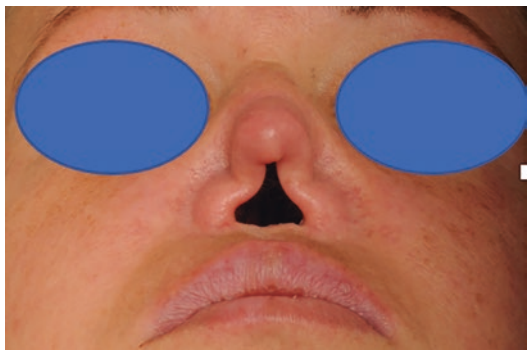

Fig. 46.8 Loss of columella due to cocaine-induced vasculitis

ised vasculitis with tissue destruction that affects particularly the nose.

Snorting cocaine powder into the nose risks possible direct damage to the nasal mucosa, due to intense vasoconstriction and ischaemia induced by cocaine, as well as direct irritation from the drug or whatever it is combined with. The topical mucosal trauma eventually results in mucosal atrophy, with crusting that traps underlying mucus. The static mucus can then become infected with pathogenic bacteria. Attempts to clear the crusts can also cause direct trauma to the mucosa. However, a small number of people progress to develop serious tissue destruction causing large septal perforations, saddle deformities, and marked deformity of the anterior nose.

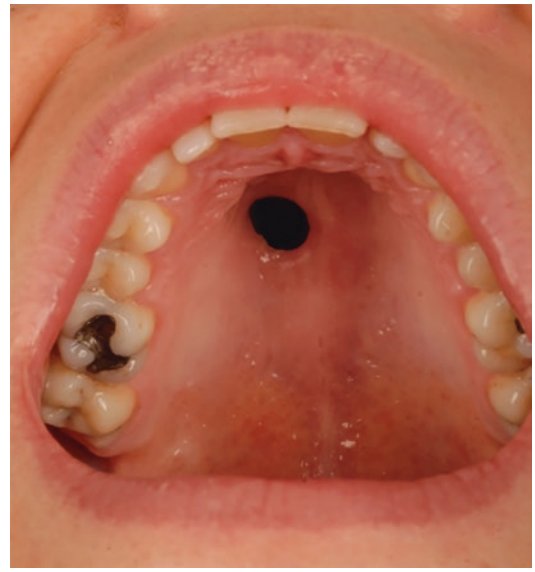

Fig. 46.9 Palatal perforation due to cocaine-induced vasculitis

The Mechanism Behind the Vasculitis

The antigen induced by the cocaine/filler powder stimulates the production of ANCA and activates neutrophils. The ANCA binds with the activated neutrophils causing them to be overactivated. The neutrophils produce antibacterial neutrophil extracellular traps (NETS) around the blood vessels and induce vascular inflammation. However, the overactivated cells soon expire, releasing granule proteins and chromatin that induces a further cycle of ANCA production and neutrophil stimulation that bind all over again in a positive feedback loop.

Whilst knowledge of these drug-induced vasculitides has rapidly increased over the last decade, the overall pathogenesis of this condition still remains poorly understood. The interesting question is why the condition only affects a small proportion of people who regularly use cocaine, and why it is so destructive once it is induced. The likely reason for this effect is probably down to individual susceptibility due to genetics and epigenetic factors.

Drug-Induced Vasculitis (CIV) and Levamisole-Induced Vasculitis (LIV)

Vasculitis can be caused by a range of drugs that are used as medications (drug-induced vasculitis: DIV). Whilst drug-induced vasculitis is highly unusual, there is a wide range of medications that can induce this. Medications that have the potential to induce this reaction that are encountered in otolaryngology include antithyroid drugs (carbimazole, propylthiouracil), various antibiotics (cefotaxime and vancomycin), allopurinol, atorvastatin, phenytoin, clozapine, and sulfasalazine [1].

The reaction from street cocaine is linked with the use of powders combined with the cocaine. The powders, known as fillers, are used to 'cut' the cocaine. There are a multitude of agents used for this purpose, some of which are inert, some are psychoactive, other induce topical anaesthesia, and a few are toxic agents. Unfortunately, almost all cocaine users have little knowledge as to what has been mixed with their cocaine, and what concentrations have been used.

A long-term popular mixing agent is levamisole. Levamisole is an immunomodulator that was used in rheumatology until it was banned from clinical use following complications from serious side effects such as agranulocytosis, and encephalopathy. Levamisole is widespread in farming, where it is used as an antihelminth agent. It is easily accessible, inexpensive, difficult to detect and enhances the stimulant effect of cocaine, making it a popular choice for combining with cocaine.

Levamisole is known to cause cutaneous vasculitis [19]. Levamisole combined with cocaine may also induce neutropenia and ANCA-positive or negative vasculitis, known as cocaine/levamisole-associated syndrome (CAAS) or, more recently, referred to as levamisole-associated vasculitis (LAV) (9). LAV is a newly described vasculitic condition based on the premise that about 70% of the world's cocaine is contaminated with levamisole [20, 21]. In addition to inducing ANCA positive autoantibodies, levamisole can also induce antinuclear antibodies (ANA) [22].

However, there is still a dilemma with regard to the presence of levamisole, especially since cocaine users typically have no knowledge of the cutting agents that have been used. Also, this group of patients develops tissue destruction within the head and neck, and the cutaneous vasculitis previously associated with levamisole seems to be infrequent.

Investigation of Suspected GPA and CIV

On suspicion of the possible diagnosis of a vasculitic condition, the standard investigation should include a range of blood tests to include inflammatory factors, a vasculitic screen and renal function; a CT scan of the sinuses and thorax; and urinalysis for protein and blood cells. A vasculitic screen includes a full blood count as well as inflammatory factors (ESR, CRP), angiotensin-converting enzyme (ACE), and anti-neutrophil cytoplasmic antibodies (ANCA) (see below).

Urinalysis for cocaine metabolites should be considered when cocaine abuse is suspected, as key information may be withheld or mis-leading. Cocaine metabolite assessment is also recommended pre-operatively prior to reconstructive nasal surgery in patients with a history of cocaine abuse.

Anti-neutrophil Cytoplasmic Antibodies (ANCA) and Vasculitis

Vasculitis is an autoimmune disease often associated with anti-neutrophil cytoplasmic antibodies (ANCA). The latter is from a group of disorders known as ANCA-associated vasculitis (AAV) and includes eGPA, GPA, and CIV. However, whilst these disorders are all associated with ANCA, the antibodies are not always detected or may occur at various stages of the disease.

ANCA is detected by immunofluorescence and is categorised according to the pattern of staining distribution within the neutrophil. The stain may target the cytoplasm, when it is referred to as c-ANCA, or be perinuclear, termed p-ANCA pattern. Testing has become more sophisticated and includes the combination of staining with quantified specific antibody identification. C-ANCA is active against a specific protein enzyme called proteinase-3 (PR3), but p-ANCA can target several proteins, of which a prominent one is myeloperoxidase (MPO).

Positive ANCA levels can help with confirming the diagnosis of a vasculitis but are not always present at the onset of the disease. The specific ANCA profile helps guide us towards a particular vasculitic diagnosis. Anti-PR3 c-ANCA is typically seen in GPA, whereas anti-MPO ANCA is associated with a range of other autoimmune disorders. Interestingly, CIV most often demonstrates a mixed ANCA pattern with elevated p-ANCA but raised titre levels to PR3-c-ANCA.

ANCA levels may change from detectable to undetectable and vice versa, or even remain undetectable [18]. ANCA titres do not accurately predict the course of the disease [20] and serial measurements do not always reflect disease activity. It is therefore important to include the clinical picture and other inflammatory markers when assessing disease activity [21, 22].

Nasal biopsy: Nasal mucosal biopsy and examination under anaesthesia should always be considered at presentation as a positive result will confirm the diagnosis.

Mucosal biopsy should be substantial and be taken from unhealthy mucosa to increase the likelihood of a diagnostic finding. However, in many cases, the histology just shows chronic inflammation and does not include the typical features of granuloma, vasculitis, and tissue necrosis. Biopsy is recommended by the American College of Rheumatology; will exclude other unusual pathology such as a tumour or lymphoma; should be considered if there is anything unusual in the appearance or behaviour of the disease [23].

Management of GPA and CIV

Medical Management

Treatment needs to be focused on disease activity, prevention of tissue destruction, and symptom relief. Nasal crusts will typically respond to regular saline rinses and long-term antibiotics. Oral steroids are often very effective in GPA. Systemic steroid use in CIV may be effective, but their use is controversial. Interestingly, if cocaine use ceases, facial pain associated with CIV resolves and general well-being improves.

The medical treatment of vasculitis is best managed in collaboration with medical colleagues in rheumatology and nephrology, where treatment regimens may include immunomodulatory and biologic therapy.

Surgical Management

The surgical management of GPA and CIV is in many ways similar, but the localised tissue destruction that follows cocaine abuse is often much more severe than GPA. Typically, patients who experience a flare-up of GPA are likely to seek urgent help, and immunosuppressive anti-inflammatory treatment can be rapidly instigated.

Historically, the teaching was that surgery on GPA should be avoided until a remission-free period of 5 years had been reached. Nowadays, this stringent strict dictum is unnecessary as medical control is much improved and maintained, but an understanding of the patient's individual disease is required during the decision-making process.

In GPA, surgery is best avoided, if possible, but surgery should not be refused where severe deformity has occurred [14]. The timing of surgery in the GPA group is important, and patients should be in sustained remission for greater than 6 months and on stable, low-dose maintenance immunosuppressive regimen. Localised GPA patients report an overall higher surgical success

rate (88%) when compared to the generalised forms (60%) [24]. Nasal surgery per se does not exacerbate or influence the course of the disease, but immunosuppressive medication should be continued after surgery. Patients with GPA should also be warned of the possibility of relapse affecting surgical reconstruction, particularly in those who are ANCA positive.

For the cocaine group with CIV, surgery should be avoided if cocaine use continues. It is also essential that smoking should also stop prior to surgery to enhance wound healing.

The key areas that need to be addressed regarding surgery are as follows:

The Nasal Septum

Whilst small to moderate anterior septal perforations are amenable to repair, large, or subtotal ones are best managed conservatively. In patient with excessive crusting and a septal perforation, inserting silastic splints will often provide symptom relief by moderating crusting and alleviating local pain. The splints can remain in situ for up to 12 months.

There are several techniques for repairing septal perforations that vary according to personal expertise and preference. Surgical techniques of septal perforation repair are described in Chap. 45. Local septal flaps are ideal for small perforations, but moderate perforations may require a unilateral transposition/rotation flap from the lateral nasal wall. Larger perforations may require the addition of a superior septal mucoperichondrial flap, with an underlay graft of BioDesign (*Cook Medical, Bloomington, IN, USA).*

The Hard Palate

Perforations of the hard palate induce a significant disability that affects speech and eating and should initially be closed by a palatal obturator on a plate. Surgical closure is the optimum method of management: a simple rotation flap is suitable for small perforations; large perforations may require a vascularised free flap harvested from the forearm (Fig. 46.10).

Saddle Deformity

Generally, mild to moderate saddle deformities can be corrected by extended spreader grafts secured to a columellar strut or septal extension grafts (SEG), combining overlay septal/conchal

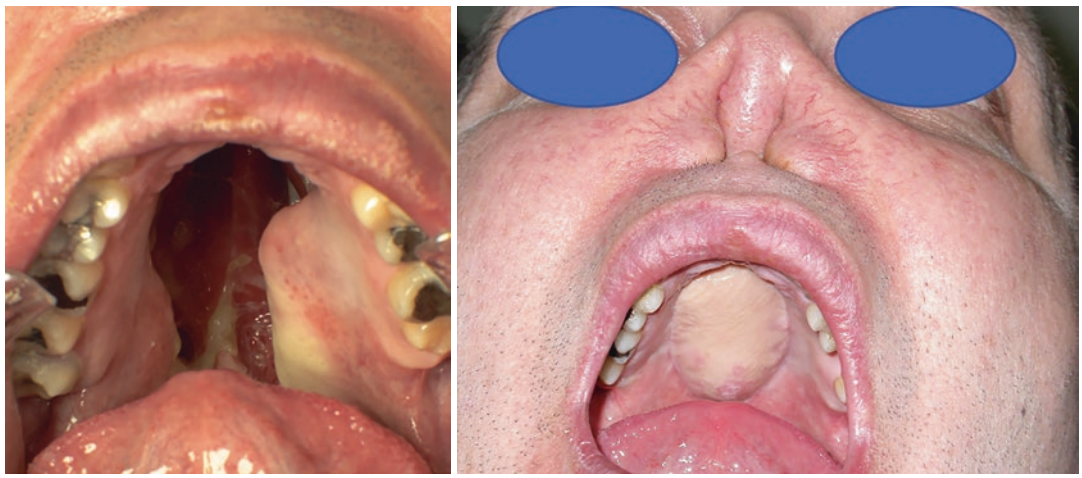

Fig. 46.10 Large palatal perforation in a patient with cocaine-induced vasculitis. Repaired with a vascularised free flap from the forearm

cartilage cushioned using perichondrium to camouflage any graft irregularities.

A severe saddle deformity with loss of septum and upper lateral cartilages is best corrected using the modified osseocartilaginous rib graft (OCRG) technique recently described in 2020 (Figs. 46.11, 46.12) [25]. The latter was a modification of a technique that harvested osseocartilaginous rib and divided it into two sections [26]. One section formed the nasal dorsum reconstruction and the other the caudal strut reconstruction. The bony rib component ossifies with the residual nasal bone having been fixated to the glabella using a titanium screw and the distal cartilaginous end is

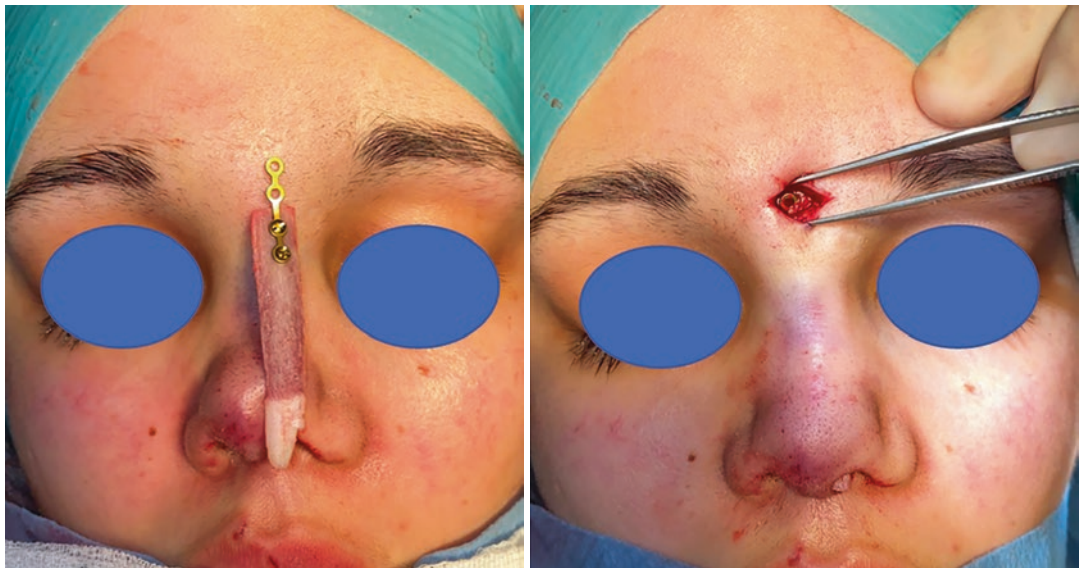

Fig. 46.11 Dorsal costal cartilage graft and columella strut shown prior to insertion beneath nasal skin. The fixation plate is used to firmly attach the dorsal graft to the glabella. The plate is fixed with a titanium screw through a glabella incision

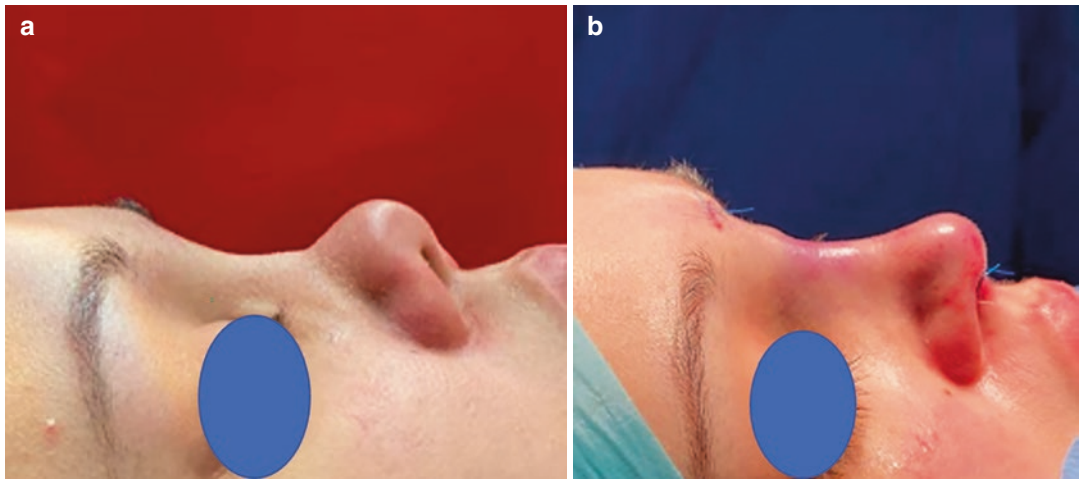

Fig. 46.12 (**a, b**) Operative images showing pre-reconstruction (**a**) and post-OCRG reconstruction (**b**) in a patient with GPA

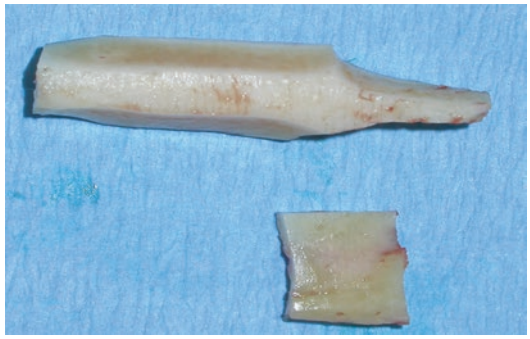

Fig. 46.13 Carved costal cartilage grafts for reconstruction of nasal dorsum and columella strut

secured to the osseocartilaginous caudal strut, forming an 'L-strut'. This technique replaces 'like with like'. In order to establish a vertical support of the lower two-thirds of the nose, the lower lateral cartilages (LLCs) are then rebuilt around the new OCRG strut. Reconstruction of the external nasal valve is then addressed and scored according to the external nasal valve collapse (ENVC) grading system [27].

An alternative technique with similar principles is to harvest costal cartilage and fashion a graft for the nasal dorsum and one for the columella (Figs. 46.13, 46.14). The dorsal graft is precisely carved to create a natural-looking shape, including support for the lower lateral cartilages. The two grafts are secured together, often with a joint at the nasal tip, and the columellar strut is firmly fixed to the premaxilla with wire [28].

Rib grafts are generally very stable and avoid the risk of graft atrophy that occurs with ear cartilage grafts. However, warping is a problem on occasions [28].

Resorption of grafts even after reconstruction with autologous material remains a key challenge in these patients, with resorption rates ranging from 0 to 19% [24]. It has been shown that the risk of complications decreases with the use of L-shaped struts and increases as the number of individual grafts placed increases [29].

Alternatively, processed allograft cartilage (Tutoplast, Wescott Medical Ltd., UK) has recently been used to good effect with little risk of warping or resorption.

Columella Reconstruction

Loss of soft tissues of the columella is a difficult, challenging deformity that may require nasolabial flaps, a pedicled forehead flap, buccal flaps, a vascularised free flap or various combinations to facilitate skin cover, and an internal nasal mucosal repair. Repairs may be complicated by anterior nasal stenosis and may require dilatation, division of scar tissue or insertion of compound grafts.

Epiphora

Mucoid epiphora is a well-recognised ocular complaint in GPA patients and is associated with inflammatory obstruction of the nasolacrimal duct. After careful assessment by an oculoplastic surgeon, it is managed surgically via endonasal or external dacryocystorhinostomy.

Fistulae

Rarely, a fistula into the nasal cavity can form and discharge from an epicanthal defect. Defects will require internal and external closure with a pericranial flap, a glabella rotation flap, or a vascularised pericranial flap.

Key Learning Points

- The ENT clinician should maintain a high index of suspicion and an awareness of vasculitic conditions.
- Vasculitic conditions are likely to affect the nose and sinuses and are either specific or non-specific autoimmune disorders.
- A detailed medical history is recommended in patients presenting with excessive nasal crusts or non-traumatic nasal deformity.
- Investigations should include an assessment of renal function and the respiratory system.
- Investigations should include blood tests to assess ANCA patterns and titres. Nasal biopsy of abnormal tissue should be considered before commencing treatment.
- Patients with suspected cocaine-induced vasculitis may not reveal the actual truth of their

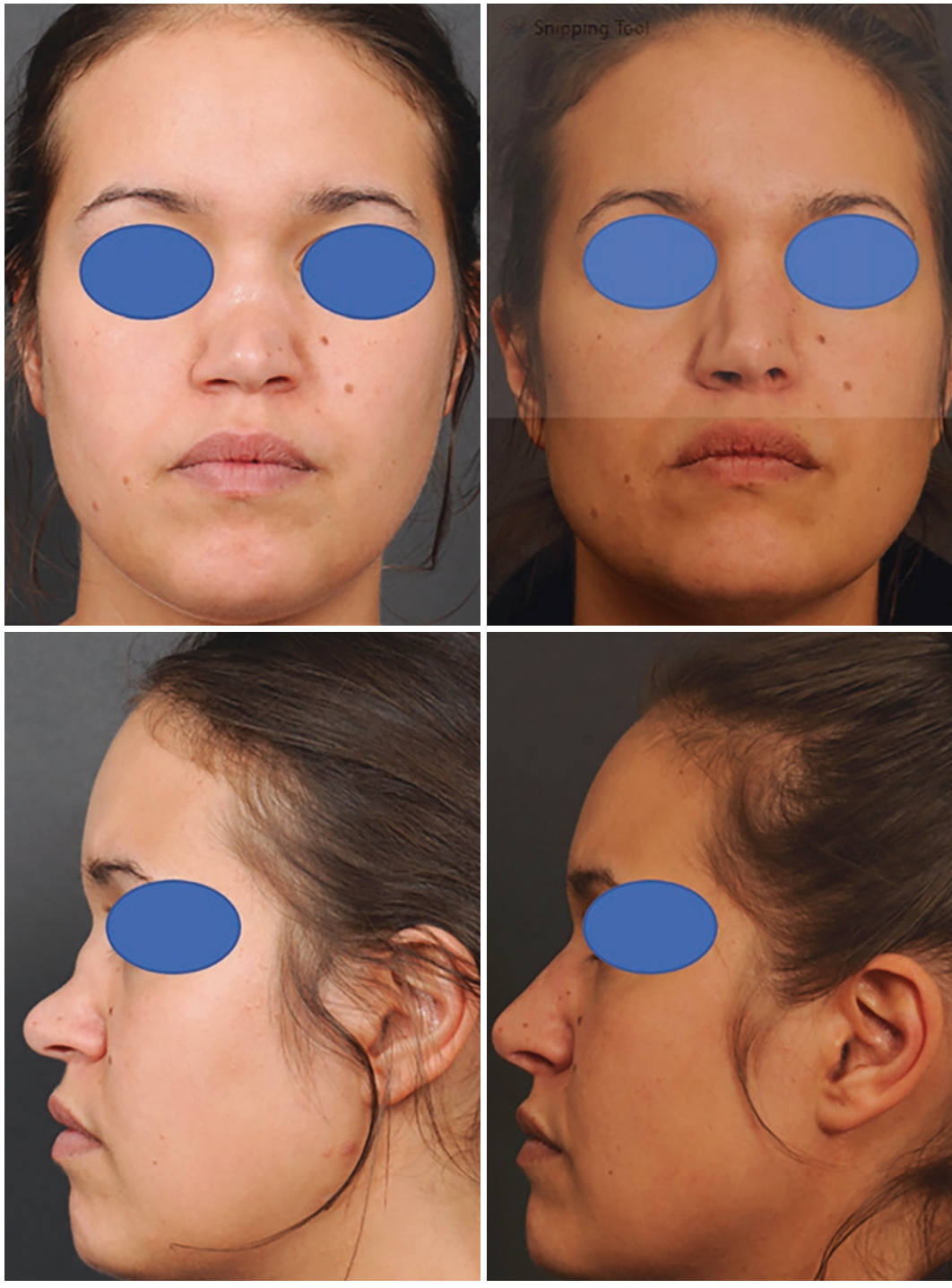

Fig. 46.14 Before and after reconstruction to correct a severe saddle deformity. Reconstruction performed with carved costal cartilage

drug-taking habit and may conceal information.

- Deformities in GPA and cocaine-induced vasculitis are often similar and include a saddle nose and septal perforation. Soft tissue scarring of the nasal tip, loss of the columella and perforation of the hard palate are more likely in cocaine abuse.
- Medical therapy for GPA is immunosuppressive and should be prescribed alongside an expert in medicine such as a rheumatologist, pulmonologist, or renal physician.
- Surgical reconstruction can be performed as long as patients with GPA are in remission and cocaine users are no longer taking cocaine.

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Empty Nose Syndrome

47

Isma Z. Iqbal

Introduction

Empty nose syndrome (ENS) was first described in 1994 by Kern and Stenkivist to describe an empty space in the region of the inferior and middle turbinates on coronal CT imaging [1]. Although it was first described as a radiological diagnosis it is now recognised as a combination of clinical, subjective, objective and radiological findings. Empty nose syndrome (ENS) is an iatrogenic disorder most often recognised for the presence of paradoxical nasal obstruction despite an objectively wide, patent nasal fossa [2]. The term can also be synonymous with iatrogenic or secondary atrophic rhinitis. Its incidence in the population is not known however it is rare. Only a fraction of patients undergoing turbinate surgery develop ENS [3]. The most common finding is that patients present following nasal surgery commonly inferior turbinate removal. The complainant can present months or years after the initial surgery. The incidence is not known; however, the introduction of the Empty Nose Syndrome 6-item Questionnaire (ENS6Q) may improve diagnosis [4].

I. Z. Iqbal (✉)
The Newcastle Hospitals NHS Foundation Trust, Freeman Hospital, Newcastle upon Tyne, UK
e-mail: isma.iqbal1@nhs.net

Pathophysiology

The underlying pathophysiology is unknown and most likely multifactorial, encompassing anatomical and neurosensory alterations [5]. Commonly ENS is secondary to middle or inferior turbinate surgery but can also be associated with minor surgical procedures such as submucous diathermy, submucosal resection, laser therapy and cryotherapy if performed in an aggressive manner [6]. The presence or absence of a significant portion of the turbinates does not uniformly predict ENS development [7].

A healthy nose provides about half of the resistance of the entire respiratory tract [6]. A significant reduction in this may in turn impair the resistance required for deep pulmonary inspiration resulting in shortness of breath due to an effect on the nasopulmonary reflex.

A combination of change in nasal airflow dynamics, humidification, thermoregulation and neural sensitivity components are thought to be triggered. It is however unclear as to why certain patients develop this condition. Interestingly, some patients present with unilateral symptoms despite both nasal cavities appearing the same.

Mechanoreceptors, proprioceptors, thermoreceptors and nerve endings are present within the nasal mucosa, in numbers largest in the region of the inferior and middle turbinate [1]. Computational fluid dynamics (CFD) have been used to try to understand the pathophysiology of

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ENS. It is estimated that the middle and inferior turbinates are responsible for up to 70% of total nasal air conditioning and that loss of the turbinates' surface area reduces the efficacy of nasal air conditioning by nearly 30% [8]. Similarly, a computer simulation of nose models demonstrated a reduction in heating and humidification following total turbinectomy as well as an effect on nasal velocity distribution and formation of recirculation zones [9, 10]. A change in nasal physiology has been demonstrated following inferior turbinectomy (decreased mucociliary clearance and IgA secretion, loss of humidification and warming).

It has been demonstrated that heat flux (the rate of the heat loss from nasal mucosa to inspired air) is strongly related to the perception of nasal obstruction in a number of studies [11]. Li et al. [7] compared CFD between ENS and healthy subjects. ENS patients had significantly lower (~25.7%) nasal resistance and higher (~2.8 times) cross-sectional areas compared to healthy controls (both $p < 0.001$). There was also a distorted airflow jet towards the middle meatus with no airflow in the majority of the inferior nasal region in ENS patients. Subsequently, a reduced air-mucosa interaction in the inferior region was observed which correlated strongly with the 'suffocation' and 'nose too open' parameters on the ENS6Q.

The lack of turbulence following nasal surgery leads to inspired air reaching the nasopharynx with a higher speed ultimately causing dehydration of the pharynx and nasal dryness.

It has been shown that mucosal surface area cooling by inhaled air, and subsequent trigeminal activation, better correlates with subjective nasal patency than measuring the anterior nasal resistance or total nasal airflow [12]. Both ambient air temperature and humidity significantly modulate an individual's perception of patency through heat loss in the nasal mucosa and trigeminal sensory input [13].

Nasal airflow activates the **trigeminal cool receptors** (TRPM8) on inspiring ambient cool air [3, 13]. Airflow leads to the evaporation of fluid which causes a reduction in the associated temperature causing reduced fluidity of the membrane phospholipids. This is detected by the TRPM8 receptor which activates neural stimulation causing a feedback to the respiratory centre in the brain [3]. This 'cool' message is interpreted as open nostrils and open airways leading to a decrease in intercostal and accessory muscle work of breathing [14]. The activation of these receptors is reduced in ENS patients [7]. Menthol activates the TRPM8 receptor providing the patient with a sense of improved nasal patency without any physiological change. Trigeminal lateralisation testing (one side activated with trigeminal stimulation while other side odourless solution) seems to be a more reliable diagnostic tool than rhinomanometry in ENS [15]. Studies have shown significantly decreased trigeminal lateralisation in ENS patients when compared to controls or post-inferior turbinate reduction patients without ENS symptoms [7, 15].

As the ENS nose tends to be warmer than a normal nose, the lack of a significant temperature gradient further compounds this issue. Differences in nerve recovery after surgery may explain why only some patients develop ENS despite identical turbinate surgeries [3]. Nerve damage secondary to poor mucosal healing may also affect thermoreceptor availability.

When the overall surface area of the nasal passages is reduced and the airflow pattern is altered as is the case in ENS patients, mucosal cooling is compromised and so the sensation of nasal patency is not elicited [3]. It is therefore understandable that a change in the mucosa in this region may result in symptoms of obstruction, shortness of breath and congestion. Additionally, structural change, i.e. turbinate surgery will have an impact on the rate, temperature, and distribution of airflow through the nasal cavity.

Diagnosis

The diagnosis of ENS is subjective with patients presenting months or years after previous nasal surgery. Patients with ENS complain of nasal obstruction or 'stuffiness' with seemingly enlarged nasal cavities. Crusting and dryness may or may not be present.

A combination of patient symptoms, clinical findings and radiological imaging as well as previous history of surgical intervention are used to reach a diagnosis.

Symptoms

The mainstay of diagnosis is the patient symptoms. A summary of patient symptoms is described in Table 47.1.

It is important to exclude differentials such as autoimmune disease or primary atrophic rhinitis (AR). The main differentiating factor between ENS and primary AR is the iatrogenic nature of ENS and the resorption of the turbinate and adjacent mucosa in primary AR. Primary AR is associated with chronic infection, nutritional and endocrine abnormalities (vitamin A, D and iron deficiency) and with organisms isolated from nasal cultures, e.g. Klebsiella ozaena [16]. Other organisms which may be cultured include *Staphylococcus aureus* and *Corynebacterium diphtheriae*.

Patients with ENS often report a quantitative decrease in their ability to smell, although their qualitative identification of odours remains intact [17]. This may be due to the reduced moisture and airflow to the olfactory region in the nose.

It is essential to recognise that ENS can be a debilitating condition that affects mental health and is strongly associated with anxiety and depression. A study of 53 ENS patients revealed ENS6Q symptom severity was significantly correlated with more severe levels of depression ($p < 0.001$), anxiety ($p < 0.001$), impairment of workplace productivity ($p < 0.001$), overall pain/discomfort ($p = 0.002$) and impairment in activities of daily living ($p = 0.003$) [18]. The incidence of concomitant anxiety or depression in this population can be as high as 66% [18].

Table 47.1 Symptoms associated with ENS

• Nasal obstruction	• Depression	• Pharyngitis
• Shortness of breath	• Anxiety	• Laryngitis
• Dryness	• Pain	• Sleep disturbance
• Crusting • Epistaxis • Rhinorrhoea	• Headache • Cacosmia • Postnasal drip	• Disrupted concentration • Anosmia/ hyposmia

Types of ENS

Depending on the level of previous surgical resection ENS can be subdivided into the following [6]:

1. ENS-IT—Inferior turbinate [IT] was fully or sub-totally resected.
2. ENS-MT—middle turbinate [MT] was fully or sub-totally resected.
3. ENS-both—both the IT and MT were at least partially resected.
4. ENS-type—adequate turbinate tissue after minor turbinate surgery with symptoms of ENS.

Houser [6] describes different symptoms in the different subtypes of ENS. Crusting is most prominent in ENS-IT, facial pain with inspiration in ENS-MT and depression and anosmia or hyposmia in ENT-both (most severe) [2].

Symptom Scores

The Empty Nose Syndrome 6-item Questionnaire (ENS6Q) has been validated to identify patients suspected of developing ENS [Table 47.2] [4]. ENS6Q has a sensitivity of 86.7% and a specificity of 96.6%. A score of 11 or greater out of a possible total of 30 was determined as the cut-off criterion to predict ENS [7].

Table 47.2 Empty Nose Syndrome 6-item Questionnaire (ENS6Q)

Suffocation	Five-point scale No problem—0 Very mild—1 Mild—2 Moderate—3 Severe—4 Extremely severe—5
Nose feels too open	
Nasal burning	
Crusting	
Dryness	
Sense of diminished nasal airflow [cannot feel air flowing through nose]	

The SNOT-22 and Nasal Obstruction Symptom Evaluation (NOSE) scores have been shown to be elevated in ENS [7]. The Sino-nasal Outcome Test (SNOT20) was modified by Houser to develop the validated SNOT-25 by adding five additional ENS Specific domains [2, 19]. The SNOT-25 was shown to be a good predictor of moderate-severe depression when the total score was >60, sleep dysfunction domain score was >18 and empty nose symptoms domain score was >14.

Signs

There are no specific clinical signs to identify ENS and the mucosa itself may appear normal. Endoscopic examination may reveal evidence of previous turbinate surgery with an open nasal cavity. Figure 47.1 is a picture of a patient with ENS. In some cases, depending on the extent of previous surgery there may also be mucosal atrophy and crusting. In some cases, mucopurulent drainage from secondary infection of atrophic mucosa may also be present [16].

Diagnostic Cotton Test [2]

A diagnostic cotton wool test involves placing isotonic saline-soaked cotton in the widest area in the nasal cavity where the previous surgery was performed, for 20–30 min. It [2] has been hypothesised that cotton placement in ENS directs airflow to other functional areas of the upper airway which may explain the improvement in symptoms despite a lack of inferior turbinate pressure and thermoreceptors. A diagnosis of ENS is favoured if the patient feels their symptoms are better with the test. These patients would also be likely to benefit from surgical intervention. ENS-type patients have the most favourable response to this test as well as benefitting from surgery.

The cotton test has been validated [20] using the ENS6Q. The study demonstrated a significant correlation with cotton placement and ENS6Q scores. A positive cotton test with an improvement/reduction of ≥7 on the ENS6Q score is the threshold required to improve ENS symptoms. This may also guide surgical decision making as well as managing patient expectations.

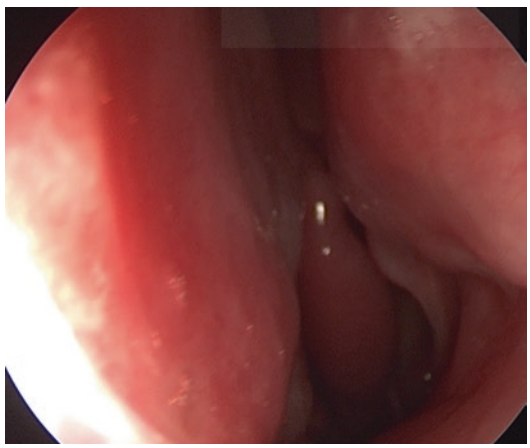

Fig. 47.1 Endoscopic image of the left nasal cavity in an ENS patient following inferior turbinectomy

Imaging

CT imaging may demonstrate widened nasal passages from previous surgery but does not add any diagnostic value. Hong et al. [21] demonstrated that reduced inferior turbinate volume is significantly associated with ENS symptoms; in particular nasal dryness. It may be useful in CFD studies to assess airflow and potentially target sites for surgical intervention.

Rhinomanometry

Rhinomanometry poorly correlates with perceived nasal patency and is not recommended as a diagnostic tool for ENS patients [5]. Although rhinomanometry is not useful in diagnosis it may be helpful in obtaining a baseline prior to any surgical intervention.

Management

Medical

Topical treatment with humidification, nasal saline sprays and emollients is the first line of

treatment. For those with severely debilitating symptoms and psychological manifestations, referral to psychosocial services is appropriate [16]. Menthol may also be added to lubricants as well as using cold humidifiers in doors.

Trigeminal training has demonstrated improvement in SNOT22 and NOSE scores in a small cohort of patients [5]. The regime involves smelling levomenthol and eucalyptol three times a day for at least 10 seconds over a minimum of 30 days. A particular improvement was noted in the nasal obstruction, sleep disturbances and emotional status parameters in the SNOT22. However, no improvement in ENS6Q scores was observed. As this is a non-invasive, low cost and quick intervention, it may be employed prior to considering surgical intervention.

As ENS has a significant burden on mental health and quality of life cognitive behavioural therapy may also have a role.

Surgical

Surgical intervention aims to recreate the anatomy in order for nasal physiology to return to normality. In essence, creating increased resistance and ability for greater air-mucosa interaction. The surgery also aims to deflect the airflow away from a somewhat insensate area toward 'virgin' or unoperated tissue [17]. It is recommended to wait at least 1 year after turbinate surgery prior to attempting surgical intervention [6, 22].

Table 47.3 Grafts used in turbinate reconstruction

Autografts/allografts	Biomedical implants
Conchal cartilage	Medpor (porous high-density polyethylene)
Costal cartilage	AlloDerm (non-cellular dermis)
Temporalis fascia	Silastic
Tutoplast (processed costal cartilage)	Hyaluronic acid gel
Fat	Nonporous β-tricalcium phosphate

Medpor (Porex surgical Inc., GA), Tutoplast (Tutogen Medical GmbH, Neunkirchen am Brand, Germany), Hyaluronic acid (Juvederm; Allergan Inc., CA), Nonporous β-tricalcium phosphate (SINUS UP; Kasios, Launaguet, France).

Autografts or biomedical implantable materials may be used for turbinate reconstruction [Table 47.3]. The ideal synthetic biocompatible material should have cartilage-like elasticity, be resistant to infection, and have immunologic inertness, so that it elicits a minimal foreign body reaction [17]. Injectable implants are of limited use as they tend to resorb and can spill into the surrounding tissues.

A transnasal approach with the placement of the graft in a submucosal plane is the commonest surgical technique. In IT and MT reconstruction, the implant is tunnelled into the submucoperichondrial plane of the septum or floor of the nose adjacent to the location of the former turbinate or submucosal plane in the case of a residual turbinate [6]. A subjective assessment on the size and thickness of the implant is made depending on the extent of reconstruction deemed necessary to increase nasal resistance. The primary objective is to narrow the nasal valve region. The implant is placed in layers allowing for gradual augmentation until the desired result is achieved followed by closure with a dissolvable suture.

A systematic review [22] reported postsurgical improvement in SNOT-20 and SNOT-25 scores in 103 patients from 48.3 and 65.9 to 24.4 and 33.3 ($p < 0.05$), respectively. In the eight studies included in the review, 47% used AlloDerm and Medpor and 38% used cartilage (autologous and tutoplast). SNOT subdomain analysis for 64 patients demonstrated the most significant improvement in the ENS and psychological sub-group. In a small subset of patients, no significant post-operative improvement was noted, and only mild post-surgical improvement was reported in 21% of patients.

No implant material was shown to be favourable, however, silastic had a higher extrusion rate and hyaluronic acid was resorbed at 12 months [22].

In a cohort of 20 patients who had Medpor implantation for ENS, Lee et al. [23] reported an improvement in depression and anxiety scores postoperatively ($p < 0.001$). Similarly, postsurgical improvements were seen in Beck Anxiety

Inventory (BAI) and Beck Depression Inventory (BDI-II) and SNOT-25 scores following Medpor implantation [19].

Chang et al. [24] demonstrated improvement in objective (Sniffin' Sticks 12-items odour identification test [SS-12]) and subjective olfaction rating following ENS surgery. This was most marked in younger patients. Interestingly, only 25% of the ENS patients in the study had detectable olfactory dysfunction on SS-12.

Complications of surgery include chronic rhinosinusitis, partial or complete absorption of implant, rejection, chronic infection and implant extrusion. In addition to this, some patients may require revision surgery in cases of under correction.

Surgery should be considered following careful assessment and a positive cotton test and ENS6Q score. Choice of surgical implant and technique should be made in accordance with surgical expertise and implant availability.

Conclusion

ENS is a rare diagnosis following previous nasal surgery. The combination of patient symptoms, validated ENS6Q score, cotton test as well as endoscopic and imaging adjuncts help reach a diagnosis. Treatment options include initial medical management as well as consideration for trigeminal retraining followed by surgical intervention in a selected group of patients. Further research to understand the neurosensory role of trigeminal receptors and the significance of psychological factors is needed to better understand and manage this condition.

Key Learning Points

- ENS is a rare postsurgical condition defined as a paradoxical sensation of nasal obstruction in an open nose.
- The severity of ENS is variable and can have a severe impact on mental health and quality of life.
- A combination of ENS6Q (subjective, >11), cotton test (objective) as well as endoscopic and CT findings lead to a diagnosis.
- Nasal lubricants and humidification are currently the mainstay of treatment.
- Surgical treatment with implants may improve patient symptoms.
- The impact on neurosensory disruption and its role in ENS patients is still poorly understood and an area in which greater research is needed.

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48 Management of Lacrimal and Orbital Disorders

Hisham S. Khalil and Marios Stavrakas

Applied Anatomy and Physiology

Anatomy

The pertinent and relevant anatomy of the orbit is illustrated in a close-up view of a model of the head (Fig. 48.1).

Orbital septum: The orbital septum comprises a diaphragm of tough fibrous bands that connect the orbital periosteum with the upper and lower eyelids. This septum supports the orbital contents within the bony orbit. The orbital septum limits the spread of infection and will initially contain infection within a pre-septal or post-septal compartment. It also forms a barrier to the spread of neoplastic disease.

Canaliculi: Lacrimal secretions drain through punctae in the medial aspect of the upper and lower eyelids to upper and lower canaliculi, that combine to form a common canaliculus, that subsequently drains into the lacrimal sac.

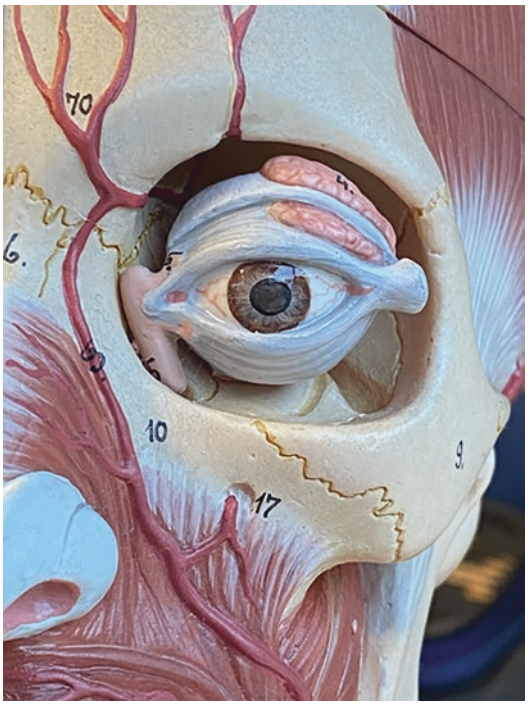

Fig. 48.1 An anatomical model illustrating the left orbit with the orbital septum removed. The blue area is part of the tarsus, and the space behind is the post-septal space of the orbit. The lacrimal sac is housed in the lacrimal fossa and leads to the nasolacrimal duct

H. S. Khalil (✉)
University Hospitals Plymouth NHS Trust, Plymouth, UK

University of Plymouth, Plymouth, UK
e-mail: hisham.khalil@nhs.net

M. Stavrakas
University Hospitals Plymouth NHS Trust, Plymouth, UK

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Lacrimal sac: Lacrimal sac lies in the lacrimal fossa. The fundus of the lacrimal sac is approximately 9 mm above the area of attachment of the middle turbinate to the lateral nasal wall (referred to as the middle turbinate axilla). It is important to expose this area during endoscopic dacryocystorhinostomy to achieve the optimum surgical outcome.

Nasolacrimal duct: The lacrimal sac drains into the nasolacrimal duct (NLD). The NLD lies within a bony canal created by the maxillary and lacrimal bones and opens below the inferior turbinate into the inferior meatus of the nasal cavity.

Lacrimal bone: The thin lacrimal bone is wedged between the thick frontal process of maxilla anteriorly and the uncinate process posteriorly. It supports the medial wall of the lacrimal sac posteriorly.

The area of the lamina papyracea behind the lacrimal bone is especially thin and easily damaged during endoscopic dacryocystorhinostomy (DCR).

The distal opening of the NLD into the inferior meatus is partially guarded by a mucosal valve, the valve of Hasner, that prevents reflux of air and mucus into the duct. The nasolacrimal duct is at risk of damage or being crimped whilst enlarging the anterior border of the maxillary sinus ostium during the middle meatal antrostomy.

Lacrimal Physiology

Lacrimal gland secretion forms a tear film over the conjunctiva, which spreads by the movement of the upper lid with blinking and gravity. Capillary attraction moves the tears into the punctae. The tear film drains via the canaliculi to the lacrimal sac and nasolacrimal duct. Blinking, cause by the action of orbicularis oculi, actively pumps the tears along the canaliculi into the lacrimal sac. The valve of Rosenmüller prevents the backflow of tears from the sac. The tears pass along the nasolacrimal duct to the nose valve of Hasner at the lower end of the NLD prevents reflux.

The Nasolacrimal System

Assessment of the Nasolacrimal System

Assessment of Nasolacrimal Disorders

Ophthalmological Assessment

A logical sequence to the assessment includes the following:

1. History of epiphora, pain and swelling in the inner aspect of the eye.
2. Observation for an increase ‘tear film’, redness and or swelling over the inner aspect of the eye.
3. Palpation of the lacrimal sac and expression of mucus/mucopus.
4. Slit Lamp examination to exclude pathology such as foreign bodies and keratitis if suspected from the history (Fig. 48.2).

Fig. 48.2 A mobile slit lamp used in the lacrimal clinic

5. Dilatation of the punctae in the eyelids.
6. Fluorescein dye test.
7. Syringing of the nasolacrimal system if the dye test is negative.

Relevant ENT Assessment

1. History of sinonasal symptoms and manifestations of rhinitis/rhinosinusitis.
2. History of trauma, eye surgery or conjunctivitis.
3. Nasal endoscopy to assess nasal patency (to determine ease of an endoscopic dacryocystorhinostomy approach/possible requirement for septal surgery), rhinitis, and other nasal pathology that may impact on nasolacrimal duct drainage, e.g. nasal tumours.

Imaging

Nasolacrimal imaging is highly selective and may be limited to the following scenarios:

- Planned elective DCR in patients with epiphora who have previously undergone Functional Endoscopic Sinus Surgery.
- Patients with suspected lacrimal tumours.
- Patients with suspected dacryocystitis/lacrimal mucocele where the diagnosis is uncertain.

CT Orbits and sinuses: The recommended initial imaging modality is a high-resolution CT scan of the sinuses and orbits.

Dacryocystography: This is now rarely used, especially since lacrimal syringing is often used as a routine in clinical practice.

MRI Orbits: However, in complex cases, it may be helpful to supplement the information from the CT scan with an MRI scan of the orbit and sinuses. Such situations may include patients with tumours or those with significant diagnostic uncertainty.

Disorders of the Nasolacrimal System

Epiphora and Dacryocystitis

Epiphora, or 'watery eye', is a symptom that can occur for several reasons:

- Increased production of lacrimal secretions that cannot be cleared fast enough by the lacrimal system. The secretions then run as tears across the cheek. Excess production may arise from conjunctival irritation by a foreign body, irritant,s or allergy.
- Lacrimal pump failure, as may occur with ectropion, or facial paralysis.
- Obstruction of the naso-lacrimal system.

The level of nasolacrimal obstruction may be before the lacrimal sac (pre-saccal), at the level of the lacrimal sac (saccal), or beyond the lacrimal sac (post-saccal).

Retention of mucus secretions is termed a mucocele of the lacrimal sac.

Dacryocystitis refers to inflammation of the lacrimal sac that may escalate to infection.

Epiphora, mucocele, or dacryocystitis usually occur due to obstruction of the nasolacrimal duct. Nasolacrimal obstruction may arise from trauma, stones in the lacrimal sac, mucosal oedema related to sinusitis, or from surgery to the nose or sinuses.

Clinical Features

Acute dacryocystitis presents with pain, swelling, redness, and tenderness over the area of the lacrimal sac/inner canthus below the medial palpebral ligament.

Chronic dacryocystitis is more commonly associated with recurrent mucopurulent discharge and regurgitation of secretions from the punctae on digital pressure applied to the lacrimal sac.

Differential Diagnosis of Dacryocystitis

The differential diagnosis of dacryocystitis includes facial cellulitis, pre-septal and post-septal orbital cellulitis, mucocele of the lacrimal sac, mucocele of the frontal and ethmoidal sinuses, and tumours of the lacrimal sac.

Lacrimal Stones

Lacrimal sac stones or dacryoliths of the nasolacrimal system are fairly common. They can occasionally be expressed through the lid punctae by pressure on the lacrimal sac or encountered during a DCR procedure. They are often associated with *Actinomyces* spp. infection.

Lacrimal Tumours

Tumours of the lacrimal sac are rare. They are best divided into epithelial and nonepithelial tumours both of which may be benign or malignant.

Benign tumours include squamous papilloma, transitional cell papilloma, fibrous histiocytoma, and oncocytoma. Glomangiopericytoma is a tumour with a spectrum that ranges from benign to malignant features.

Malignant tumours include squamous cell carcinoma, adenocarcinoma, transitional cell carcinoma, lymphoma, and melanoma. Benign tumours tend to occur in young adults and malignant tumours in elderly patients. Lacrimal sac tumours often present as recurrent dacryocystitis associated with a lacrimal mass in the medial canthus. Their management should involve an orbital surgeon in association with input from the Head and Neck Multidisciplinary team (MDT).

Management of Nasolacrimal Disorders

Treatment of Dacryocystitis

The treatment includes gentle lid hygiene (using a cotton bud dipped in cooled boiled water to remove debris/crusting between eye lids and lashes), chloramphenicol eye drops or ointment, and a systemic antibiotic such as co-amoxicalv (amoxicillin/clavulanate), or a macrolide, such as erythromycin, if the patient is allergic to penicillin.

Management of Nasolacrimal System Obstruction

The procedures offered for treatment of nasolacrimal obstruction include:

- Syringing.
- Nasolacrimal intubation.
- External dacryocystorhinostomy.
- Endoscopic dacryocystorhinostomy.

Lacrimal syringing: Syringing is performed after applying local anaesthetic drops to the eye. The inferior punctum is cannulated with a sterile fine lacrimal cannula. The cannula is initially inserted vertically for 2 mm, the lower lid is then retracted laterally to straighten the canaliculus. The cannula is gently advanced in a medial direction until it stops. The stop is either soft, indicating tissue between the canula and the bone, or hard, which implies that a false passage has been created outside of the lacrimal system.

The patient is sat upright in a semi-recumbent position with the head supported during the procedure. They are asked to look away during this process to protect the cornea from inadvertent damage and asked to if, and when, they taste the saline irrigation.

The system is then gently irrigated with saline in a 2 mL syringe connected to the cannula. Should the patient taste the saline, the NLD must be patent. Saline may also exit via the superior punctum, indicating that this section of the system remains unblocked. The process can be repeated via the upper punctum.

It is most important to avoid causing tissue trauma during this procedure, as the resulting soft tissue swelling will make it impossible to cannulate the punctum, should this occur.

External Versus Endoscopic Dacryocystorhinostomy (DCR)

DCR is traditionally offered to patients with obstruction at the level of the lacrimal sac or the nasolacrimal duct. It is not an effective procedure for patients with pre-saccal obstruction, such as canaliculi or common canaliculus stenosis.

The level of obstruction can usually be determined through syringing. With a common cana-

Table 48.1 Comparison between endoscopic and external DCR surgery

Advantages of endoscopic DCR	Advantages of external DCR
Active lacrimal infection does not contraindicate surgery	Enables a wider naso-lacrimal neo-ostium
Preserves pumping mechanism of orbicularis oculi	Reported success rate slightly higher
More effective for revision DCR surgery where adhesions may obstruct the naso-lacrimal neo-ostium	
Generally less bleeding compared to external surgery	
Avoids injury to medial canthus and/or pathologic scar formation	
Correction of associated nasal pathology	
No external scar	

licular obstruction, there is a prompt regurgitation of saline from the lower canaliculus when the upper canaliculus is syringed and vice versa. This is not the case with more distal obstruction. With partial obstruction of the nasolacrimal system, there is some resistance encountered in syringing and before the patient can detect and taste saline in their mouth.

The choice of external versus endoscopic DCR should be based on patient choice, local surgical expertise, and the type of any previous DCR procedure.

It is the senior author's practice to offer patients requiring revision surgery an alternative procedure from what they had previously experienced, such as an external DCR if they had an endoscopic DCR and vice versa.

The quoted success rates in the literature for external DCR are slightly higher than endoscopic DCR [1].

A comparison between endoscopic DRC and external DCR is provided in Table 48.1.

Surgical Management of Pre-saccal Obstruction

Pre-saccal obstruction due to common canaliculus obstruction is an ophthalmic procedure.

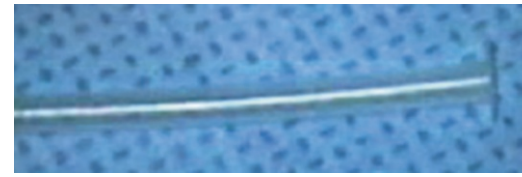

Fig. 48.3 Lester-Jones tube

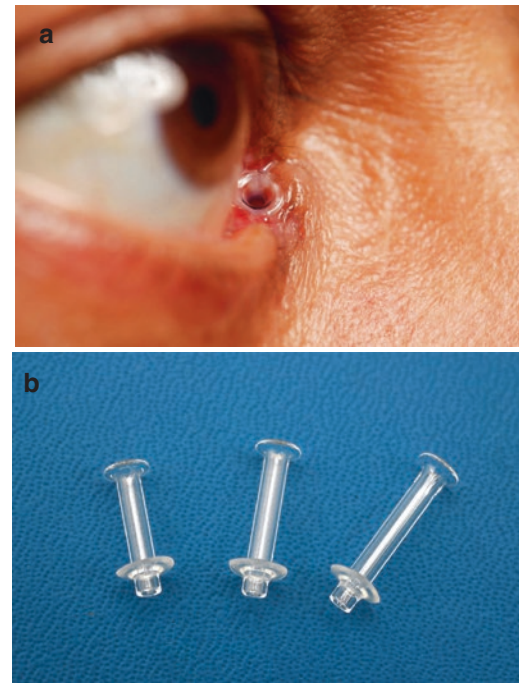

Fig. 48.4 (**a**) Stopless-Jones tube in-situ at the medial canthus of the left eye. (**b**) Stopless-Jones tube with distal flange for stability

A glass Lester-Jones tube is inserted between the medial canthus and the nasal cavity to bypass the common canalicular obstruction. The Lester-Jones tube is fixed by a temporary suture (Fig. 48.3) The Stopless-Jones tube is a recent modification that is stabilised by a flange (Fig. 48.4 a,b).

Endoscopic DCR Procedure

This operation can be carried out under general or local anaesthesia, particularly if the patient is unfit for a general anaesthetic.

Local Anaesthesia and Vasoconstriction

1. Topical co-phenylcaine applied to the nasal passages.
2. 1:10,000 adrenaline neurosurgical patties applied to the middle meatus and area anterior to the attachment of the middle turbinate to the lateral nasal wall.
3. Infiltration with 2% xylocaine:1,80,000 adrenaline at the 'axilla' area of the middle turbinate, over the frontal process of maxilla, lacrimal bone and uncinate process.

Surgical Procedure

1. Illumination of the lacrimal sac with a vitreo-retinal light pipe inserted through the lid punctum is optional but preferred by the senior author (Fig. 48.5).
2. Reflection of a posteriorly based rectangular mucosal flap to expose the bone covering the medial wall of the lacrimal sac (Fig. 48.6).
3. Removal of the bone covering the medial aspect of the lacrimal sac (frontal process of maxilla and lacrimal bone) with a Kerrison rongeur.
4. Incision of the medial wall of the lacrimal sac and excision of most of the medial wall (marsupialisation).

Placement of a Stent

Insertion of an O'Donoghue silastic stent (Fig. 48.7). This should be stabilised whilst avoiding tension in the medial canthus. A vascular clip or Watski sleeve is used to keep the limbs of the stent together to prevent subsequent displacement.

Controversies in the Treatment of Epiphora Due to Saccal and Post-saccal Obstruction

There are a number of controversies in the treatment of epiphora due to nasolacrimal system obstruction:

Removal of bone to expose the lacrimal sac: During endoscopic DCR, the bone of the frontal process of maxilla is removed to expose the sac.

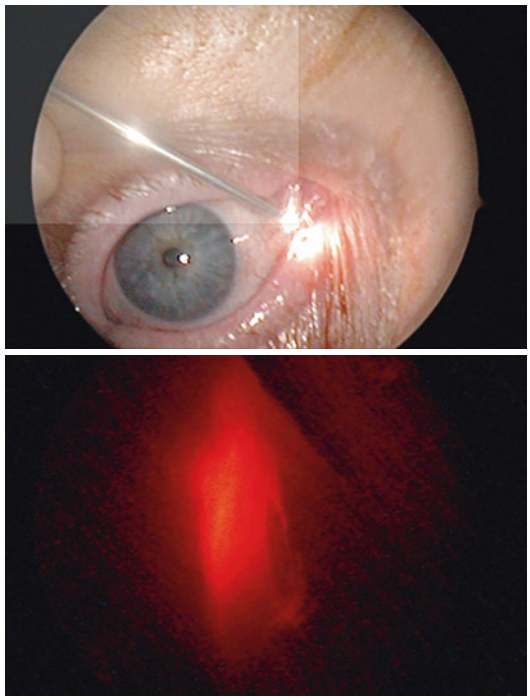

Fig. 48.5 Illumination of the right lacrimal sac using a vitreo-retinal light pipe introduced through a lid punctum

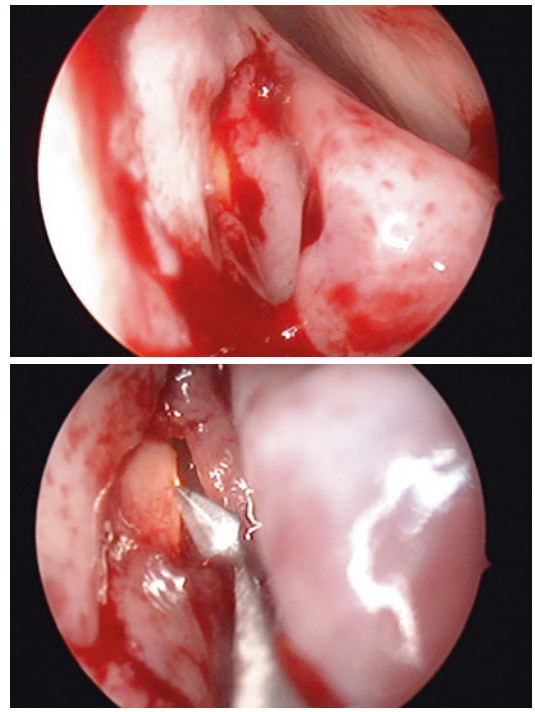

Fig. 48.6 Mucosal flap displaced inferiorly exposing the bone covering the medial aspect of the right lacrimal sac and incision of the medial wall of the lacrimal sac

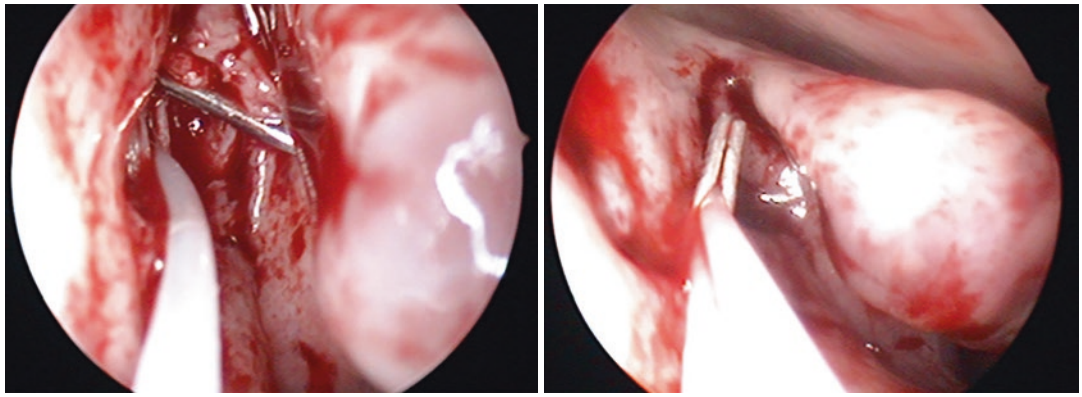

Fig. 48.7 Insertion of silastic stent and vascular clip applied

Bone can be removed with a Kerrison rongeur, endoscopic drilling with a diamond burr or a dedicated DCR burr, a sharp chisel or a KTP or Holmium Laser.

Lacrimal sac drainage: Once the lacrimal sac is exposed, it is then accessible to drain and form a lacrimal fistula. There are a number of variations possible that range from complete removal of the medial sac wall to the fashioning of medial wall flaps.

There is no conclusive evidence to suggest the superiority of one technique over another, with the exception of the use of Laser. Laser became the preferred technique many years ago, but subsequent scrutiny of outcomes showed that Laser surgery is associated with late stenosis of the naso-lacrimal neo-ostium and higher failure rates.

Whether or not to insert a silastic stent and the duration of stenting remains as a further area of controversy.

In the senior author's practice, we use Kerrison rongeur to remove the bone medial to the lacrimal sac. This is a quick procedure and avoids 'overheating' the bone that may occur with the use of a DCR drill. We then marsupialise the lacrimal sac by removing the medial sac wall. A silastic stent is then inserted with the limbs of the stent kept together by a vascular clip or a Watski sleeve. The silastic stent is removed approximately 8 weeks after surgery, when healing has occurred.

The Orbit

Orbital Complications of Rhinosinusitis

Orbital complications of rhinosinusitis are rare and should be managed as an ENT emergency. The incidence of orbital complications is higher in the paediatric population and is encountered more in tertiary referral centres.

Bacterial pathogens include *Haemophilus influenza*, *Streptococcal* spp., and *Staphylococcus aureus*.

These complications are traditionally categorised according to anatomical site and severity:

- Anatomical site: Pre-septal/periorbital—vs.—post-septal/orbital
- Severity: Cellulitis/subperiosteal abscess/intra-orbital abscess

The most severe but the rarest complication is intracranial cavernous sinus thrombosis.

The most accepted classification of the orbital complications is that described by Chandler (Table 48.2).

Clinical Features: A detailed review and an ophthalmological assessment is recommended. Specific features include the presence or absence of proptosis, limitation of ocular movement, conjunctival injection/chemosis, and direct and indirect pupillary reflexes. An afferent pupillary defect should be excluded.

Table 48.2 Chandler's classification of orbital infections

Chandler's stage	Clinical stage
I	Preseptal cellulitis
II	Orbital cellulitis
III	Subperiosteal abscess
IV	Orbital abscess
V	Cavernous sinus thrombosis

Loss of colour vision (tested by an Ishihara Chart) is one of the early signs or a threat to vision.

Assessment can be particularly challenging in children and where it is difficult to assess the eye and pupillary reflexes due to an inability to separate swollen closed eyelids.

Imaging: A CT scan of the sinuses with contrast is the investigation of choice.

Management: The care of patients with orbital complications/infections is best carried out by a multidisciplinary team comprising an otolaryngologist, an ophthalmologist, a microbiologist, and a paediatrician if the patient is a child [1].

Surgical drainage is indicated in the presence of a subperiosteal abscess. The classical approach to drainage of a subperiosteal abscess is via an external approach (Lynch/Seagull incision). The periosteum over the medial orbital wall, along the fronto-ethmoidal suture, is reflected whilst the orbital contents are gently retracted. This dissection is best assisted using a nasal endoscope. After drainage of the pus, a communication is established with the nasal cavity through the lamina papyracea, and an external Yates drain is inserted in the medial orbital compartment. Alternatively, experienced endoscopic sinus surgeons can drain pus in the medial orbital compartment endoscopically by opening the anterior and posterior ethmoid cells and removing the lamina papyracea to facilitate good drainage.

Cavernous sinus thrombosis is rare but life-threatening. Diagnostic delay must be avoided.

Treatment includes urgent intravenous broad-spectrum antibiotics, in accordance with microbiological advice and neurosurgical input.

Controversies in the Management of Orbital Complications

Drainage of subperiosteal abscess: The classical approach to draining a subperiosteal abscess was external surgery via a skin incision. However, incisions can now be placed through the conjunctiva and thus prevent an external scar.

The biggest controversy is now between endoscopic drainage versus external drainage. In most specialist centres, the endoscopic technique is preferred. However, this differs within the UK. This is probably best explained by our UK healthcare system and the fact that on-call systems in the UK do not permit a sinus endoscopic surgeon being always available for emergencies. Endonasal endoscopic surgery in an acute inflamed situation can be technically challenging and not all ENT surgeons would feel comfortable with this situation, especially within small nasal cavities in young children.

A subperiosteal abscess in the child is another area of controversy. Whilst most abscesses will be drained in theatre, there is evidence to show that a small abscess may respond to IV antibiotics without the need for surgery. Should this strategy be chosen, very careful ophthalmological and ENT regular assessment is essential.

Cavernous sinus thrombosis: The optimum management of cavernous sinus thrombosis is also controversial. The use of anticoagulants is variable and dependent on the experience and philosophy of the caring team and the patient profile.

Orbital Tumours

The management of orbital tumours is complex, and this has to do with the various pathologies and the numerous surgical approaches. A multidisciplinary approach is essential. All cases should be discussed by the head and neck multidisciplinary team (MDT). If surgery is indicated, the appropriate surgical team should include an orbital surgeon in combination with a rhinological surgeon, neurosurgeons, maxillofacial surgeons, and plastic surgeons, according to the local set-up.

Several studies have analysed the diverse pathologies and the characteristics of orbital tumours. Most lesions are extraconal. Malignant

tumours represent 32–63% of all tumours; benign are found in 35–68% of patients. Lymphoma is the most common malignant tumour and cavernous haemangioma is the most prevalent benign pathology. Patients over 60 years old typically present with a malignant tumour; patients less than 60 years old normally present with benign tumours (Fig. 48.8) [1–6] (Table 48.3).

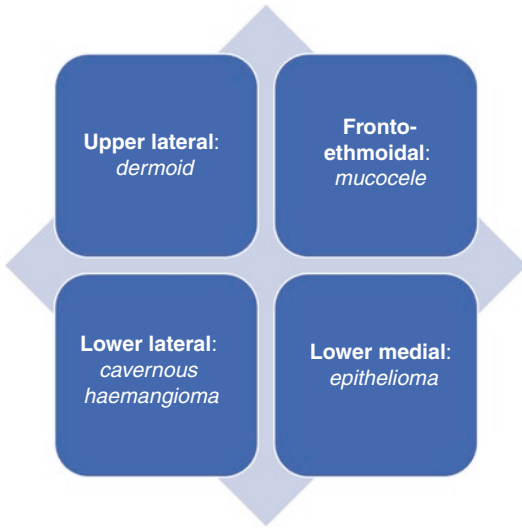

Fig. 48.8 Most common orbital tumour pathology according to anatomical location within the orbit [3]

Surgical treatment varies depending on the location, pathology, and expertise. In general, tumours located medially and infero-medially can be managed with endonasal endoscopic approaches. It is of interest that the rate of extraocular muscle paralysis has been higher for medial orbital approaches than lateral approaches [4].

Grave's Orbitopathy

Grave's orbitopathy (GO) is the primary extrathyroid manifestation of thyroid disease, with a significant impact on quality of life. It is a challenging pathology to treat, as the pathogenic mechanisms are not completely clear; hence the available treatments are not always pathology specific.

Pathophysiology: Although the pathophysiology remains unclear, it is known that fibroblasts play an essential role in the pathogenesis of GO. Activation of orbital fibroblasts that express insulin-like growth factor-1 receptor (IGFR-1) and thyrotropin receptor leads to the production of pro-inflammatory cytokines. This leads to increased production of hyaluronan, and its deposition in combination with increased adipogenesis results in the enlargement of orbital soft tissues. Finally, hypertrophy of the extraocular

Table 48.3 Common histopathological subtypes [7]

Histopathology	Subtypes	Comments
Pseudotumours	Lymphoid type (majority)	Can be a cause of proptosis at any age
Dermoids		Generally present during the second decade of life
Vascular tumours	Haemangioma Glomangiopericytoma Haemangioendothelioma	Protrusion of eye, diplopia, palpable swelling, limited ocular movements
Optic nerve tumours	Intraorbital meningioma Optic nerve glioma	Axial proptosis, defective pupillary reaction, papilloedema, optic atrophy
Mesenchymal tumours	Lipoma Fibroma Fibrosarcoma Rhabdomyosarcoma Leiomyoma	
Peripheral nerve tumours	Neurilemoma Neurofibroma Plexiform neuroma	
Epithelial tumours	Pleomorphic adenoma Adenoid cystic carcinoma Mucoepidermoid carcinoma	

Table 48.4 Grave's Orbitopathy (GO) activity according to *Clinical Activity Score* (CAS)

1	Spontaneous retrobulbar pain
2	Pain on attempted upward or downward gaze
3	Redness of eyelids
4	Redness of conjunctiva
5	Swelling of caruncle or plica
6	Swelling of eyelids
7	Swelling of conjunctiva (chemosis)

Inactive = CAS < 3, Active = CAS ≥ 3

muscles and expansion of the orbital fat results in the characteristic strabismus, eyelid retraction, and proptosis [8].

Management: Regarding patient management and treatment of GO, the European Association/European Group of Grave's Orbitopathy published guidelines in 2016, focusing on a patient-orientated approach, always following the multidisciplinary team (MDT) decision-making principles. Assessment of the activity and severity are significant steps, and the clinician has to follow the clinical activity score as demonstrated in the following table [9]. Severity ranges from mild, moderate to severe or sight threatening (Table 48.4).

Basic principles of management are smoking cessation, as the association of smoking with GO is well established, restoration of euthyroidism, and local measures of eye care.

The general practitioner should consider referring most cases (except very mild GO) to dedicated centres with relevant expertise. The treatment recommendations of the European Group on Grave's Orbitopathy, as based on the severity, are summarised below:

Mild GO

- Local treatments, general measures to control risk factors, selenium supplementation.

Moderate to Severe GO

- For active GO, high-dose intravenous steroids.
- For inactive GO, rehabilitative surgery if required.

Sight-Threatening GO

- High-dose intravenous steroids ± surgical decompression [9].

Other available treatment modalities include Rituximab, Tocilizumab, and Teprotumumab, with encouraging results in controlling disease activity [8].

Finally, when it comes to decompression surgery, there are various techniques described, and they all aim to enlarge the bony orbit or remove an amount of orbital fat. Our practice includes endoscopic medial or medial and inferior orbital decompressions. We aim to relieve the pain and reduce intraocular tension and improve the other sequelae of GO, such as strabismus and postural visual obscuration [9].

The Joint Lacrimal Clinic

It is the senior author's practice to hold a regular combined lacrimal/rhinology clinic and have a joint lacrimal clinic in our institution where patients are referred for consideration of lacrimal surgery. Patients are normally referred by other ophthalmologists, ENT surgeons or directly by general practitioners and then triaged to the clinic. The clinic is run jointly by a rhinologist and ophthalmic, oculoplastic surgeon. There are facilities for nasal endoscopy, syringing, fluorescein dye test, and a mobile slit lamp.

Key Learning Points

- Knowledge of the differential diagnosis and treatment of lacrimal and orbital disorders is within the realms of rhinologists and ENT surgeons.
- Orbital complications of rhinosinusitis are a medical emergency and patients should be admitted to hospital, investigated, and treated promptly.
- Epiphora and dacryocystitis occur due to obstruction of the nasolacrimal system which may be pre-saccal, saccal, or post-saccal.

- Endoscopic DCR has high success rates that almost match external DCR procedures in published series.
- An MDT approach is recommended for the effective, evidence-based management of lacrimal and orbital disorders.

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49 Rhinological Dilemmas and Questions from Clinical Practice

Stephen P. Williams and Andrew C. Swift

Introduction

Whilst most specialist rhinologists are likely to have a very expansive knowledge of their chosen subspecialty, there are some areas commonly seen in routine clinical practice where a clear evidence-based understanding is still elusive. We have focused on a few such topics within this chapter with the aim of elucidating some clarity of thought or stimulating further interest and research.

As an ever-evolving speciality, we are both aware and hopeful that ongoing research and development may well confirm or refute what follows but we will weigh the current evidence base and propose management strategies, making recommendations based on both this and clinical experience.

Steroid Use for Sinonasal Disease

Corticosteroids take their name from their site of physiological production: the cortex of the adrenal gland. Of the two main types of corticosteroids, glucocorticoids and mineralocorticoids, it is synthetic analogues of the former which are widely used in rhinology, primary for their anti-inflammatory and immunosuppressive actions. Indeed, the phenotypic descriptions of both primary chronic rhinosinusitis (CRS) and allergic rhinitis are one of a chronic inflammatory disorder and so glucocorticoid treatment in both conditions aims to decrease mucosal inflammation within the sinonasal cavity.

Systemic Corticosteroids

Systemic corticosteroids are usually prescribed for oral use in the setting of rhinological disease and have been shown to be effective at reducing symptom burden in patients with CRS [1].

Whilst often effective, it is extremely important to consider other medical disorders that may contravene their use, such as previous steroid psychosis, diabetes mellitus, anticoagulation with warfarin and previous adrenal insufficiency.

Their use is usually confined to short courses given concerns over their side effects. These include changes in mood, glaucoma, hyperglycaemia, hypertension, insomnia, peptic ulceration and weight gain. Bone demineralisation and osteoporosis is a recognised concern in patients receiving prolonged systemic steroid therapy and has been frequently reported with use in other inflammatory conditions. Whilst it is challenging to truly extrapolate such findings (by excluding disease-specific processes in each setting), it has

S. P. Williams (✉) · A. C. Swift
Liverpool Head and Neck Centre, Liverpool University Hospitals Foundation Trust, Liverpool, UK
e-mail: spwilliams@doctors.org.uk

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been shown that in patients with CRS receiving more than three short courses of high-dose systemic steroids per year, roughly one in ten will demonstrate signs of osteoporosis [2].

Whilst the application of short courses of oral corticosteroids is well-established practice in the medical management of CRS, there exists no uniformity regarding the regimen prescribed. The most recent Cochrane review noted a large degree of heterogeneity in both the choice of corticosteroid (with methylprednisolone, prednisolone and prednisone all prescribed) and in dosage (with daily dosages ranging from 25 mg/day to 60 mg/day of prednisolone, or equivalent) [1].

Moreover, the length of treatment also varies between institutions—generally between five and 21 days. To date, there is no comparative study which has made a compelling argument as to the benefits of one regimen over another but, importantly, it has been noted that seemingly irrespective of dosage or treatment length, beneficial effects wane with time, with no sustained effect demonstrable at 6 months [1].

After prolonged use, a tapered reducing dosing schedule is usually necessary to safely reverse the suppression of the hypothalamic-pituitary-adrenal axis. Again, there exists variation in when a tapered dose is instigated, and the manner in which this is done. Within the United Kingdom (UK), the British National Formulary (BNF) advise a reducing schedule for any patient who has received greater than 40 mg prednisolone for more than 7 days or those who have received more than 3 weeks of treatment, irrespective of dose [3].

Topical Nasal Steroids

The use of topical intranasal glucocorticoids finds its place established in the paradigm of therapy for both CRS and allergic rhinitis and aims to minimise the side effects incurred with systemic steroid use. As with the use of systemic steroid use, however, there is a wide range in practice with aerosol devices, aqueous nasal sprays, and topical nasal drops all in regular usage. A variety of different agents are also available, as listed in *Table 49.1*.

All topical intranasal corticosteroids seem to be beneficial in the setting of CRS though recommended treatment regimens are usually of a minimum of 3–6 months. One of the main factors for success is consistent daily use and applying the correct administration technique, both being important things to consider in patients who fail to respond to treatment.

The main side effect of note is epistaxis which seems to increase in risk with stronger preparations. Of the agents listed in Table 49.1, all have been found to be safe during both pregnancy and breastfeeding other than triamcinolone which is associated with respiratory tract abnormalities [4]. Raised intraocular pressure is an unusual side effect of INCS sprays, but this has not been demonstrated with second-generation steroid sprays. Occasionally, patients may experience a burning sensation during use, most likely to be caused by sensitivity to excipients, especially benzalkonium chloride.

Table 49.1 Topical intranasal corticosteroids (INCS) sprays and drops (Dosage listed for adults as per British National Formulary, BNF, guidance)

Nasal sprays	Dose
First generation INCS	
Beclometasone dipropionate	50 mcg/dose; 1–2 sprays each side, once or twice daily
Budesonide	64 mcg/dose; 1–2 sprays each side, once daily
Triamcinolone acetonide	55 mcg/dose; 1–2 sprays each side, once daily
Second generation INCS	
Fluticasone furoate	27.5 mcg/dose; 1–2 sprays each side, once daily
Fluticasone propionate	50 mcg/dose; 1–2 sprays each side, between once and twice daily
Mometasone furoate	50 mcg/dose; 1–2 sprays each side, between once and twice daily
Nasal drops	**Dose**
Betamethasone sodium phosphate	0.1% solution; 2–3 drops each side, two to three times daily
Fluticasone propionate	0.1%; each container provides 400 mcg; 1 container between both sides, once to twice daily)

Caution does need to be applied with the dose of betamethasone drops as these are very effective and this can encourage excessive use in patients with severe symptoms. However, the systemic absorption of betamethasone is relatively high, and prolonged use may lead to natural steroid suppression [5]. This contrasts with the use of newer second-generation INCS sprays, such as those containing fluticasone or mometasone furoate which have a much lower bioavailability and so are considered appropriate for use in paediatric groups.

There is no good evidence to propose one type of intranasal steroid is superior, irrespective of agent or whether delivered as spray, aerosol or as nasal drops [6]. Other inflammatory nasal conditions, such as allergic rhinitis, have seen the introduction of more novel steroidal agents in recent times—with the use of a combination preparation of intranasal azelastine and fluticasone propionate having a significantly faster onset of action than other agents [7].

Unfortunately, no new steroidal agents have been introduced for some time and attention has subsequently shifted to optimising the method of delivery.

Delivery Systems

The main delivery system for administering topical medication within the nose is the nasal spray. What is known is that the penetration of these sprays is very limited with their distribution largely confined to the anterior nasal cavity around the septum, inferior turbinate and head of the middle turbinate.

Accordingly, attempts have been made to modify delivery techniques for topical steroids, particularly with their use as an additive in high-volume saline irrigation.

Novel intranasal medicinal delivery systems are emerging and have recently been developed. Examples include the EDS-FLU (Exhalation Delivery System with Fluticasone) and the IC-MDFD (Intranasal Cleaning & Medicinal Delivery Flush Device; NADU™). The EDS-FLU system aims to improve topical corticosteroid delivery over conventional sprays and drops, particularly in the setting of CRSwNP. The IC-MDFD is an Australian innovation that aims to improve patient-specialist treatment management through the use of personalised premeasured dosages for self-delivery through a combination of inhalation and irrigation therapy (Fig. 49.1). This delivery method offers options for an array of water-soluble medications, including pain relief or corticosteroids. Whilst this delivery system and the EDS-FLU system have been shown to be effective, comparative studies are required to assess if they are better than conventional therapies [8].

Fig. 49.1 Intranasal Cleaning & Medicinal Delivery Flush Device (NADU™)

Saline and the Nose

Nasal saline irrigations are an evidence-based treatment for the management of rhinitis and rhinosinusitis [9]. Though their exact mechanism of action remains unclear, logical proposals posit that a combination of reducing antigens and inflammatory mediators, mucus clearance and an improvement in ciliary beat frequency may all play a part. Due to the low cost and wide availability, saline irrigations have been quickly adopted within treatment pathways for CRS and are well tolerated by patients [10].

Saline Preparations

Nasal saline comes in a variety of different preparations from an array of different manufacturers but can generally be divided into those of low volume (in the form of either saline drops or sprays) and those of large volume (which are referred to as either rinses, irrigation, lavage or douche). Likely as a consequence of the sheer variety of preparation and delivery mechanisms, Cochrane review reported that it was not possible to weigh the effect or indeed suggest whether one method could be proposed above others [11].

Saline solutions also differ in their concentration. The decongestant properties of hypertonic preparations had been proposed as an alternative to sympathomimetic treatment though the summated results from comparative studies to date seem to suggest that isotonic solutions have proven to be a more effective preparation for reducing symptom burden in CRS.

Attention has also been drawn towards the use of hypotonic preparations, based on knowledge of the impact of sodium concentration of local immune function.

Current Research on Low-Sodium Nasal Rinses

(Information from Professor Simon Carney, University of Adelaide)

Current research has shown that lysozyme is the largest secretory component of the innate immune system and has proven bactericidal and fungicidal properties [12]. It kills bacteria and fungi via several mechanisms, including enzymatic action and ionic action against the cell wall [13]. This latter action requires a low-Na^+ environment to function effectively, and this is found in the peri-cellular area of the nasal mucous membrane blanket.

In-vitro experiments have demonstrated that commercially available saline irrigation solutions inhibited the natural killing activity of lysozyme [14]. By replacing the Na^+ with other ionic molecules, but still retaining isotonicity, new modified irrigation solutions have been created. In an RCT following endoscopic sinus surgery, a modified Ringer's lactate solution demonstrated better mucosal healing and SNOT scores when compared to isotonic saline and a hypertonic saline solution [15] Furthermore, as yet unpublished work has looked at the nasal proteome at baseline and after 14 days of saline and low-salt isotonic irrigations. Both solutions seem to 'prime' the nasal mucosa to produce more innate peptides after irrigation, with the low-Na^+ solution providing the best benefit with a 211% increase in lysozyme when compared to isotonic saline at 14 days.

Saline with Additives

Whilst saline rinses have become established as an effective mode of therapy in sinonasal disorders, the addition of agents such as steroids has gained much support. However, the addition of medications to saline is not a new concept. This form of therapy was proposed by WEG Thudichum in the late nineteenth century. Thudichum (who also designed the well-known nasal speculum) described regular rinsing with a range of additives according to the disorder being treated (Fig. 49.2) [16] (*Thudichum Queens Jubilee Hospital Monograph 1892*). These additives included deodorant substances (common salt, phosphate of soda, phosphate of ammonia, soda and permanganate of potash) as well as medicinal solutions (alum, sulphate of zinc and copper, nitrate of silver, bichloride of mercury, chloride of calcium with oxide of mercury, cocaine, Eau de Cologne).

Current day practice includes the effective use of topical steroids mixed with the saline delivery system. Indeed, it has been demonstrated that when mometasone furoate was used as an additive to a conventional bottle of a sinus rinse (Santa Rosa, CA, USA) and that it had a significant benefit over the use of the two agents separately, in terms of endoscopic, radiologic and patient symptom burden (Sino-Nasal Outcome Test-22; SNOT-22) at 12 months [17].

Budesonide is also widely used as an additive in saline irrigation. Whilst there are no studies

making direct comparison of its efficacy versus more conventional methods of topical corticosteroid use, it has been shown to be safe for sustained use with no significant derangements detected in cortisol levels on testing [18]. Whilst combined budesonide/saline rinses are effective and well-established internationally for use in treating chronic rhinosinusitis, it is expensive and unlicensed within the UK. Fluticasone propionate solution can be used as an alternative additive in this situation.

A number of alternative additives have been considered, though initial hopes around the potential benefits of surfactants (such as those found in baby shampoo) and Manuka honey have not been supported by research to date [19, 20]. Recent work has explored roles for agents such as xylitol and mupirocin though the benefits of each remain unclear [21]. Indeed, based on the current evidence base, it has been recommended that the use of novel additives should be limited to use within the research setting.

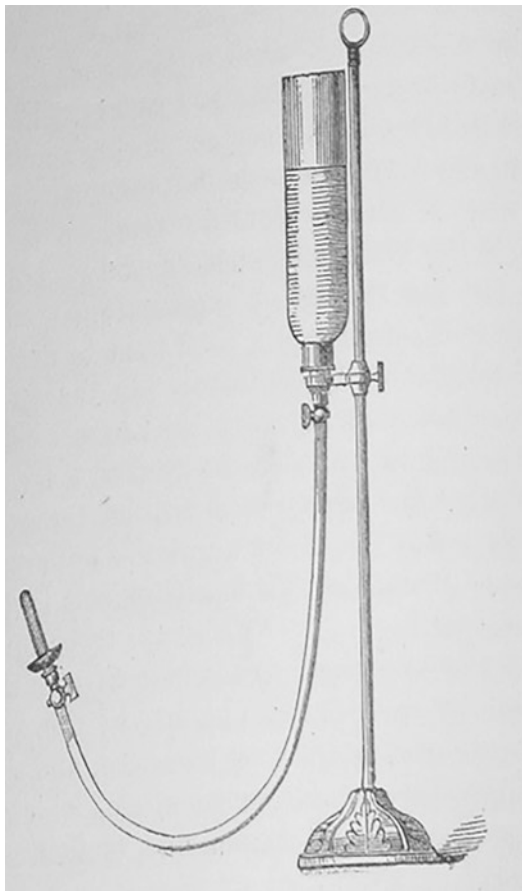

Fig. 49.2 Saline irrigation system devised by WEG Thudichum, 1892

The Anterior Localised Mucosal Atrophy and Septal Ulcer

Within the nasal cavity, mucosa septal insult can present as a spectrum ranging from atrophic mucosa, ulceration, or even full-thickness perforation, based on the extent and depth of injury. Although poorly defined, the term atrophy generally denotes the more superficial thinning and erosion of the mucosa and submucosal layers with ulceration used to describe deeper erosion of the perichondrium or nasal septal cartilage itself. The majority of pathologies responsible for mucosal atrophy and ulceration are also responsible for nasal septal perforation which is discussed in detail elsewhere in this text. Though more generalised atrophy, involving the majority of mucosa within the nasal cavity, can be seen in many patients with forms of rhinitis, the localised region of nasal septal atrophy (or ulceration) can often be a concerning finding on examination, which though it has a broad differential, includes more concerning pathology such as malignancy (see Table 49.2).

Isolated septal atrophy and ulceration are most commonly found anteriorly. Nasal trauma, from over-zealous repetitive digitation of the nasal cavity, is likely the most common precipitant and the major-

Table 49.2 Causes of nasal septal atrophy and ulceration

Domain	Possible causes
Idiopathic	
Trauma	Nasal digitation, external trauma, nasal surgery
Infection	*Staphylococcus aureus*, *Mycobacterium tuberculosis*
Inflammatory disorders	SLE, GPA, eGPA, sarcoidosis, Crohn's disease
Neoplasia	T-cell lymphoma, squamous cell carcinoma
Irritants	chrome, lime, cocaine

ity of such injuries will be incurred anteriorly. Furthermore, the anterior nasal septum is exposed to a greater degree of turbulent airflow, which will have a deleterious and exacerbating effect on dryness and crust formation in patients with established breach of mucosa. It will also be exposed to a greater burden of irritant when carried within inspired nasal airflow with those involved in the industry using chrome compounds particularly at risk [22].

Though concerns have been expressed as a potential link between intranasal corticosteroid use and mucosal atrophy, there is no evidence to support this in the literature [23].

Much of what will guide the treating rhinologist towards the likely aetiology may well be apparent in the history. The patient who acknowledges a compulsion towards nasal digitation or those who have had significant nasal trauma or previous nasal surgery will likely indicate a traumatic cause. Similarly, patients with occupational risk factors or those with recreational drug use may support irritants as the precipitator of ulceration. In the setting of immunosuppression, invasive fungal disease should be considered, but additional definitive features would be expected.

Despite the myriad of potential aetiologies driving nasal atrophy and ulceration, concerns over possible malignancy have prompted many institutions to favour biopsy as their investigation of choice. In the absence of other concerning clinical features (such as exophytic features or associated lymphadenopathy), we would not advocate such an approach initially and this is borne out in other series which suggest that it is very rare that histological results are of great use for either diagnosis or guiding further investigation or management [24].

Laboratory testing is often more fruitful and testing for inflammatory and vasculitic conditions (such as SLE, GPA, eGPA, sarcoidosis and tuberculosis) should be considered in these cases. Of particular note, rhinologists practicing in areas endemic for TB should consider lupus vulgaris, with risk of progressive nasal septal ulceration and progression to saddle nose deformity. Blood tests are frequently augmented with computer tomography (CT) imaging of the rest of the paranasal sinuses. It should be noted, however, that a large proportion of such lesions (nearly half in some series) are considered to be idiopathic in nature though the above investigations are often of reassurance to both the patient and clinician alike [25].

In general, treatment is targeted at the cause in each individual case and we would stress the importance of multi-disciplinary working as it is essential to have good links with dermatology and rheumatology colleagues in particular. Medical strategies which aim to increase nasal moisture and the use of barrier ointments are useful though in management of idiopathic cases or for the symptomatic management in all aetiologies. It is also important to embark on close follow-up with these patients to ensure that the region of atrophy or ulceration does not progress to perforation or change in morphology, which might make one reconsider the value of biopsy.

Management of the Isolated Opaque Sinus

In an era where access to cross-sectional imaging is increasingly part of routine investigations for a variety of different medical specialties, patients with incidental findings regularly present to the rhinology clinic. Unfortunately, there is no consensus in the literature as to the optimal approach to the management of patients presenting with an isolated opacity within a single sinus. As the majority of chronic rhinosinusitis presents as diffuse inflammatory disease, and so will demonstrate bilateral opacification throughout multiple sinuses on CT imaging, the potential exists for such isolated findings to represent neoplasia and so clearly these patients require specialist review.

We would strongly advocate the importance of taking a detailed history in this patient group, allowing the division of these patients into those who have truly asymptomatic incidental findings and the patient with cardinal symptoms of sinonasal disease who has simply been prompted to present by different means. A thorough and detailed endoscopic examination in the clinic should also be considered mandatory.

The site of the opacification is important and could potentially provide clues as to the possible

aetiologies at play, a brief list of which is tabulated in Table 49.3. Isolated maxillary sinus disease is commonly due to odontogenic pathology, be it from propagation of a dental infection or other pathology such as ameloblastoma or the dentigerous cyst. Mycetoma formation (the fungal ball) also has a predilection for the maxillary sinus, though such fungal pathology can also be seen in other sinuses, particularly the sphenoid (Fig. 49.3). Of course, isolated sinusitis and mucocoele formation will also form part of the differential and a more thorough account of each of these pathologies can be found detailed elsewhere in this text.

The management of patients with isolated sinus opacification and concordant symptoms and/or examination findings is not a contentious one. As alluded to above, these patients have often simply been prompted to attend clinic through different means, via their incidental finding, but should be treated no differently than if they had presented with their symptoms directly. Where there does exist a degree of division in the literature is with the management of the incidental finding in the asymptomatic patient, particularly in the form of isolated sphenoid sinus opacification.

Table 49.3 Potential causes of isolated sinus opacification

Maxillary sinus	Sphenoid sinus
Odontogenic disorder	
Antrochoanal polyp	
Fungal disease (mycetoma, allergic fungal rhinosinusitis)	Fungal disease (mycetoma, allergic fungal rhinosinusitis)
Isolated sinusitis	Isolated sinusitis
Mucocoele formation	Mucocoele formation
Neoplasia	Neoplasia

Isolated sphenoid sinus disease, of all sites, has a tendency toward more insidious subtle symptoms atypical of disease elsewhere in the paranasal sinuses. Headache, particularly that over the vertex and occiput, is the most common presenting symptom, and can pose a significant diagnostic challenge with regard to the true cause of the headache. Endoscopic sphenoidectomy may be recommended as a means of confirming or excluding sphenoid disease as the cause of the headache. Other features of sphenoid pathology include retro-orbital pain, cranial nerve pathology such as diplopia, and changes in visual acuity [26].

Indeed, the proximity of the sphenoid sinus to crucial neurovascular structures, which can be involved if and when disease spreads beyond the confines of the sinus itself, will make the clinician naturally cautious against missing any potential pathology in this anatomical site.

Clearly, if there are features suggesting neoplasia then surgical management should take priority. Similarly, if there are features to suggest inflammatory or infective aetiology then appropriate medical treatment should be commenced in the first instance. These may include endoscopic findings such as oedema, discharge or the direct visualisation of a mass lesion. One should also closely inspect the CT imaging, as signs such as bony erosion and destruction of adjacent structures could suggest more sinister pathology.

A large systematic review has reported that a significant proportion of isolated sinus opacifica-

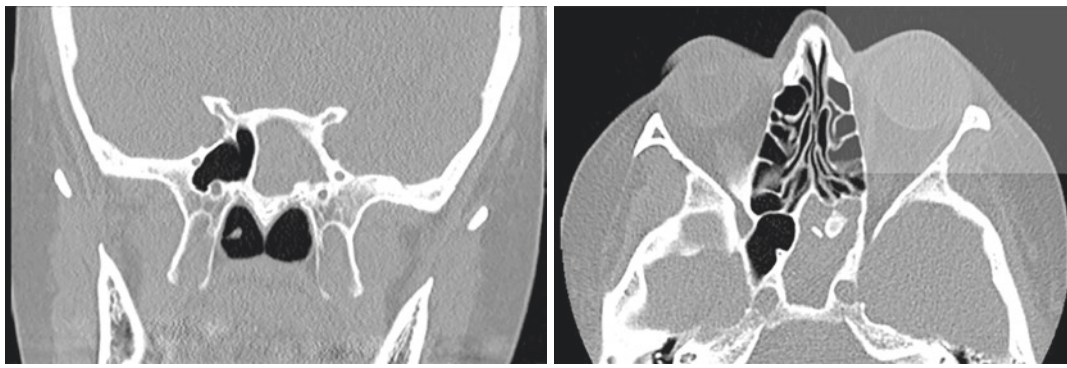

Fig. 49.3 CT sinus scan showing opacity of the left sphenoid sinus due to fungal sinusitis. The ipsilateral opaque ethmoid cells were due to inflammatory non-fungal sinus disease

tion represents malignant pathology (noted to be approximately 11% of isolated sphenoid opacification and 7% of isolated maxillary opacification) [27].

Whilst these findings might caution against conservative management, it should be noted that such results do not guide the rhinologist on the probability that a given asymptomatic patient with incidental isolated sphenoid opacification will have a high probability of underlying malignancy. Many of the studies collated overestimate the malignant potential of isolated sinus opacification including only those patients who have undergone surgery or only those with symptoms or concerning features on examination. This is obviously not representative of all patients seen with this finding in routine clinical practice. They are also extremely unlikely to have truly captured all patients with isolated sinus opacification. Indeed, the number of patients with incidental isolated sinus opacification is likely to be much higher; previous studies have suggested that as many as 39% of the asymptomatic general population demonstrate incidental opacification on CT imaging of the paranasal sinuses [28].

Accordingly, we would advocate an approach that weighs CT findings against symptom burden and examination findings and so considers the patient as a whole. Magnetic resonance imaging can be a complementary investigation to CT and is of particular utility in the characterisation of fungal disease and neoplasia. Surgerical exploration may be the preferred decision, particularly if there are any diagnostic concerns, but should be reserved for selected cases. Alternatively, consideration should be given to repeated examination and serial imaging, taking account of the risks and benefits of all management options to facilitate shared decision making with the patient.

Osteoneogenesis: Significance and Management

Whether described as hyperostosis, osteitis or osteoneogenesis, increased bony thickening can frequently be found on review of imaging in sinonasal disease, particularly on CT scanning. However, whilst the majority of research into the pathogenesis of CRS focuses on mucosal disease, the role of bony inflammation, and crucially its impact upon disease severity, treatment and prognosis, is more challenging to define. Indeed, there remains a degree of uncertainty as to how chronic inflammation within the sinuses induces bony remodelling, though clear and established links have been found between long-standing mucosal disease and histological findings in keeping with osteitis [29].

Bony partitions within the ethmoidal sinuses are those most commonly affected in CRS and this presumed susceptibility to periosteal inflammation has been hypothesised to be driven by a combination of these partitions being the thinnest of the bones of the paranasal sinuses and the only bones surrounded on both sides by chronically inflamed mucosa [30].

Whilst osteitic bone has a classical honeycomb-like appearance intraoperatively and diagnosis of osteitis can be obtained, ultimately, from histological analysis of bony tissue, it is typically observed on CT imaging during preoperative work-up (Fig. 49.4). Based on such imaging, a number of staging systems have been proposed, based on either site and extent of bony thickness within sinus partitions or walls [31], or radiodensity, as measured via Hounsfield units, which has been suggested to be higher in areas of new bone formation [32].

Links between findings of osteitis and disease severity vary on the measure employed. However, whilst preoperative SNOT-22 scores have not been found to vary due to the presence (or absence) of osteitis, osteitis has been reported as a negative prognostic finding upon symptom burden measures following sinus surgery and is also a more common finding in the setting of patients with recalcitrant CRS [33].

Such findings have utility when counselling patients on their expectations but there remains something of a paucity of guidance as to how the rhinologist should approach osteitis when considering treatment. Surgical excision of osteitic bone is the most widely employed approach with such a strategy most achievable possible when approaching the more frequently involved ethmoidal sinuses. The finding of osteitis elsewhere

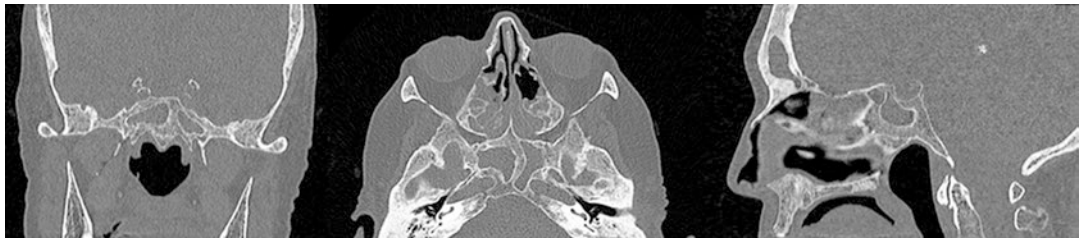

Fig. 49.4 Multiplanar CT scan of sinuses showing osteoneogenesis of the sphenoid sinus in a patient with chronic rhinosinusitis without polyps

in the paranasal sinuses obviously complicates such an approach, however, though the use of more aggressive surgery with radical resection of bone (including the use of a Denker procedure) suggested by some in the setting of recalcitrant disease. Unfortunately, there remains limited data to suggest that more extensive bony resection correlates with improved postoperative outcomes, though a recent small study has suggested that more radical surgery may be beneficial in the setting of recalcitrant CRS with osteitis [34].

It should be stressed, however, that we would advocate a balanced step-wise approach, with the extent of surgery matched to both the extent of a patient's disease and their symptom burden. Reports of patients undergoing extensive bone resection are from series in which patients have usually exhausted all other avenues of therapy and we would suggest that, on review of current evidence, such procedures be undertaken with caution and remain limited to those patients with truly recalcitrant aggressive bony disease.

Indeed, the utility of medical management should not be overlooked, particularly as the years ahead will hopefully show increased adoption of newer strategies, targeting specific inflammatory pathways. Osteitis is associated with higher levels of eosinophilia in both tissue and serum [35], increased expression and upregulation of both cytokines and growth factors [36].

This suggests that a focused immunological approach to medical treatment could well pay dividends, either as standalone treatment or in association with surgery. Again, data of such treatment remain lacking to date though as current reports which have proposed the utility of immunotherapy in CRS have not specifically considered osteitis. The rhinological community eagerly await reports of their effect in the future since given osteitis may well play a significant role in the setting of more recalcitrant CRS, a greater understanding of both its prevention and treatment are key for the management of these patients who often require more long-term management.

At present, our understanding as to whether the osteoneogenesis is purely representative of the severity and duration of chronic sinus inflammation, or whether it is a driver of inflammation remains an enigma.

Silent Sinus Syndrome

Silent sinus syndrome, enophthalmos associated with apparent collapse of the ipsilateral maxillary sinus, is an uncommon diagnosis (Fig.49.5a, b). The literature is generally restricted to small cohort series that typically describe fewer than 20 cases [37].

This rarity is likely responsible for both the ambiguity and brevity in its general discussion as there are differences to be found with the terminology employed for this condition doubtlessly underscored by limitations in the present understanding of its possible aetiology. Indeed, the condition can also be found referred to as maxillary implosion syndrome, in keeping with its presentation within the maxillary sinus, and there exists considerable contention as to whether silent sinus syndrome is simply an advanced presentation of chronic maxillary atelectasis rather than representing a clinical entity with its own distinct pathophysiology [38].

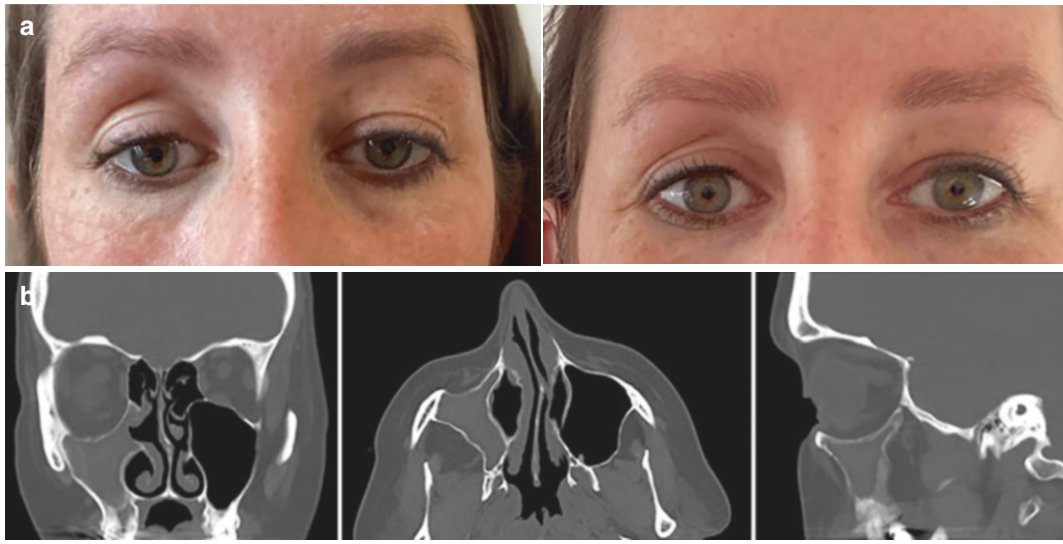

Fig. 49.5 (**a**) Note the increased skin crease and lack of natural fullness of the right orbit. (**b**) CT scan of sinuses. Note how the maxillary sinus walls are all drawn inwards. Orbital features and CT scan from a 35-year-old woman with silent sinus syndrome affecting the right maxillary sinus

Chronic maxillary atelectasis can be considered as more of an umbrella term, encompassing findings of first membranous and then bony deformity of the maxillary sinus before eventual progression to the visible clinical deformity as found in silent sinus syndrome. However, in its original description, silent sinus syndrome is noted to present in the absence of what could be considered as cardinal rhinological symptoms such as obstruction, rhinorrhoea or facial discomfort [39].

As such, silent sinus syndrome has been found to present more frequently to ophthalmology colleagues. In contrast, chronic maxillary atelectasis is thought to follow remodelling following an episode of rhinosinusitis and is differentiated from silent sinus syndrome by the presence of rhinological symptoms.

However, the division of patients into either silent sinus syndrome or chronic maxillary atelectasis based on symptomatology is likely an overly simplistic approach as summated systematic review of cases of chronic maxillary atelectasis suggests that, in advanced cases where extensive bony changes in the maxillary sinus have resulted in clinical deformity, the majority of patients are noted to be asymptomatic from a rhinological point of view—in keeping with those with silent sinus syndrome [38].

Such findings add weight to these syndromes being two descriptions of the same process though again the rarity of reports of each limit any further extrapolations, particularly as to why these patients will undergo such extensive remodelling following blockage of the maxillary sinus rather than developing more typical chronic maxillary sinusitis.

Treatment for silent sinus syndrome should follow a staged approach with endoscopic sinus surgery first targeted at the middle meatus to open the maxillary sinus in an effort to arrest the presumed underlying mechanism. Caution should be exercised when performing such surgery, particularly during uncinectomy as displacement of orbital contents places important structures at greater risk of potential iatrogenic injury. Reconstructive surgery for orbital malposition is then considered as a subsequent adjunctive procedure, if required.

In the absence of more detailed knowledge of the pathophysiology of this condition, it is challenging to present any forms of treatment other than corrective surgery for those with silent sinus syndrome (or advanced chronic maxillary atelec-

tasis). Hopefully, the future will bring a more nuanced understanding of the natural history of chronic maxillary atelectasis. If it were possible to firmly establish that early mucosal or bony changes, in keeping with chronic maxillary atelectasis, were predictive of progression to silent sinus syndrome then there would be a greater argument towards early decompression of the maxillary sinus as a more proactive and preventative treatment strategy.

Pleasingly, the aesthetic results of staged corrective surgery are generally good [37].

Key Learning Points

- Oral steroid regimes for CRS lack a standardised or consistent approach.
- Osteoporosis is associated with as little as 3 courses of high-dose oral steroids per year.
- There are several topical nasal steroids but there is no good evidence to favour any particular steroid over another.
- Beclomethasone nasal drops are effective but must be used with caution as systemic absorption occurs and may lead to natural steroid suppression.
- New delivery systems for applying topical nasal medication are being developed and combined with saline irrigation.
- Saline irrigations are sometimes combined with additives, but there is no current evidence base that these are effective.
- Localised mucosal atrophy is an uncommon, typically idiopathic condition, that is likely to affect the anterior nasal septum when it occurs. Biopsy should be considered if there are any unusual features.
- Isolated opaque sinuses may be identified as an incidental finding. A full clinical assessment is recommended and may include an MRI scan. Surgical intervention is not mandatory but should be considered alongside long-term surveillance.
- Thickened sinus bone is referred to as hyperostosis, osteitis or osteoneogenesis that may be associated with recalcitrant disease. However, it remains an enigma as to whether it is a driver of sinus inflammation or just represents long-term sinus inflammation.
- Silent sinus syndrome is rare but presents with enophthalmos and indrawn walls of the affected maxillary sinus.

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