Nasal Infections

16

Marlene L. Durand

Introduction

The most common nasal infections are due to viruses, such as rhinoviruses, that cause the common cold. These are self-limiting unless a bacterial superinfection occurs. Acute bacterial nasal infections, such as cellulitis or vestibulitis, are also common and usually caused by *Staphylococcus aureus*, a normal colonizer of the skin and nasal vestibule. Aside from acute viral and bacterial infections, most other nasal infections are rare. Some infections primarily affect the nasal septum, such as post-traumatic nasal abscess, while others involve multiple sites and present as chronic masses, ulcers, or atrophic rhinitis. Some nasal infections, such as mucosal leishmaniasis, are very rare outside of an endemic region. However, many of these infections are chronic or have a long latency so may appear in a patient who immigrated from an endemic country months or years earlier. This chapter reviews the diagnosis and treatment of common and rare nasal infections due to bacteria, fungi, and parasites.

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Anatomy

The structure of the nose and nasal septum is comprised of bone and cartilage, with bone proximally and cartilage distally (Fig. 16.1). A small portion in the roof of the nasal cavity contains the cribriform plate, through which olfactory neurons extend to the overlying olfactory bulb. The nasal cavity is lined with respiratory epithelium that secretes mucus. Turbinates along the lateral walls of the nasal passages increase the mucosal surface area and help direct the inhaled air. Inhaled air is heat-regulated, humidified, and cleansed of foreign particles and microbes during passage through the nose. The nasal vestibules, areas just inside the nostrils, are lined with skin which contains small hairs (vibrissae). The hairs trap large inhaled particles. The venous drainage of the nose communicates indirectly with the cavernous sinus. The veins draining the nose were previously thought to lack valves, but recent research has proved otherwise [1]. However, infections involving the nose can spread rapidly to the cavernous sinus, and usually do so via the ophthalmic veins.

"The danger zone". For over 160 years, there has been recognition that seemingly minor infections in the mid-face could lead to fatalities.

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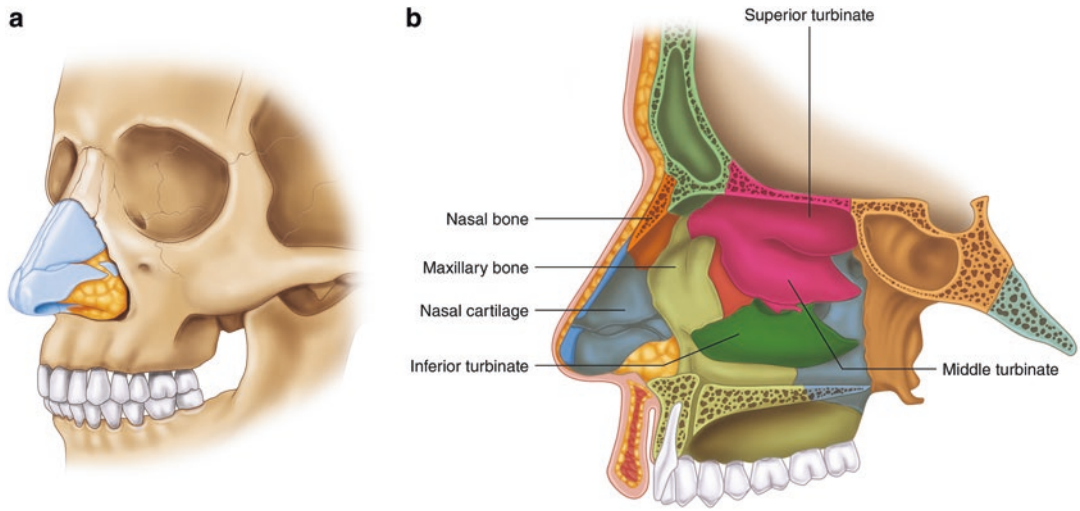

Fig. 16.1 (**a**, **b**) Anatomy of the nose. (**a**) External view, demonstrating nasal bones and cartilage. (**b**) Lateral wall of the nose, demonstrating the superior, middle, and inferior turbinates

Infections in the "dangerous area" of the face were first mentioned in 1852, when Dr. Harvey Ludlow, a general surgeon in London, reported six cases including three fatalities that followed a simple pimple or "boil" on the upper lip [2]. The pathophysiology was explained in 1883, when Sir Frederick Treves noted that a "carbuncle of the face or other diffuse and deep-seated inflammatory conditions, especially of the upper lip and in the neighborhood of the alae nasi, may induce fatal thrombosis of the cerebral sinuses." [3] In 1922, Walton Martin wrote a classic paper on the subject and described the risk from *S. aureus* infections in a danger triangle extending from the angles of the mouth to the bridge of the nose [4]. In 1937, Urban Maes reported 20 fatal cases of cavernous sinus thrombophlebitis that arose from lesions in the "danger triangle" that had been described by Martin, as well as 24 cases that arose from lesions in the face outside this triangle [5]. Maes noted that these cases typically occurred in young, previously healthy patients, often began as a trivial skin infection ("carbuncle or simple boil"), and were nearly always caused by *S. aureus*. Maes also noted that progression to septic cavernous sinus thrombosis typically occurred rapidly (days).

Recent reports corroborate Maes's observations. Pannu et al. described a healthy 55-year-old man who developed a minor furuncle and cellulitis on the nasal tip, then presented 15 days later with persistent fevers and third and sixth cranial nerve palsies due to cavernous sinus thrombophlebitis [6]. Munchkoff et al. described a healthy 26-year-old man who developed a post-traumatic pustule on the skin adjacent to the nares and then presented 3 days later with bilateral ophthalmoplegia and proptosis due to methicillin-resistant *S. aureus* (MRSA) cavernous sinus thrombosis [7] (Fig. 16.2). Varshney et al. reported a series of eight children in India who developed septic cavernous sinus thrombosis 4–10 days following minor nasal or sinus infections (furuncles, vestibulitis, ethmoiditis) [8]. All eight children were febrile on presentation, 75% presented with orbital signs and symptoms, and *S. aureus* was the pathogen in most—all features typical of cavernous sinus thrombosis following nasal infections. Cavernous sinus thrombophlebitis can be caused by bacteria besides *S. aureus*, and cases have been described due to streptococci (e.g., *Streptococcus anginosis/milleri* group, *S. pneumoniae*), Gram-negative bacilli, and anaerobes [9].

Microbiome of the Nose

The nasal passages are not sterile. *Staphylococcus aureus* is part of the normal microbiome in up to one-third of the population, and MRSA colonizes

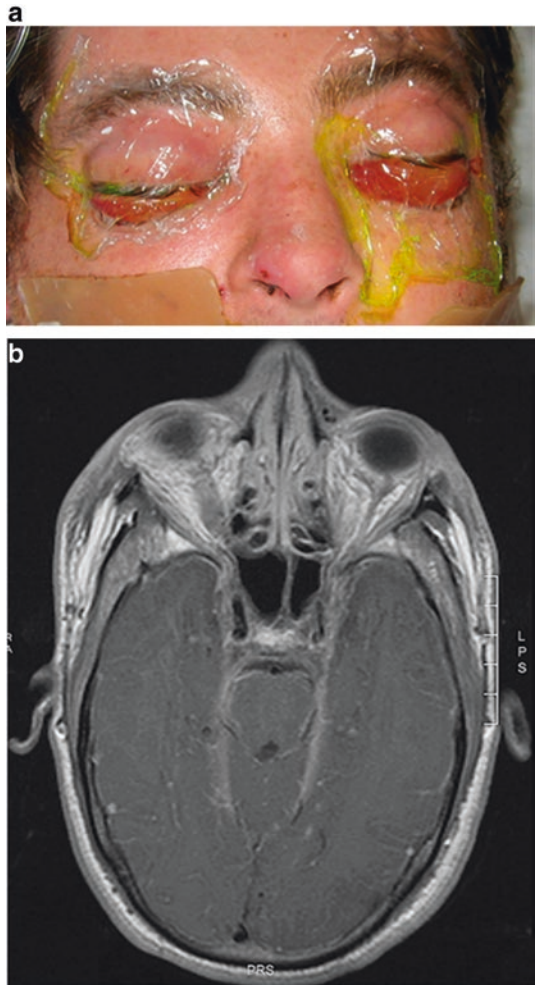

Fig. 16.2 (**a**, **b**) Cavernous sinus thrombosis from methicillin-resistant *Staphylococcus aureus* (MRSA). The patient was a previously healthy man who suffered a minor injury to the skin next to the right nostril 3 days earlier. (**a**) Examination showed bilateral ophthalmoplegia, proptosis, and a right nasal skin lesion. (**b**) Magnetic resonance imaging (MRI) demonstrated enhancement of the cavernous sinuses and prominence of the right superior ophthalmic vein, suggesting early thrombus formation. Reproduced from Munckhoff et al. [7], with permission from John Wiley and Sons

the noses of approximately 2% of the U.S. population [10]. The rate of MRSA colonization is often higher in healthcare workers and others with frequent contact with the healthcare system, as well as residents of long-term care facilities. The location of various microbes in the nose varies by location along the nasal passage. The technique used to detect microbes will influence results, and genetic sequencing techniques have demonstrated a much wider variety of organisms than was previously appreciated. Wos-Oxley et al. performed genetic sequencing on samples at four intranasal locations of 79 individuals (some with chronic sinusitis) and found nearly 450 distinct bacterial phylotypes, although 20 of these accounted for 75% of the total standardized sequence readings [11]. Predominant species included *Corynebacterium*, *Propionibacterium acnes*, *S. aureus*, coagulase-negative staphylococci, *Cupriavidus/Ralstonia*, *Dolosigranulum pigrum*, Enterobacteriaceae, and *Moraxella lacunata/nonliquefaciens*. Some of these bacteria, such as coagulase-negative staphylococci and *P. acnes*, do not appear to cause intranasal infections. The types of bacteria colonizing the nose may vary depending on whether the patient lives in the country or a city. Shukla et al. compared the intranasal microbiota of dairy farmers and urban dwellers and found that dairy farmers had a significantly greater microbial diversity and lower rate of staphylococcal colonization [12].

Fungal spores are present in the air we breathe, and one of the functions of the nasal mucus is to trap these spores and other allergens. It is not surprising, therefore, that cultures of the nasal mucus will grow fungi. A study by Ponikau et al. found fungi, especially molds, in cultures of the nasal mucus of nearly all patients with chronic rhinosinusitis and in all healthy control patients [13].

Nasal Vestibulitis

Nasal vestibulitis usually arises from an infection around one of the hairs in the vestibule. Most cases are caused by *S. aureus* (including MRSA). The clinical presentation is usually redness, swelling, and pain around the involved nostril (Fig. 16.3) [14]. Extension to the tip of the nose may occur. Systemic symptoms such as fever are rare, and if present suggest a more extensive infection. Minor, localized vestibular infections may be treated with a combination of oral and topical antibiotics, or in some cases with topical antibiotics alone. The antibiotic chosen should have activity against *S. aureus*, including MRSA in regions where MRSA is prevalent. Any antibiotic with activity against MRSA will also be

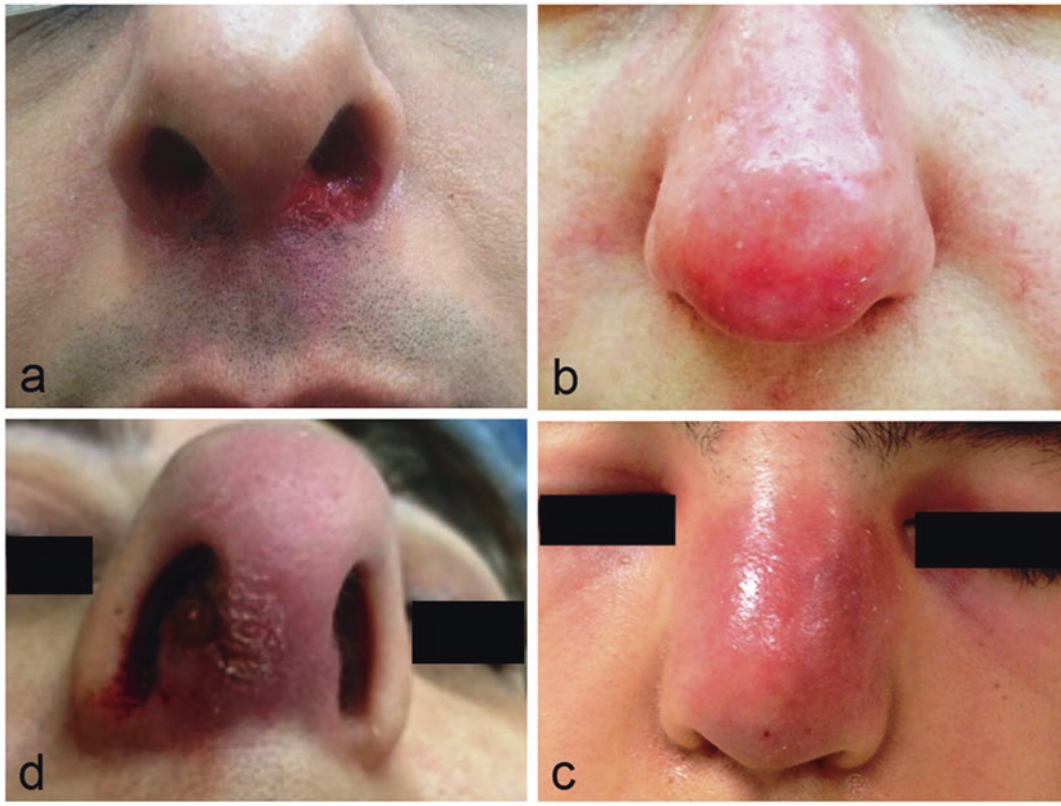

Fig. 16.3 (**a**–**d**) Nasal vestibulitis. (**a**) Left nasal vestibulitis with crusting. (**b**) Nasal vestibulitis with localized cellulitis. (**c**) Mid-face cellulitis. (**d**) Vestibular abscess. Reproduced from Lipschitz et al. [15], with permission from Sage Publishing

active against methicillin-sensitive *S. aureus*. Topical mupiricin generally has excellent activity against MRSA and may be more effective for nasal vestibulitis than triple antibiotic ointments (e.g., combination of bacitracin, neomycin, polymixin). A patient with nasal vestibulitis and nasal tip cellulitis has been described who failed initial treatment with triple antibiotic ointment plus oral doxycycline but rapidly responded to topical mupiricin ointment [15]. Cephalexin will treat methicillin-sensitive *S. aureus* but not MRSA, while trimethoprim-sulfamethoxazole will generally treat both although local susceptibility patterns should be considered.

More significant infections will require intravenous antibiotics. Patients with intranasal abscess and extension of cellulitis to the nasal bridge or face should be admitted for drainage of the abscess and intravenous antibiotics. Lipschitz et al. reported results of 115 patients admitted to a tertiary care center in Israel 2008–2015 for nasal vestibulitis [15]. The average age was 44 (range 8–96), and 40% of the patients had received oral antibiotics (most often amoxicillin-clavulinate) prior to admission. Indications for admission included failure to improve on oral antibiotics, mid-face cellulitis (present in 79%), or nasal vestibular abscess (present in 48%). Patients were treated with intravenous antibiotics and drainage of any abscess. Nasal abscess cultures were positive in 15 patients and grew *S. aureus* (87%), MRSA (7%), and *Prevotella* (7%). All infections resolved with treatment. Ruiz et al. reported a series of nasal vestibulitis in 115 cancer patients referred for outpatient dermatology consultation in New York City and the Netherlands [16]. Most were receiving "targeted therapy" for their cancer with an agent such as an

epidermal growth factor receptor inhibitor, a therapy associated with dermatologic side effects. Positive nasal vestibule cultures grew *S. aureus* (43%) or MRSA (3%), Group A or B streptococci (2%), Gram-negative bacilli (13%), and normal skin or respiratory flora; 28% of cultures were polymicrobial. Most vestibulitis cases in this series were considered mild or moderate and the majority responded to a topical antibiotic.

While *S. aureus* is the major cause of nasal vestibulitis and abscess and most patients present acutely, recurrent cases may be due to an unusual microbe or due to an underlying tumor. Rudramurthy et al. described a diabetic patient in India who presented with a vestibular abscess that was drained, only to relapse with fever, nasal erythema, and vestibular abscess 1 month later [17]. The abscess was again drained and branching, Gram-positive and partly acid fast organisms were seen on stains; a *Nocardia*-like organism (*Nocardiopsis dassonvillei*) grew on culture. The infection responded to 4 weeks of combination antibiotic therapy. Some patients diagnosed initially with chronic nasal vestibulitis have been found to have underlying cutaneous neoplasms such as basal cell or squamous cell cancer [18]. Patients with chronic or relapsing vestibulitis should have cultures of the vestibule for routine and unusual organisms, along with evaluation for a local malignancy.

Nasal Septal Infections

Acute Nasal Septal Abscess

A nasal septal abscess is uncommon, and usually develops in the anterior portion of the septum between the septal cartilage and the overlying mucoperichondrium. Rarely, the abscess is more posterior and develops between septal bone and mucoperiosteum. Most septal abscesses occur in children and adolescents. The most common etiology is trauma. Typically, a posttraumatic septal hematoma develops and becomes superinfected. Nasal septal trauma may occur following accidents, falls, or fights, and septal abscesses may be difficult to diagnose initially. Other causes of septal abscess include dental or sinonasal infections, such as nasal vestibulitis, and postoperative complications following nasal surgery. Rarely, septal abscess occurs spontaneously [19] (Fig. 16.4). Because the septal cartilage receives its blood supply by diffusion from the overlying mucoperichondrium, damage to the mucoperichondrium, as often occurs with trauma, can lead to rapid cartilage damage and subsequent septal perforation [20]. Secondary infection accelerates this process.

Septal abscesses are often bilateral, particularly in posttraumatic cases, and patients complain of bilateral nasal obstruction [20]. Symptoms typically develop within 1 week of the

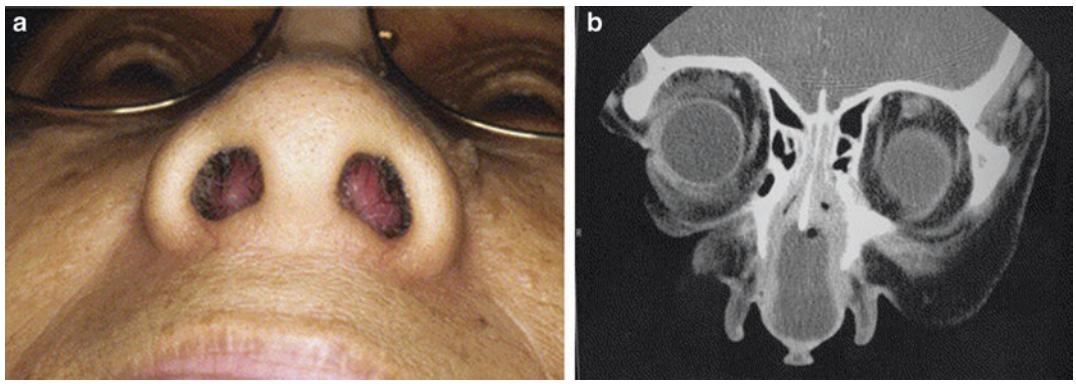

Fig. 16.4 (**a**, **b**) Nasal septal abscess. A 69-year-old woman presented with 4 days of nasal obstruction and pain. (**a**) Examination showed bilateral septal swelling causing obstruction. (**b**) Coronal computed tomography (CT) showed septal abscess with gas bubble. Surgical drainage revealed necrotic septal cartilage and pus, and culture grew penicillin-sensitive viridans streptococci. Reproduced from Huang et al. [19], with permission from Sage Publishing

trauma. Nasal pain, including over the bridge of the nose, is often present in septal abscesses but fever is uncommon and purulent nasal drainage may be absent. Examination reveals a swollen tender nose and bilateral dusky-appearing nasal septal swelling, often obstructing the nasal airway [20]. Most cases involve the anterior nasal septum, but rare cases involve the posterior septum [21]. Radiologic imaging should be performed as part of the evaluation. Computed tomography (CT) with contrast should be performed first, followed by magnetic resonance imaging (MRI) if there is concern for central spread of infection.

Nasal septal abscesses require immediate drainage to prevent further destruction of the cartilage. Samples of the abscess should be sent for Gram stain and culture. The most common cause of septal abscess is *S. aureus*, which accounts for approximately 70% of the cases [20]. Other etiologies include MRSA [22], streptococci (e.g., Group A *Streptococcus*, *S. pneumoniae*, *S. anginosis/milleri*), *Haemophilus influenzae*, anaerobes, and rarely Enterobacteriaciae [20]. Cases of septal abscess due to molds (e.g., *Aspergillus*, *Fusarium*) have been described but are very rare [23, 24]. Tuberculosis and leprosy, both mycobacterial infections, may cause septal infection and perforation, as discussed later.

In addition to urgent drainage of the abscess, treatment should include broad-spectrum intravenous antibiotics (e.g., vancomycin plus ampicillin-sulbactam, or vancomycin plus metronidazole plus ceftriaxone), with subsequent narrowing of the antibiotic regimen based on culture results. The optimal duration of antibiotics following surgical drainage has not been established, but a minimum of 2 weeks is recommended. Some cases require much longer (e.g., 4–6 weeks), since infections in cartilage can be difficult to eradicate. In cases with slow or no improvement on antibiotics after drainage, repeat cultures and imaging should be obtained. Further surgical drainage may be necessary, including in the operating room. Once the acute infection has been treated, cartilage grafting of any septal perforation may be necessary in growing children to prevent the later development of a facial deformity.

Cocaine Abuse, Septal Perforation, and Superinfection

Cocaine causes vasoconstriction, and intranasal abuse of cocaine often leads to osteocartilaginous destruction of the nasal septum due to ischemic necrosis. Secondary infection as well as chemical irritation from adulterants in the cocaine can add to the destructive process [25]. Septal perforations are well described in patients who use intranasal cocaine. However, persistent cocaine use can also lead to perforation of the palate and an oral-nasal fistula [25], or even a midfacial cavity resulting from the destruction of the turbinates and medial maxillary walls [26]. Secondary infection leading to acute or chronic osteomyelitis of the septum or hard palate may occur. In one advanced case, a biopsy of the bone at the edge of the central cavity revealed acute osteomyelitis, and cultures grew a mixture of bacteria including staphylococci, streptococci, and *Serratia* [26]. Although bacteria, especially *S. aureus*, are the usual cause of superinfection, molds can play a role. Cases of cocaine-related septal and palatal perforations with chronic invasive *Aspergillus* superinfection have been described [27].

Snorted narcotics can also lead to septal perforations. In a series from 50 years ago, Messenger found that all but seven of the 2185 drug users he examined over an 8-year period snorted heroin rather than cocaine (cocaine was more expensive), and that the incidence of septal perforations was 4.8% [28]. A recent report described a patient who developed total destruction of the septum, soft palate, and sinus walls from snorting crushed tablets of sustained release oxycodone [29].

Rare Intranasal Infections

Bacterial Infections

Tuberculosis

Tuberculosis (TB), an infection caused by *Mycobacterium tuberculosis*, is prevalent worldwide but primarily affects the lungs. Extrapulmonary TB is less common and rarely involves the nose. A review of the twentieth cen-

tury literature found only 35 cases of nasal TB [30]. Nasal TB may occur without pulmonary involvement, although this is uncommon. Nasal TB involvement is usually unilateral, and symptoms include nasal obstruction and discharge [30]. Physical examination reveals a granular intranasal mass in most cases, with the most common site of involvement being the cartilaginous septum followed by the inferior turbinate (Fig. 16.5). Polyps and nasal ulceration may be rarely seen (6% of patients in one study) [30]. The mass of nasal TB can mimic malignancy, and a septal perforation may be present [31]. A biopsy of the nasal mass, rather than a swab culture, should be sent for acid fast bacilli (AFB) stains and mycobacterial cultures. Patients with TB affecting any part of the airway, including the nasal passages, should be placed on airborne precautions to prevent transmission to others. An infectious disease expert should be consulted to help with isolation precautions and TB treatment. Treatment for TB can lead to resolution of the nasal lesion and the septal perforation.

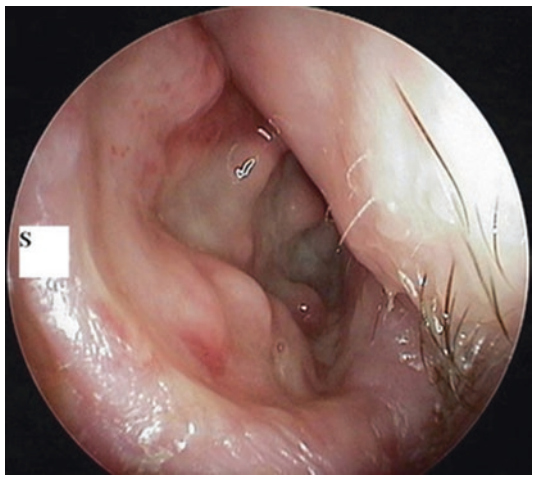

Fig. 16.5 Nasal tuberculosis. A 79-year-old woman presented with 6 months of unilateral nasal obstruction, crusting, and epistaxis. Chest x-ray was clear. Rhinoscopy revealed an irregular, friable, "apple jelly" consistency mass on the left side of the nasal septum (S = septum). Four biopsies over 18 months were required to make the diagnosis; one finally showed caseating granulomas and culture for mycobacteria grew *Mycobacterium tuberculosis* (TB). The infection resolved on anti-tuberculous therapy. Reprinted from Masterson et al. [31], with permission from Cambridge University Press

Leprosy

Leprosy, a bacterial infection caused by *Mycobacterium leprae*, has been known since 600 BC but is now rare in developed countries. Over the past 20 years, 16 million people with leprosy have been successfully treated and the prevalence of the disease has decreased by 99% [32]. However, there are still approximately 200,000 new cases per year worldwide, with 94% of cases occurring in 13 countries [32]. Three large population countries (Brazil, India, and Indonesia) report the most cases [32]. Fewer than 200 new cases occur in the U.S. annually and 75% of these occur in immigrants [33].

The bacterium multiplies very slowly (12 days), and is an obligate intracellular organism that cannot be cultured. It has a predilection for cooler parts of the body including the ears and nose. Symptoms usually take 1 to several years (up to 20) to develop [32], so even a remote travel history to an endemic region may offer a clue to diagnosis. Only 5% of the population is susceptible to leprosy, while 95% have natural immunity. Leprosy is not very contagious, but household contacts of an untreated patient are at increased risk for developing leprosy and may also be nasal carriers of *M. leprae* [34]. A respiratory route of transmission is very likely: the bacterium can be found in abundance in nasal secretions of lepromatous leprosy patients. Leprosy affects the skin and peripheral nerves early in disease. The nose is affected early in lepromatous leprosy, as discussed later.

The clinical manifestation of leprosy depends on the patient's immune response to the bacterium: those with a robust immune response to *M. leprae* have limited disease ("tuberculoid" or "paucibacillary"). Skin biopsy in these patients demonstrates well-formed granulomas and very few acid fast bacilli (*M. leprae*). Patients with minimal immunologic response to the bacterium are at the opposite end of the spectrum and have "lepromatous" leprosy ("multibacillary"), characterized by sheets of foamy macrophages laden with acid fast bacilli on histopathology. Borderline categories fall between these extremes. Patients with tuberculoid disease typically have 1–3 skin lesions that are large, hypopigmented (or reddish) macules or "patches" with distinct borders

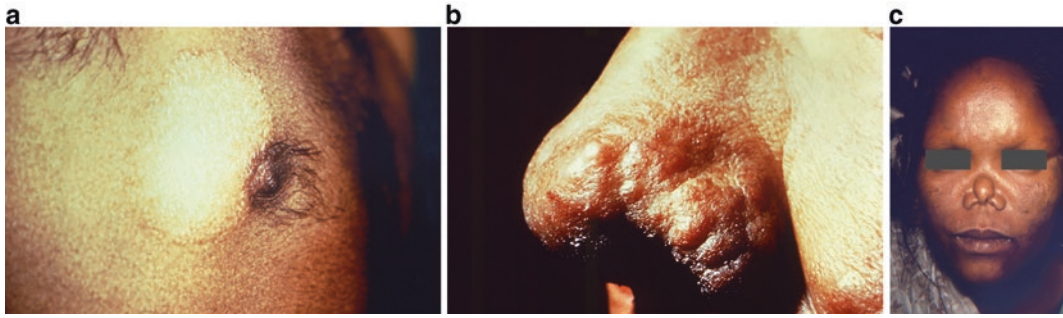

Fig. 16.6 (**a**–**c**) Leprosy. (**a**) Hypopigmented lesion of tuberculoid leprosy; anesthesia within the lesion is typical. (**b**) Lepromatous leprosy with nodules involving the nose. (**c**) Chronic lepromatous leprosy with saddle nose deformity. From the Centers for Disease Control and Prevention (CDC), Public Health Images Library

(Fig. 16.6a). The lesions have decreased or absent sensation, a feature that distinguishes these from other skin lesions. In lepromatous leprosy, there may be diffuse thickened skin or multiple macules and nodules, with the nodules typically involving the earlobes and face (Fig. 16.6b). Hair loss of the outer eyebrows is common. Involvement of peripheral nerves occurs in all types of leprosy, and can lead to nerve enlargement and peripheral neuropathy, with paresthesias of the hands and feet. Chronic infection can lead to "claw hand" and foot drop, and resorption of fingers and toes. The diagnosis of leprosy is made by biopsy of the skin lesion (leading edge), and treatment is with a prolonged course (up to 2 years) of oral dapsone plus rifampin, plus clofazimine in lepromatous cases [33].

Nasal manifestations of leprosy occur in lepromatous leprosy, and nasal discharge in lepromatous disease contains abundant *M. leprae*. Intranasal findings may be the only manifestations of early lepromatous leprosy. Barton and Davey's 1976 description of intranasal findings in 300 leprosy patients remains helpful [35]. In this series, intranasal infection was not seen in patients with tuberculoid leprosy, but was seen in 97% of patients with lepromatous leprosy. These patients usually complained of nasal congestion, crusting, and bleeding; 40% had hyposmia. Early findings included nodular thickening of the nasal mucosa, which often appeared paler than surrounding tissues, or isolated mucosal nodules. The anterior end of the inferior turbinate was the site involved first. Patients with later stage lepromatous leprosy had "gross inflammation of the nasal mucosa and severe obstruction" [35], and some also had perforation of the septal cartilage. With progressive untreated infection, perichondritis and periosteitis of the septum and inferior turbinates develops and leads to the classic saddle nose deformity (Fig. 16.6c). A very rare nasal manifestation of lepromatous leprosy is an intranasal mass, or leproma. This was described recently in a Korean patient who had no other apparent signs of leprosy [36].

Syphilis

The bacterium *Treponema pallidum* causes syphilis, and infection may be transmitted congenitally or acquired sexually. The classic stages of untreated acquired infection include primary syphilis, characterized by a painless chancre at the site of inoculation that resolves spontaneously; secondary syphilis, characterized by a diffuse rash often involving the palms and soles; latent syphilis, defined as having positive serology but no clinical manifestation of syphilis; and tertiary syphilis. Tertiary syphilis, which occurs years or decades after the primary infection, is characterized by cardiovascular, neurologic, or gummatous disease. Gummas are necrotizing granulomatous lesions that most often affect the skin, mucous membranes, and bones but may affect any organ.

In early congenital syphilis, nasal involvement is evident as rhinitis ("snuffles") (Fig. 16.7). A generalized periostitis and perichondritis can also occur in early congenital syphilis and this can

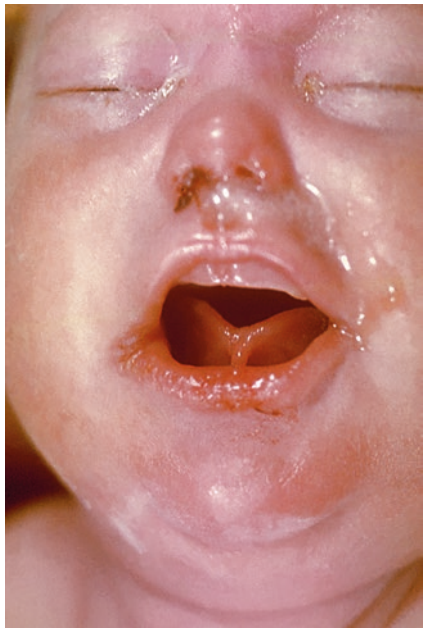

Fig. 16.7 Congenital syphilis; early stage showing infant with "snuffles" from inflammation of the nasal mucosa. From the Centers for Disease Control and Prevention (CDC), Public Health Images Library

involve the nasal septum [37]. The resulting bone and cartilage loss in the nasal septum leads to loss of the structural support in the nose and subsequent saddle nose deformity in "late" (>2 years) congenital syphilis. In a series of 271 patients with late congenital syphilis (average age 29 years old) seen in the 1960s, a saddle nose deformity was common and seen in over 70% of patients [38].

In acquired syphilis, nearly all nasal manifestations are due to gummatous (tertiary) syphilis. The gumma may cause a chronic ulceration inside the nose or of the nose and skin above the upper lip. A case of a slowly destructive midfacial gumma in an HIV-positive patient has been described [39]. The ulcerative mass of a syphilitic gumma may be mistaken for a malignancy until biopsy demonstrates granulomatous changes [40]. *Treponema pallidum* cannot be cultured, and diagnosis of tertiary syphilis is made by serologic studies and histologic findings on biopsy. Nontreponemal tests such as rapid plasma reagin (RPR) spontaneously decline in titer with time and can be negative in up to 50% of tertiary syphilis cases, so treponemal tests such as TPPA (*Treponema pallidum* particle agglutination assay) should be ordered along with the nontreponemal test in any patient who may have a gummatous nasal lesion. Treatment of syphilis with penicillin is curative.

Ozena

Ozena, which means "stench" in Greek, is also called primary atrophic rhinitis. Atrophic rhinitis is characterized by progressive atrophy of the nasal mucosa, crusting, and foul odor. Atrophic rhinitis may be either primary (ozena) or secondary (e.g., resulting from prior sinonasal surgery, trauma, radiation, or various infectious and noninfectious granulomatous conditions). Ozena is very rare outside endemic regions in Africa, the Middle East, and Asia. It may be seen in nonendemic areas in immigrants from endemic regions. Several recent cases have been described in the U.S. and the United Kingdom in immigrants from Nigeria, countries in east Africa, and Saudi Arabia [41, 42]. Patients with ozena complain of excessive crusts, a sensation of nasal obstruction, and thick, often foul-smelling nasal discharge. On examination, there is atrophic nasal mucosa, crusting, and usually an enlarged nasal cavity. There may be resorption or destruction of intranasal bones such as the inferior turbinates. If the mucosa is biopsied, histopathology demonstrates a squamous epithelium rather than the normal respiratory epithelium. Ozena is thought to be idiopathic, although *Klebsiella ozenae* can be cultured in many cases [41–43]. Culture-directed antibiotics are usually given, often for prolonged courses, but without uniform success [41]. Randomized controlled trials to determine optimal treatment have not been performed. A fluoroquinolone has been effective in several cases that were culture-positive for *K. ozena*e [41, 42], and this class of antibiotics may prove to be most effective.

Rhinoscleroma

Rhinoscleroma, or "scleroma," is a chronic granulomatous disease of the nose and upper airways caused by *Klebsiella rhinoscleromatis*. The disease was first described in 1870 by Hans Von

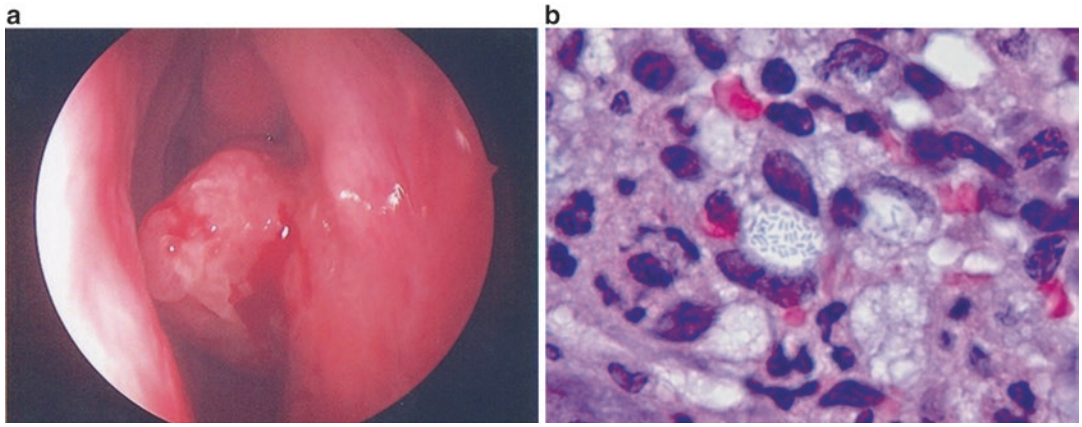

Fig. 16.8 (**a**, **b**) Rhinosclerma. (**a**) Fleshy, friable mass arising from the nasal septum. (**b**) Hematoxylin-eosin stain of laryngeal biopsy (100×) showing the classic Mikulicz cells of rhinoscleroma. These cells are foamy or vacuolated histiocytes, some containing the causative bacterium, *Klebsiella rhinoscleromatis* (note tiny rod-like structures in the central white oval area). Reproduced from Suchanova et al. [47], with permission from Sage Publishing

Hebra in Europe, but it is very rare in Europe now. It is primarily seen in Central and South America, Egypt and several other African nations, and India, Indonesia, Papua-New Guinea, and other areas of southern or southeastern Asia. Occasionally rhinoscleroma is reported in non-endemic areas such as western Europe or the U.S., but then primarily in immigrants from endemic regions [43–47]. The disease is chronic, so immigrants may reside in the non-endemic country for several years prior to diagnosis. For example, one report described an Egyptian man who had lived in Italy for 8 years prior to onset of symptoms due to rhinoscleroma [46].

The disease involves the nose in nearly all cases (90–100%), sometimes with extension to the nasopharynx, larynx, oral cavity, trachea, bronchi, Eustachian tube, and middle ear. Occasionally, the larynx is involved without evidence of nasal disease. Molumi and Dubey reported 134 cases seen in Papua New Guinea 1995–2013 [48]. The nose and nasopharynx were involved in 92%, including cases with extension to other areas, while the remaining 13% of patients had primary involvement of the larynx without nasal involvement. Rhinoscleroma has three stages, catarrhal-atrophic, granulomatous or hypertrophic, and fibrotic. The first stage usually lasts weeks to months, while the second and third stages may last for years before diagnosis and treatment. During the first stage, patients have persistent rhinorrhea or foul-smelling discharge with crusts [43]. During the second stage, there are intranasal nodules, granulomatous tissue, or masses that may be mistaken for malignancy (Fig. 16.8a). The masses may be polypoid and often arise from the anterior septum; nasal deformity from the destruction of cartilage and intranasal masses may occur [43]. In the third stage there is scarring, and a tracheostomy may be necessary if there is laryngeal involvement.

Diagnosis is usually made by biopsy and culture during the granulomatous phase of disease. The classic foamy or vacuolated macrophages ("Mikulicz cells") seen on histology in biopsies of this phase were first described by Mikulicz in 1876; intracellular bacilli can be seen in some cells (Fig. 16.8b). Cultures are positive for the causative organism, *Klebsiella rhinoscleromatis*, in approximately 50% of the cases. The organism is sometimes described in the literature as a subspecies of *K. pneumoniae*, but recent genome analysis suggests it is a separate species [49]. Although other *Klebsiella* species are widely distributed in the environment (water, soil, plants), *K. rhinoscleromatis* has never been found in a non-human host and it has a characteristic somatic: capsular antigenic fingerprint of O2:K3 [45]. Treatment is usually with an antibiotic such as ciprofloxacin or trimethoprim-

sulfamethoxazole for one to several months [45], although the optimal duration has not been defined. Surgery may be required in some cases. Relapses may occur, requiring retreatment.

Fungal Infections

Invasive Aspergillosis and Mucomycosis

These mold infections usually occur in the immunocompromised host and arise from the sinuses. The nose may also be involved occultly, as demonstrated by biopsy of middle turbinate mucosa. Invasive fungal sinus infections are discussed further in Chap. 15.

Histoplasmosis

Histoplasma capsulatum is a fungus that is endemic in many locations worldwide, including the Ohio and Mississippi River valleys in the U.S., parts of Mexico, Central and South America, Africa, Asia, and Australia. It is thermally dimorphic, being a mold in the environment but a yeast in human tissues. The fungus lives in the environment, particularly in soil that contains large amounts of bird or bat droppings. Activities that disturb soil can lead to aerosolization of the microscopic fungal spores and inhalation. Primary infection almost always occurs in the lungs and is usually asymptomatic and self-limited in the immunocompetent host. Infection may remain dormant for years, however. An immunocompromised patient may develop evidence of disseminated infection from either recently or remotely acquired primary infection. A history of even remote residence in an endemic area may be significant. At the time of presentation with extrapulmonary disease, the lungs may be clear. Evidence of disseminated histoplasmosis may occur in immunocompetent hosts but this is rare.

Disseminated histoplasmosis may involve the upper airway, usually oral cavity, pharynx, or larynx. Nasal involvement is very rare and typically presents as an ulcerated intranasal lesion with overlying crusts [50] or as a granulomatous intranasal lesion that may mimic a tumor. Diagnosis is by biopsy and fungal culture. Treatment is with antifungal therapy, usually with an induction course of liposomal amphotericin followed by a very prolonged course of itraconazole. Another endemic fungal infection, blastomycosis (cause by *Blastomyces dermatiditis*), may very rarely cause intranasal lesions [51].

Conidiobolomycosis

This infection is a localized zygomycosis that is also called rhinofacial Entomophthoro-mycosis (order Entomophthoromycosis, class Zygomycetes). The infection, due to the fungus *Conidiobolus coronatus*, is rare and affects immunocompetent hosts, especially those engaged in farming or other outdoor activities. The disease occurs in Africa, Central and South America, and Southeast Asia. It may be seen in non-endemic regions in immigrants [52]. The fungus is present in soil and decaying vegetation, and is probably acquired by inhalation. The clinical presentation is usually chronic and symptoms include nasal obstruction, discharge, or deformity. The nose may develop gradual and painless swelling (Fig. 16.9) [53]. Intranasal exam usually shows masses or nodules [53]. The classic finding on biopsy is short broad hyphae ensheathed by eosinophilic material (Splendore-Hoeppli phenomenon). The organism may grow on fungal culture. Treatment is with antifungal agents.

Parasitic Infections

Leishmaniasis (Mucosal)

Leishmaniasis is a parasitic disease caused by an obligate intracellular protozoan that is transmitted by the bite of the sand fly. The sand fly is one-third (or less) the size of a mosquito. Different species of sand fly transmit different *Leishmania* species so the manifestations of disease vary across the world, and the disease is often categorized as New World (Mexico, Central and South America) or Old World (Asia, Africa, southern Europe). The disease has three main clinical syndromes, cutaneous, mucosal, or visceral, with cutaneous being the most common and mucosal being the type that affects the nose.

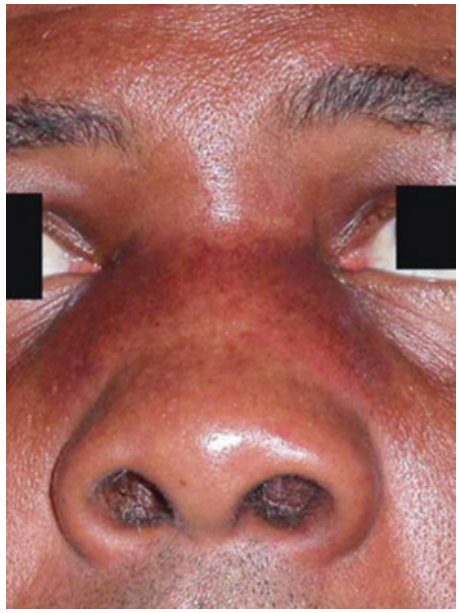

Fig. 16.9 Conidiobolomycosis (rhinofacial Entomophthoromycosis). A Sundanese immigrant to Switzerland complained of 9 months of painless swelling of his nose. Cultures of a nasal biopsy grew *Conidiobolus coronatus*. Reproduced from Fischer et al. [53], with permission from Springer

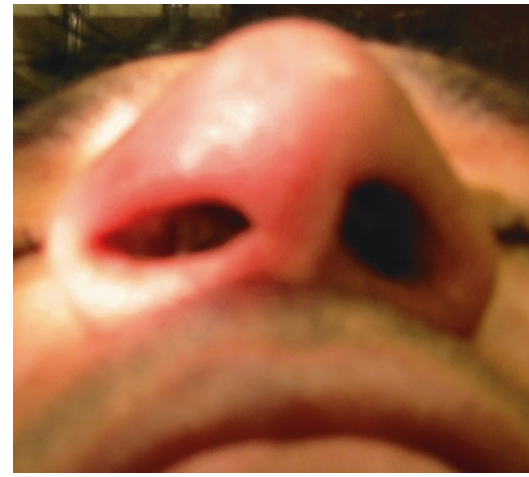

Fig. 16.10 Leishmaniasis (mucosal). A 35-year-old immigrant from Brazil to the U.S. presented with a history of an intranasal ulcer for 6 months and nasal congestion, swelling, and pain for 2 months. The right nostril was partially collapsed and tissue under the rim was thickened. The nasal septal mucosa was inflamed and had a cobblestone appearance. Diagnosis of *Leishmania* (*V.*) *braziliensis* was made by special culture of a biopsy specimen for *Leishmania*. The case is further described in reference [55]. (Photograph courtesy of Dr. Marlene L. Durand)

The mucosal form is found only in New World leishmaniasis. Mucosal leishmaniasis, also called espundia, occurs in parts of Mexico, Central America, and South America except for Chile and Uruguay [54]. Cases are occasionally seen in non-endemic countries, such as the U.S., in immigrants from Mexico and Central and South America [55].

All mucosal leishmaniasis cases result from occult metastatic spread of an earlier cutaneous inoculation of the *Viannia* subgenus of *Leishmania*, especially *L.* (*V.*) *braziliensis* (or less often by *L. amazonensis*). The first manifestation of infection is a painless cutaneous lesion occurring at the site of a sand fly bite but weeks to months later. The skin lesion begins as a papule but becomes an ulcerated plaque, which heals spontaneously over several months. A scar may result. In a small percentage of untreated cases, the patient develops mucosal leishmaniasis one or more years later. The skin lesion may have gone unnoticed. Amato et al. reported a series of 140 patients with mucosal leishmaniasis seen in Brazil and less than half recalled a skin lesion [56]. Rarely, cutaneous and mucosal lesions are present simultaneously (mucocutaneous leishmaniasis). The risk of developing mucosal leishmaniasis after untreated cutaneous leishmaniasis is unknown, but probably less than 5%.

The initial symptoms of mucosal leishmaniasis usually relate to the nose, although some cases may have oral or pharyngeal symptoms first [54]. Nasal congestion, rhinorrhea, and epistaxis are the most common presenting symptoms. Most patients have nasal mucosal disease or septal perforations (87% in the Amato series), while some also (or only) have oral/palatal disease (24%) or laryngeal disease (16%) [56]. Clinical signs in the nose may evolve over time and may include hyperemia and edema, nodules, ulceration, and nasal perforation [57] (Fig. 16.10). Diagnosis of mucosal leishmaniasis is made by biopsy of abnormal areas of mucosa for pathology, culture, and polymerase chain reaction (PCR) testing. The parasite does not grow on routine culture media and the necessary specialized media (e.g.,

Novy-MacNeal-Nicolle) can be obtained from the reference laboratory, ideally prior to biopsy. In the U.S., physicians should contact the Centers for Disease Control and Prevention (CDC) (see the CDC website, http://www.cdc.gov/parasites/leishmaniasis/resources/pdf/cdc_diagnosis_guide_leishmaniasis_2016.pdf). Mucosal leishmaniasis is treated with liposomal amphotericin, miltefosine, or antimonial compounds. Guidelines for the diagnosis and treatment of leishmaniasis have been published recently by the Infectious Disease Society of America [57].

Rhinosporidiosis

Rhinosporidiosis is a chronic infection that typically causes intranasal masses. It is caused by an unusual organism, *Rhinosporidium seeberi*. The infection occurs in tropical regions worldwide (e.g., South America, Africa, Asia) but is most prevalent in southern India and Sri Lanka [58]. The infection can occur in several animal species in addition to humans. The organism cannot be propagated in the laboratory and classification has been difficult. It was originally thought to be a parasite, then a fungus, and most recently an aquatic protistan parasite. Through phylogenetic analysis, it has been placed in a new clade named Mesomycetozoa that also includes some fish parasites [59]. It is postulated that humans acquire infection during bathing in contaminated water, particularly stagnant bodies of water [58].

Most rhinosporidiosis patients are young to middle-aged, live in rural areas, and work in agriculture [60]. The disease manifests as polypoid masses that most often arise in the nose, with the second most common site being the palpebral conjunctiva; other sites, such as the urethra, may be affected. The intranasal masses may be large and obstruct the nostrils. They may be pedunculated or sessile and are usually pink or red. They may have a "strawberry" appearance because of the presence of white subepithelial dots on the pink/red background of the mass. These white dots represent the thick-walled sporangia of the organism [61]. Diagnosis is based on histology since the organism cannot be cultured. Pathognomonic sporangia are seen in tissue biopsy specimens. These sporangia are 60–450 μm in diameter and contain up to 12,000 endospores each [59]. Treatment is with surgical excision, with electrocautery of the base of the mass after excision. A prolonged course of dapsone is often given postoperatively to prevent disease recurrence.

Conclusion

The nose may be infected by viruses, bacteria, fungi, or parasites. The most common nasal infections are viral, self-limited, and occur as part of the common cold. Minor bacterial infections of the nasal skin or vestibule are usually caused by *S. aureus* and are easily treated. However, any bacterial infection involving the nose should be promptly treated to prevent the rare but life-threatening complication of septic cavernous sinus thrombosis. Rare intranasal infections include those that are mucosal manifestations of a systemic disease with a prolonged latency, such as intranasal TB, leprosy, syphilis, and histoplasmosis, or represent localized inoculation of an unusual pathogen, such as conidiobolomycosis or rhinosporidiosis. Most rare nasal infections are chronic and occur in tropical regions of the world. However, patients with such infections may present to an otolaryngologist in a non-endemic region months or years after visiting or living in an endemic region. Knowledge about rare nasal infections may be helpful to all otolaryngologists, regardless of where they see patients.

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