Inflammatory Bowel Disease Nursing Manual

Andreas Sturm
Lydia White
Editors

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For all nurses.
You have worked long shifts, gone beyond your time, studied on your days off, and done so much more than is ever seen.
Thank you.
We dedicate this book to you.

Preface

Since the 1990s, nurses specialising in IBD have increased not only in numbers but also in the scope of the role all over the world. They are now considered a key part of an effective and functional inflammatory bowel disease (IBD) care team. Although there are variations between countries, core knowledge and skills must continue to move forward to ensure that all patients with IBD get consistent, high-quality care. Our aim for this nurse manual is that IBD nurses, wherever they practice and at whatever level, are challenged to achieve greater expertise and self-assurance.

We hope to have made this easy-to-read manual relevant everywhere by involving experts from around the globe, often in joint authorship, who reflect their own background and knowledge. Indeed, this book relies heavily on a multidisciplinary approach, a principle argued to be the best in managing complex and debilitating conditions. This type of shared care enables all members of the team to competently support people living with IBD. More importantly, this book strives to cross professional boundaries and aim for a common base of knowledge for all those working in the field. Once this multidisciplinary approach is applied universally, the standard of IBD care will improve.

The book content covers all aspects of IBD management: causes, diagnosis, assessment, monitoring, disease management, complications and comorbidities, lifestyle issues such as transition, research and, last but not least, the practicalities of IBD nursing services. Specifically, the aim of this IBD nurse manual is to help caregivers provide timely, responsive and expert care, which are things that are consistently reported to be important to IBD patients. Indeed, those living with IBD have often contributed the loudest voice in the call for more IBD nurses to be trained and integrated within IBD care teams.

To the IBD nurse opening these pages, we commend your dedication and passion. We hope this book supplies a comprehensive and easily understood knowledge base, sound principles for practice and even some inspirational ideas to match your commitment. With these things you can look forward to a future as a confident member of the multidisciplinary team able to tackle the individual problems facing the IBD patient with enthusiasm.

Berlin, Germany — Andreas Sturm
Oxford, UK — Lydia White

Acknowledgment

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Contents

About the Editors

Andreas Sturm is Professor of Medicine at the Charité–Universitätsmedizin Berlin, Germany, and head of the Department of Internal Medicine and Gastroenterology at the German Red Cross Hospital Berlin, Westend, an academic teaching hospital of the Charité. His university education began in Aachen, Germany, where he gained first class honours in medicine in 1994. Since then, his medical career has involved extensive work in gastroenterology, including a research fellowship at Case Western Reserve University, Cleveland, Ohio, USA. He awarded his qualification in 2004 as a university lecturer for the field of Internal Medicine at the Charité Berlin and is since then a member of the faculty. Prof. Sturm is also certified as a fellow of the European Board of Gastroenterology. He served as coordinator of the Interdisciplinary Center for Colorectal Cancer of the Charité, president of the Inflammatory Bowel Disease working group of the German Association for Digestive and Metabolic Disorders and member and chair of the scientific committee of the European Crohn's and Colitis Organisation (ECCO). He is a founding member and was first speaker of the German IBD Study Group (GISG). He is currently a member of the Advisory Board of the Competence Network IBD and Chair of the Guideline committee of ECCO. Dr. Sturm gained the Board certification for Internal Medicine, Gastroenterology, Nutrition (DifE) and Proctology and is certified for medical cancer therapy, GI oncology (DGVS) and inflammatory bowel disease (DGVS). He has more than 100 scientific manuscripts and book chapters published in international journals, including *Gastroenterology*, *Journal of Clinical Investigations* or *Gut* and has worked as a reviewer for numerous journals and organisations. He invented and started the first German IBD nursing course in 2008, still running successfully since then.

Lydia White is IBD Advanced Nurse Practitioner has been the IBD nursing lead at the John Radcliffe Hospital tertiary referral unit in Oxford for over 10 years growing the nursing service to a team well integrated with the wider multidisciplinary team and supporting a large cohort of IBD patients. She has done her post-graduate education in Advanced Gastro-Intestinal Nursing at King's College London and Oxford Brookes University and now holds a master's degree and independent prescribing qualification in the specialty. Ms. White has also been involved in IBD nursing at regional, national and international levels in networking, project work and speaking. She started and chaired the South Central regional Royal College of Nursing IBD group and has been part of guidelines including the European consensus statement on the role of the IBD nurse. She was also privileged to serve on the Nursing European Crohn's and Colitis Organisational (NECCO) board for a term and has been a regular speaker in the NECCO school and related activities. At present Lydia is on a career break from Oxford to set up an IBD nursing service in Rotorua, New Zealand while contributing to the national role descriptors and its recognition as a burgeoning specialty there.

Part I

IBD Foundations

Anatomy and Physiology

1

Tanja Kuehbacher

Abstract

Understanding the structures and the function of the gastrointestinal tract (GI tract) in healthy individuals is the premises to understand malfunctions and diseases. It enables to explain difficult and complex interactions and modern therapeutic regimens. The GI tract consists of several organs, and the main tasks are the digestion, decontamination of food and environmental elements and most importantly the immunity. In a complex interaction with innate and adaptive immunity and, a lot of key factors like the microbiota, the intestinal immune system enables the human individuum to live in an often hostile environment. It makes it possible for an individuum to recognize and memorize protective or harmful agents and to start defensive mechanisms. Dysbalances lead to defects with malfunctions and diseases. The aetiology of these defects is in most diseases not well understood. Underlying genetic causes and environmental triggers can lead to immunological and microbiota dysbalances.

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1.1 Introduction

The intestine is the largest immune system of our body. To understand inflammatory bowel disease in patients, it is at first essential to review and understand the function of the gastrointestinal tract and its immune system in a healthy individual. Therefore, the anatomical structure of the gastrointestinal (GI) tract will be shortly described, followed by an explanation of the digestion and the intestinal immune system.

With understanding the physiology of the GI tract, it will be easier to explain malfunctions like diarrhoea, anaemia, malnutrition and dysfunction of the intestinal immune system in inflammatory bowel disease (IBD) to patients.

1.2 Anatomy of the Gastrointestinal Tract

The gastrointestinal tract starts with the mucosa of the mouth and ends at the anus (Fig. 1.1). It consists not only of the small and large bowel but also the oesophagus, stomach, pancreas and the liver are belonging to the system. The short description of the major anatomical structures begins with the oral mucosa in the oral cavity, followed by the different organs and the intestine.

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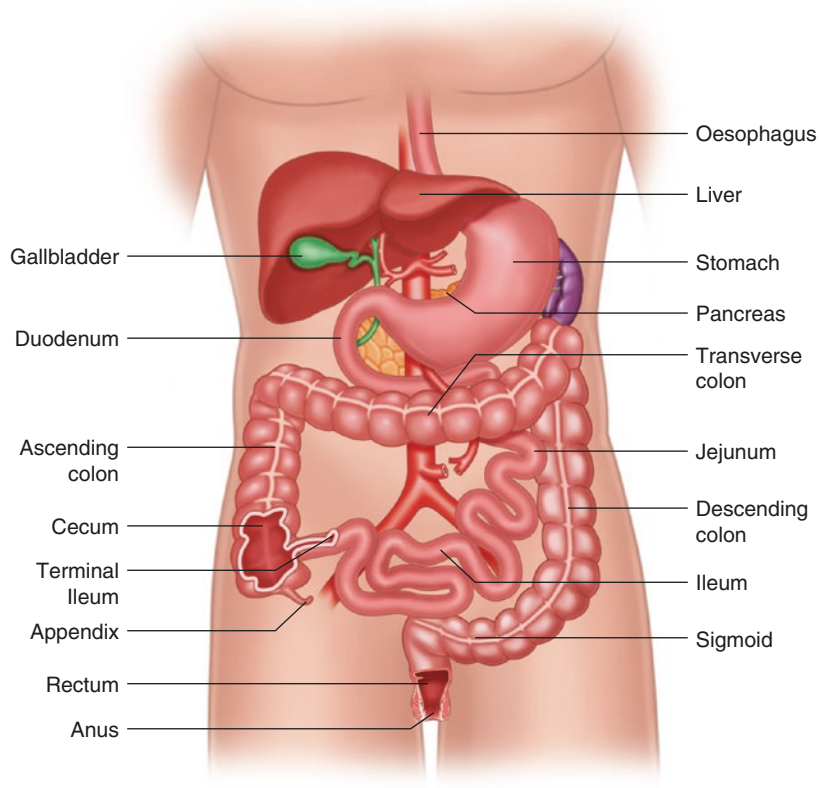

Fig. 1.1 The human gastrointestinal tract with all essential organs and differentiation of the segments of the small and large bowel

1.2.1 Oral Mucosa

The so-called stratified squamous epithelium and the lamina propria are building together the oral mucosa. Under the microscope, histologically, a non-keratinized mucosa can be differentiated from a keratinized mucosa. The keratinized mucosa can be found only dorsal at the tongue, the hard palate and the gingival. The non-keratinized mucosa consists of two (stratum basale and stratum spinosum) instead of four layers (stratum basale, stratum spinosum, stratum granulosum and stratum corneum). The function of the oral mucosa is widespread. It is responsible for the first contact with the nutrition, the taste sensation, secretion of saliva, sensation of hot and cold and, last but not least, it is the first barrier for pathogens. The mucosa of the oral cavity is a tissue, which is healing very fast. This is a big advantage in oral injuries. The disadvantage is, on the other hand, that all injuries of the oral mucosa are indeed very painful due to multiple nerve endings, necessary for tasting, smelling and feeling sensations. An effect seen in patients undergoing chemotherapy and suffering from stomatitis due to the quick cell separation, but mucosa improving rapidly after chemotherapy is finished.

In some patients, the dentist is the first person to suspect an IBD due to the appearance of aphthoid lesions on the oral mucosa as signs of the intestinal inflammation (Nanci 2003; Moore 1999; Drenkhahn and Waschke 2008).

1.2.2 Oesophagus

The oesophagus is a muscle in the form of a tube. The food is transported by this muscle from the mouth to the stomach in peristaltic waves. The length of the oesophagus adds up to about 25 cm. It begins with the upper and ends with the lower sphincters, two muscular rings, which close the

oesophagus in case no food is being transported and prevents liquids or chewed food that are fleeting back (Moore 1999; Drenkhahn and Waschke 2008).

1.2.3 Stomach

The stomach is a hollow organ for digesting and storing the incoming food. It is distensible and able to contain up to 1 L of nutrient. The stomach is divided into different parts, called antrum cardiacum, fundus, body and the pyloric sphincter (Moore 1999; Drenkhahn and Waschke 2008).

1.2.4 Duodenum

The duodenum is the first part of the small intestine. It consists of four segments: superior part, descending part, horizontal part and ascending part. The duodenum persists of a villous mucosa with a mucosa, submucosa, muscularis and adventitia (Moore 1999; Drenkhahn and Waschke 2008).

1.2.5 Pancreas

The glandular organ pancreas is structured in a head, the neckline, body and the tail. The pancreas has an exocrine and endocrine functional role, which means that it is of high importance in secreting enzymes and hormones. Dysfunction can lead to diabetes or chronic diarrhoea with fatty and large volume stools due to a malassimilation (Moore 1999; Drenkhahn and Waschke 2008).

1.2.6 Liver with Gallbladder

The liver is an organ with an extreme potential in self-regenerating. It is essential for enzymes, hormones and detoxicating processes and for the digestion of food. It also plays an important role in metabolism. The liver is the chemical factory of our body. Many medications are eliminated or metabolized by the liver. Anatomically, it is divided into lobes. The gallbladder can be found directly under the liver. It is responsible for the storages of the bile acid, which is produced in the small bile ducts in the liver (Moore 1999; Drenkhahn and Waschke 2008).

1.2.7 Small Intestine (Jejunum and Ileum)

The small intestine is the most important part in the absorption and resorption of nutrients. It consists of the duodenum, jejunum and ileum. The wall of the small intestine includes the mucosa with an intestinal epithelium, lamina propria, muscularis mucosa, submucosa, muscularis externa and the serosa. The sections differ microscopically, only the ileum shows Peyer's patches, while Brunner's glands can be found exclusively in the duodenum (Moore 1999; Drenkhahn and Waschke 2008).

1.2.8 Large Intestine (Cecum, Ascending Colon, Transverse Colon, Descending Colon and Sigmoid, Rectum)

The large intestine starts with the ileocecal valve. The cecum and appendix can be followed to the ascending colon, which belongs to the right colon. After passing the right flexure, the transverse colon appears and turning through the left flexure, the large intestine ends with the descending colon, sigmoid and finally, the rectum. The wall of the large intestine consists of colonic crypts and columnar epithelium.

Through contraction of the so-called taenia coli, three bands of smooth muscles, the haustra were built (Moore 1999; Drenkhahn and Waschke 2008).

1.2.9 Anus

The anus is the end of the rectum. It is separated into three parts, the zone columnaris, intermedia and zone cutanea. The sphincter closes the anus (Moore 1999; Drenkhahn and Waschke 2008).

1.3 Physiology of the Gastrointestinal Tract

What follows as the first important act of digestion after the mechanical grinding by chewing the food with the teeth is the salivation. Without salivation no further smooth transport and digestion would be possible. But, of course, the food has actively to be swallowed and transported into the stomach. This is done by the oesophagus.

Being finally in the stomach, the food will not only be stored but digested in a first step and disinfected with the help of acid secretion and antibacterial agents. The passage time of the nutrients can differ individually from person to person and is depending on the composition of the food. Gastric and intrinsic factors from the parietal cells and enzymes like pepsinogen and gastric lipase from the enteroendocrine system start the real digesting process. Hormones like gastrin, cholecystokinin, somatostatin, histamine and serotonin are secreted. Throughout the pyloric valve, the predigested food is processed into the duodenum (Johnson 2012).

In the small intestine, the most important part, the resorption and absorption of nutrition begins. The hormones, cholecystokinin and secretin are secreted in the duodenum following by an opening of the pylorus (Johnson 2012).

Bile acid is being released from the liver and the gallbladder, in order to process lipids in the nutrition. Glycogen storage and synthesis also take place in the liver, and the liver is responsible for amino acid and protein synthesis. The liver itself is a very complex organ, which is responsible of a huge amount of metabolism, immunological and detoxification pathways (Johnson 2012).

The pancreas, another important organ, is responsible for the insulin secretion. This happens within the pancreatic islets. The pancreas is essential, not only for controlling the blood sugar by secreting insuline, but also in secreting enzymes for the protein, lipid and carbohydrate digestion. These enzymes are amylase, lipase, trypsinogen, chymotrypsinogen, cholesterol esterase, lysophospholipase and phospholipase A2. The secretion of bicarbonate is needed to neutralize the acid from the stomach (Johnson 2012).

The major work of the digestion is taking place in the small intestine: the duodenum, jejunum and ileum. After the degradation of the nutrition by the help of enzymes and hormones, the digested nutrition parts can now be absorbed into the blood. The microvilli of the small intestine lead to an increased surface, to improve the absorption of nutrition. Not digested nutrition materials will be transported to the large intestine. Important absorption of single vitamins and nutrition parts also takes place in the small intestine: vitamin B12 and bile acids are absorbed in the terminal ileum, and iron is absorbed in the duodenum (Johnson 2012).

The large colon in the end functions as a reservoir of stool and leads to an absorption of water. Some vitamins like vitamin K are absorbed in the large colon (Johnson 2012).

The microbiota (former name gut flora) is essential for the homeostasis of the intestinal immune system. The microbiota contains more than 10^{12} bacteria per gram stool. This is more than 10 times of the human cells in a human body and weighs about 1–2 kg. The microbiota seems to be individually genetically determined and may be influenced by environmental factors (e.g. nutrition, antibiotics and infections). In IBD, the microbiota is less diverse than in healthy individuals, which means that in active IBD the population with different strains of bacteria is decreased. This results in inflammatory processes. The microbiota seems to play also an important role in neurodegenerative diseases, diabetes and obesity (Alberts et al. 2002; Abraham and Cho 2009; Hooper 2009).

1.3.1 Intestinal Immune System

The intestinal mucosal barrier has the most important task in recognizing all antigens with which an individuum comes in contact and differentiate and respond to the incorporated pathogens and foreign substances. This is named innate immune system. The innate immune system provides not a long-lasting immunity but an

immediate way of defence. It acts like fire fighters. The mucosa is overlaid by mucus, which is secreted by cells in the mucosa. The mucus and special cells in the mucosa, Paneth cells (secreting defensins, some kind of "human own antibiotics"), M-cells, dendritic cells, antibodies and antigen presentation to the adaptive immune system help to remove danger for the host. Pro- and anti-inflammatory cytokines, messengers in activating inflammatory or anti-inflammatory reactions, play a major role in holding the balance in a healthy individual. Such a cytokine is e.g. TNF alpha, which is up-regulated in inflammatory processes. Modern treatment strategies block or inhibit cytokines or signal pathways in inflammation. Innate and adaptive immunity is explained in the following in more detail (Alberts et al. 2002; Abraham and Cho 2009; Hooper 2009; Gallo and Hooper 2012; Hooper et al. 2012) (Fig. 1.2).

The mucosal wall acts as a barrier. The intestinal immune system recognizes and presents antigens to defend the host in complex pathways. Defensins, antimicrobial peptides, are secreted along with immunoglobulin A for protection from luminal bacteria. Dendritic cells, macrophages and epithelial cells recognize bacteria by pattern recognition receptors, e.g. NOD (nucleotide oligomerization domain), and Toll-like receptors. Antigens were presented by dendritic cells to T-cells, which leads to cytokine secretion and T-cell differentiation.

1.3.2 Innate Immunity

The innate immune system can be compared to an emergency room of a big hospital. In case of an attack of e.g. viruses or bacteria, it can react very fast like a first aid force. This is absolutely important for survival; otherwise, bacteria or viruses can increase in their amount in a very short period of time and lead to irreparable damage or even can result in death.

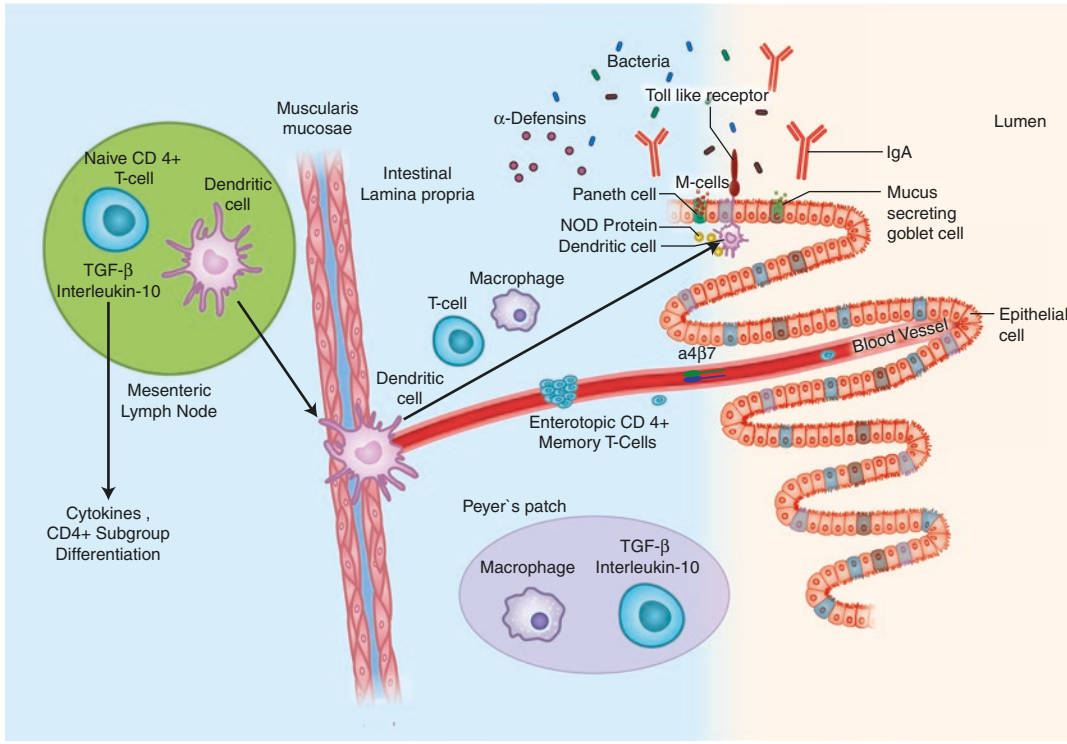

Fig. 1.2 The intestinal immune system

In contrast to the specific adaptive immune system, which, first of all, has to learn to react to pathogens and has to be triggered initially by the innate immune system, it starts working immediately after contact with a pathogen. The mechanisms therefore are evolutionarily very old, and every human being is already "equipped" and ready for use with it at birth. But, there is one big disadvantage of the system: it is non-specific. Therefore, the adaptive immune system exists.

The following actors play a major part in the innate immune system:

As a first barrier for pathogens serves the skin, epithelium or mucosal layer. The special construction like e.g. tight junctions of these barriers prevents an easy access for harmful agents. They act as some kind of mechanical frontier. In the mucosa itself, antimicrobial peptides can kill or inactivate pathogens. Some of these remarkable "body own antibiotics" are the defensins. These defensins play an important role in the pathophysiology of IBD. They are secreted by the Paneth cells.

When a pathogen bypasses successfully the front door (the epithelium or mucosa) and invades the body, the innate immune system has to differentiate between a guest or an enemy. The innate immune system relies for that on the so-called pathogen-associated molecules, which are common in most of the pathogens and not to be found in the host. After these molecules have been recognized by the innate immune system by the so-called pattern-recognition receptors, two different types of responses can be initiated: an inflammation or phagocytosis. The inflammatory response leads to typical inflammatory procedures, e.g. swelling, oedema and higher temperature, whereas the phagocytosis process eliminates the pathogen by macrophages and neutrophils. The pattern-recognition receptors are existing in the human body in the blood as soluble receptors as part of the complement system or as membrane-bound receptors. Important membrane-bound receptors are the Toll-like receptors and very important too are the nucleotide oligomerization domain (NOD) proteins. Both play an important role in the pathophysiology of IBD (Alberts et al. 2002; Abraham and Cho 2009; Hooper 2009; Gallo and Hooper 2012; Hooper et al. 2012) (Fig. 1.2).

The inflammatory process is mediated by the so-called signaling cytokines. The signal transduction pathways are very complex. Pro-inflammatory cytokines (e.g. TNF alpha) behave like postmen, delivering letters, which contain the order to start special inflammatory processes. Anti-inflammatory cytokines are the opponents. Only if both are in balance, does the individuum not suffer from acute or chronic inflammation (Alberts et al. 2002; Abraham and Cho 2009; Hooper 2009; Gallo and Hooper 2012; Hooper et al. 2012).

1.3.3 Adaptive Immunity

The human body interacts for its whole lifetime with the surrounding environment. This means, millions over millions of particles, which were inhaled, ingested by the body or had contact over the skin, have to be identified regarding their potential to be a possible threat for the individual. This is the mission of the adaptive or acquired immune system. It adapts and learns by contact with such potential pathogens over the total lifespan of an individuum and stops only with death. The action taken is slower than the innate system works, but the adaptive immune system appears as the fine and filigree special task force of the immune system (Alberts et al. 2002; Abraham and Cho 2009; Hooper 2009; Gallo and Hooper 2012; Hooper et al. 2012).

This is what happens: after once being exposed to a pathogen, the adaptive immune system uses antigens to react on it. This mechanism allows to provide an adequate answer to a special threat. The only requirement for that is the already occurred contact with this special pathogen in the past. The task of the adaptive immune system is clear: to eliminate specific pathogens and all the dangerous products of this pathogen. Therefore, it is crucial for the adaptive immune system to understand, which part is of the host, and which is not, in order to avoid self-destruction or auto-

immune diseases (Alberts et al. 2002; Abraham and Cho 2009; Hooper 2009; Gallo and Hooper 2012; Hooper et al. 2012).

The adaptive immune system is called for work by the innate immune system, when a special pathogen-associated molecule is being recognized. These antigens leading to the adaptive immune response were carried out by special lymphocytes, the B- and T-cells (Alberts et al. 2002; Abraham and Cho 2009; Hooper 2009; Gallo and Hooper 2012; Hooper et al. 2012) (Fig. 1.3).

The B-cells are responsible for the antibody response, the T-cells for the so-called cell-mediated immune response. After activation, B-cells can secrete proteins, the immunoglobulins, which act as antibodies. These antibodies can bind to specific antigens in the blood or other fluids. The binding of the antibody to the antigen inhibits therefore the binding on receptors of the host. This inactivates the antigen or leads to the destruction by phagocytosis as part of the innate immune system (Alberts et al. 2002; Abraham and Cho 2009; Hooper 2009; Gallo and Hooper 2012; Hooper et al. 2012).

The cell-mediated immune response uses either active T-cells as direct executers of antigens, when the antigens were presented on cells of the individuum, or as signal producers for macrophage activation (Alberts et al. 2002; Abraham and Cho 2009; Hooper 2009; Gallo and Hooper 2012; Hooper et al. 2012) (Figs. 1.2 and 1.3).

The molecular pathways underlying the procedures of the innate immune system and the adaptive immune system are very complex. New treatment regimes use cytokine antibodies, inhibition of signal pathways by small molecules or inhibition of cell migration in chronic inflammatory diseases (Alberts et al. 2002; Abraham and Cho 2009; Hooper 2009; Gallo and Hooper 2012; Hooper et al. 2012).

The intestinal barrier consists of cells with tight junction, mucus and defensins. Microorganisms can be permeabilized, identified and either inactivated or internalized by macrophages and killed. Paneth cells secrete antimicrobial proteins.

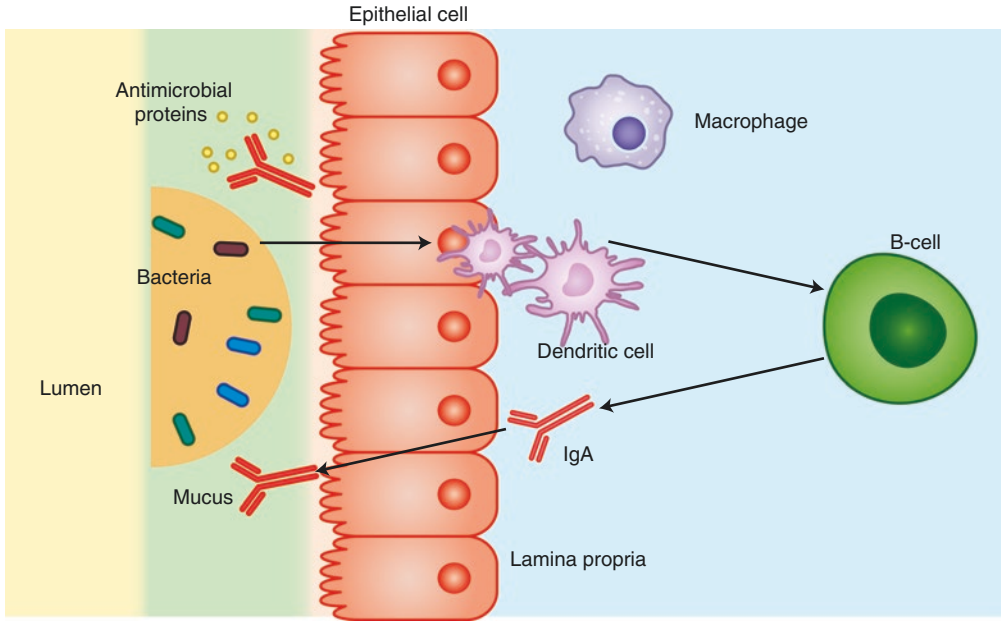

Fig. 1.3 The intestinal barrier and the adaptive immune system

1.4 Summary

The anatomical structure of the GI tract reflects quite well its function. Responsible for digesting the food by absorbing and resorbing nutritional elements, e.g. vitamins, the mucosa plays an important role for this function. But, another task which is even of higher importance than providing the daily energy uptake in the human body is the immune defence. The intestinal immunity with its complex interaction of adaptive and innate immunity and the microbiota enables the human individual to survive in an environment with an unknown number of bacteria and virus attacks per day and makes it possible to differentiate between useful and protective or harmful new agents. A dysbalance of this complex immunological interplay leads to serious malfunctions and diseases.

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Epidemiology

2

Johannes Meier

Abstract

The appearance of IBD varies widely with higher incidences in well-industrialized countries compared to industrializing and developing countries. A striking north-south and west-east gradient in IBD incidences can be observed. Overall the global incidence of IBD is still rising. The time of onset of CD shows two peaks (15–20 and 50–70 years) whereas the onset of UC is usually seen in the youth, affecting both sexes equally.

2.1 Introduction

The field of epidemiology is the study on distribution and pattern of diseases in a population.

Questions to be answered by epidemiologic studies are, e.g. "how many people suffer from IBD in a specific country," "how many people are newly diagnosed IBD in this country per year, "or "are there traceable conditions and factors that may promote the outbreak of IBD?"

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By collecting epidemiological data of IBD cohorts important information about disease appearance and development can be obtained, helping to better understand the potential etiology and pathophysiology of IBD.

2.2 Epidemiology of IBD

Two important terms are used to indicate the frequency of a disease:

- The *prevalence* of a disease is the number of *existing* cases of a disease or health condition in a specific population at a designated time or during some designated time period.
- The *incidence* is the number of *new* cases of a disease in a specific population during a specific time period.

Both prevalence and incidence of IBD vary widely across age and between different countries. They are higher in well-industrialized countries compared to industrializing and developing countries. Overall the worldwide prevalence of IBD has continued to increase in recent years and reached more than 5 million people worldwide, thereof 3 million people in Europe and 1 million people in the USA.

The highest annual incidence of UC is reported for the Faroe Islands, Iceland, and United Kingdom reaching up to 24 cases per 100,000

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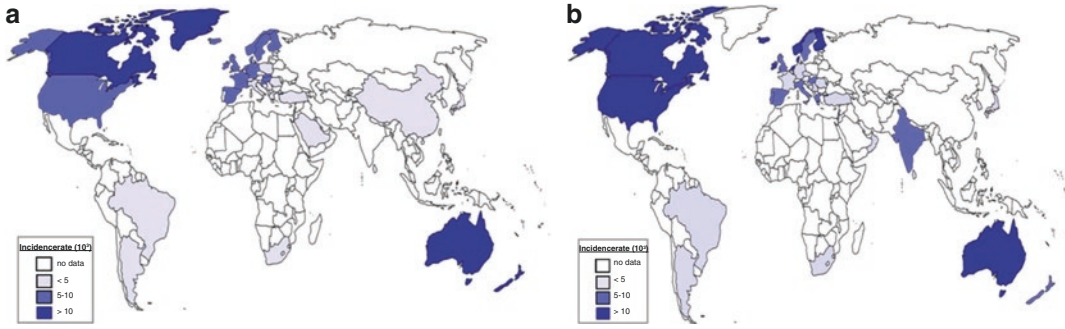

Fig. 2.1 Global map of Crohn's (**a**) and Ulcerative Colitis (**b**) incidences (Ng et al. 2013)

person years as well as North America (up to 19 cases/100,000 person-years). The highest incidence of CD is reported from Australia (29/100,000 person years) and North America (20/100,000) while the lowest annual incidence of both UC and CD is seen in the southern and eastern Europe, Asia, and the Middle East (1–8/100,000) (Molodecky et al. 2012; Burisch et al. 2013; Burisch & Munkholm 2015).

For a number of countries, the incidence and prevalence of IBD remain unknown, as there no sufficient reliable data available (white fields in Fig. 2.1 above).

2.3 North-South Gradient

As illustrated in Fig. 2.1, the highest IBD incidences are found in northern European countries in Scandinavia and the United Kingdom with lower incidences in the southern parts of Europe. Strikingly similar patterns are found in North-America, with the highest IBD burden in the northern states of North America. Reasons for this so-called north-south gradient are not yet fully understood.

It seems to be a multifactorial combination of genetic susceptibility, environmental risk factors, and effects of the western lifestyle with advanced sanitary hygiene, higher antibiotic use, less dietary intake of fruits, vegetables, fish, olive oil, and wine in the north (referred to as Mediterranean food) and less exposure to sunlight with reduced anti-inflammatory vitamin D levels.

2.4 West-East Gradient

Historical IBD incidences have shown a further *west-east gradient* with a higher IBD burden in the western parts of Europe, North America, and Asia compared to their eastern parts. New data covering the recent decades now show an increase of IBD incidence in the eastern European countries, reaching about half of the western IBD incidences, while the western incidence rates are plateauing (Burisch et al. 2014; Vegh et al. 2017). This increase cannot only be explained by the rising awareness and advances in IBD diagnostic resources but also account for a real increase in IBD incidence in the eastern countries over time. The clinical presentation (phenotypes, disease extent) and the patient's characteristics (e.g., age, sex, smoking habits) of eastern and western patients are comparable and the genetic background seems to play a minor role. This can be nicely observed when families with IBD are migrating from industrializing or least-developed countries to industrialized developed countries. With a latency of one generation the immigrant's descendants adopt the higher local IBD incidence of the country they migrated to (Ye et al. 2015). Besides the genetic background there must be more important factors that trigger the onset of IBD. By influencing the expression of a given genetic background—the so-called epigenetic influences—environmental factors—such as the adaption of a more and more "westernizing" lifestyle in the industrializing

eastern countries are discussed as reason for the rising incidence.

2.5 IBD and Gender

Crohn's disease affects both sexes equally.

2.6 IBD Onset

The time of onset of CD shows two peaks: the first, larger peak occurs between the ages of 15–30 years; the second, smaller, peak is between 50 and 70 years (Fig. 2.2 below). The diagnosis is made in 25% in children and adolescents and in 10–15% in older patients over the age of 60. Most patients are diagnosed before the age of 35, in general 5–10 years earlier than ulcerative colitis (Ye et al. 2015).

The onset of ulcerative colitis shows similar distribution with the most important peak in the youth, but is continuously diagnosed in elderly people beyond 60 years. Keep in mind that the new onset of a chronic diarrhea of the elderly (often ignored or misdiagnosed as functional diarrhea) can be the first manifestation of an active ulcerative colitis.

The disease course of IBD in youth is often more complicated compared to adult IBD patients since IBD is a chronic (life-) long lasting disease. IBD is so far not curable; therefore, the major treatment goal is to achieve a stable remission and avoid IBD related complications and morbidity over time. The prompt start of an appropriate and efficient therapy is mandatory in order to prevent malnutrition, growth retardation, and surgical interventions during their future lives. They should therefore be referred to a specialized pediatric IBD center as soon as the diagnosis is made.

2.7 Summary

More than 5 million people worldwide suffer from IBD with significantly more people affected in the industrialized northern and western countries of Europe and North-America. During recent years a rising IBD incidence in industrializing eastern and southern countries is observed. Western lifestyle and environmental factors seem to play one role in a multifactorial process of IBD etiology. The majority of patients are diagnosed with IBD at an age under 35, and it equally affects males and females.

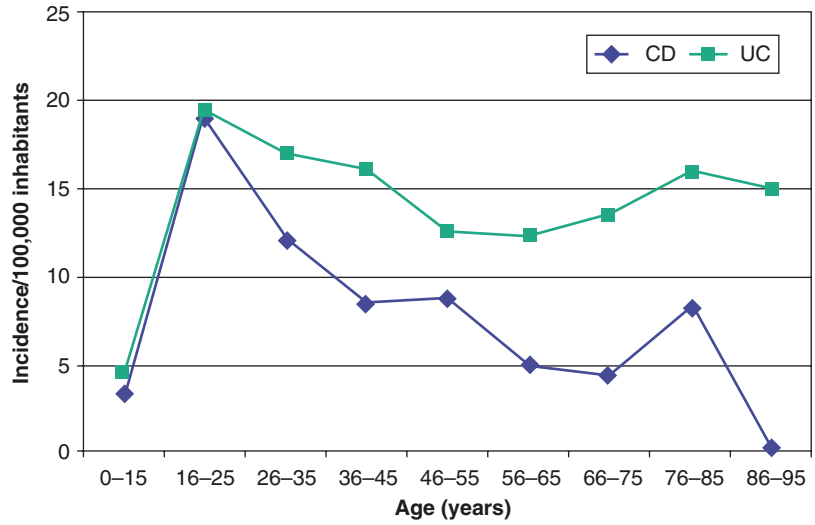

Fig. 2.2 Age-related incidence of Crohn's disease and ulcerative colitis in a Copenhagen cohort 2003–2005 (Vind et al. 2006)

Further Media of Interest

Comprehensive course on IBD epidemiology and pathology by KhanAkademie/American Association of Colleges of Nursing: https://www.youtube.com/watch?v=Ueqs7pl5OAY.

Epidemiological Committee (EpiCom) of the European Crohn's and Colitis organization (ECCO): https://www.ecco-ibd.eu/about-ecco/ecco-operational-board/epicom.html.

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3 Mechanisms of Disease, Etiology and Clinical Manifestations

Michael Böhmig

Abstract

Crohn's disease and ulcerative colitis are inflammatory diseases without a single cause. A genetic predisposition and environmental risk factors contribute to developement of the disease.

IBD are caused by an inadequate response of the immune system to the normal, non-pathogenic intestinal bacteria resulting in intestinal damage. The gut microbiome of patients shows alterations. The intestinal barrier is impaired.

Environmental factors seem to play a variable role. Smoking has negative impact on Crohn's disease.

UC is limited to the colon. CD may involve any part of the intestinal tract and is characterized by transmural inflammation, formation of stenoses, and fistulae.

While the bowel is the main place of manifestation, various other parts of the body may also be affected (extraintestinal manifestations, EIM).

3.1 Introduction

Inflammatory bowel disease (IBD) describes a group of disorders that affect the intestine or bowel. The two major disorders are ulcerative colitis (UC) and Crohn's disease (CD). They are inflammatory diseases similar to rheumatoid arthritis; in this regard they both share some characteristics and treatments in contrast to conditions such as degenerative diseases or neoplasms. In addition to a genetic predisposition and environmental risk factors, in persons affected by IBD there is a dysregulation of the immune system as well as defects of the epithelial barrier and altered composition of the microbiome. While the bowel is the main place of manifestation, various other parts of the body may also be affected. These are called extraintestinal manifestations (EIM).

Since the precise etiology is unknown, a causal therapy and cure is currently not available.

3.2 Mechanism of Disease

3.2.1 The Healthy State

The healthy intestine is protected by both an effective mechanical barrier and the immune system. The inner *mucous layer* offers protection by preventing large particles from contacting the epithelial layer while allowing small molecules to pass.

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This protection is continued by the *epithelial layer* through the secretion of defensive molecules in the form of granules that further prevent microorganisms from coming into contact with the epithelial layer as well as the presence of a single layer of securely joined cell junctions which ensure the selective uptake of luminal contents.

The GI tract, in particular the terminal ileum and the colon, harbors a huge amount of nonpathogenic bacteria. These bacteria have colonized the intestine after birth and may weigh between 1 and 2 kg in an adult. They are essential to nutrition, energy metabolism, and conditioning of the immune system and are called *gut microbiome* in their totality.

The healthy state is characterized by a balance between an adequate tolerance to dietary antigens and an appropriate responsiveness to enteric pathogens. This homeostasis is carried out by a well-balanced immune system. It is therefore imperative to understand the components of this system and how they function (see also Chap. 14).

The immune system consists of the innate and the adaptive immune system in addition to inflammatory cells and humoral factors. The *innate immune system* identifies and removes pathogens using *leucocytes* like neutrophils, granulocytes, or macrophages. In addition, specialized epithelial cells known as Paneth cells secrete defensive molecules such as the antimicrobial peptides alpha-defensins. A special type of cell, the *dendritic cells*, is constantly searching for pathogens through the use of toll-like and NOD-like receptors and, when located, present antigens to other cells which can induce *lymphocyte activation* of T and B cells (for more details please see also Chap. 1). Upon activation, immune competent cells such as macrophages, B lymphocytes, T lymphocytes, and mast cells as well as endothelial cells or fibroblasts secrete *cytokines* to balance the humoral and cell-based immune responses. Cytokines are a broad category of small proteins (~5 to 20 kDa) that are important in cell signaling. Cytokines may include chemokines, interferons, interleukins, lymphokines, and, e.g., tumor necrosis factors (TNF). The inflammatory response is dictated by the balance between pro- and anti-inflammatory mediators. Pro-inflammatory cytokines such as IL-1β, IL-6, and TNF-α are responsible for early responses and amplify inflammatory reactions, whereas anti-inflammatory cytokines, which include IL-4, IL-10, and IL-13, have the opposite effect in that they limit the inflammatory responses. Cytokines act through receptors which can be blocked to alter the inflammatory response, e.g., by TNF-a blockers.

3.2.2 The Disease State

IBD seems to result from a breakdown of the homoeostatic balance between the host's mucosal immunity and the enteric microbiome. This leads to an inadequate, exaggerated response of the immune system to the normal, nonpathogenic intestinal bacteria resulting in intestinal damage and subsequent impairment of the intestinal barrier.

A disruption of the *intestinal barrier* is implicated in the pathogenesis of UC and CD. Such damage may involve the mucus as well as the epithelial cells. The mucosal barrier can become "leaky," allowing luminal contents into the epithelium and a resulting exposure to immune cells. In a healthy state, the host protects itself by *autophagy,* the rapid detection and killing of microorganisms that penetrate the epithelial layer. In the disease state (and proven in IBD), interplay between an excessive permeability of the mucosal barrier combined with an dysfunctional autophagy triggers an inflammatory response which causes then mucosal damage as it is observed in both UC and CD.

Alterations in Microbiome Normally occurring enteric bacteria (while not being pathogenic) probably contribute to the initiation and/or perpetuation of the inflammatory response. Patients with IBD have alterations in both the composition and function of intestinal microbiota. In such patients there is diminished diversity of the commensal bacteria. This so-called dysbiosis may contribute to the development of IBD (see also Chap. 14).

3.2.2.1 Changes in the Immune System

Cellular immunity is a protective immune process that involves the activation of phagocytes and T cells and the release of cytokines in response to antigens. Cytokines have a crucial role in the

pathogenesis of IBD, where they control multiple aspects of the inflammatory response. In particular, the imbalance between pro-inflammatory and anti-inflammatory cytokines that occurs in IBD impedes the resolution of inflammation and instead leads to disease perpetuation and tissue destruction. In active IBD, the mucosal layer is thickened due to infiltration of the cells of the innate and adaptive immune system and elevated levels of cytokines. The adaptive immune system seems to mediate and perpetuate the inflammation through an imbalance of activating and suppressing effector T cells.

The inflammatory response is further amplified by the entrance of circulating leucocytes from the systemic circulation into the inflamed mucosa. This is carried out by the *endothelium*, specialized receptors on the inner lining of the blood vessels.

These changes mainly take place in the mucosal layer of the intestinal wall and are outlined in Fig. 3.1. The left part shows the healthy state with a complex network of cell populations and humoral factors. Note the homeostatic balance. The right part shows the disease state. Note the disruption of the epithelial layer and the increased number of inflammatory cells within the mucosa.

Multiple soluble factors commonly produced during an inflammatory response also promote *fibrogenesis*, normally a mechanism of wound healing and repair. However, prolonged injury such as with IBD causes deregulation of normal processes and—in patients with CD—results in the extensive deposition of extracellular matrix (ECM) proteins and fibrosis. This leads to stricturing and narrowing of the GI tract and, ultimately, stenosis. In this scenario, transforming growth factor beta (TGF-beta) is an important mediator of fibrogenesis that activates mesenchymal stem cells. This activation is initiated by epithelial cells which form an organized tightly connected sheet in which the tight junctions are disrupted and then transdifferentiate into disorganized motile mesenchymal cells, a process which is called epithelial-mesenchymal transition (EMT).

Other fibrogenic molecules include activins, connective tissue growth factor, platelet-derived growth factor, insulin-like growth factors 1 and 2, epidermal growth factor, endothelins, interleukin-13 (IL13) and others (Rieder et al. 2017).

Fistulae are an important complication in CD patients. During disease, the cumulative incidence of fistula formation in CD patients is 17–50%, and about one third of patients suffer from recurring fistulae formation (Scharl and Rogler 2014). CD-associated fistulae originate from an epithelial defect that may be caused by ongoing inflammation. Having undergone the process of EMT (please see above) through inflammation, intestinal epithelial cells (IEC) penetrate into deeper layers of the mucosa and the gut wall causing localized tissue damage: ulcerations. This penetration then forms a tube-like structure which might connect to other organs or the body surface: a fistula. EMT also activates matrix remodeling enzymes, e.g., matrix metalloproteinases MMP-3 and MMP-9, which also cause further tissue damage and inflammation. Additionally, soluble mediators like TNF and interleukin-13 further induce their own expression in an autocrine manner and enhance expression of molecules associated with cell invasiveness, aggravating the inflammation and fistulae formation (Scharl and Rogler 2014).

3.3 Etiology

IBD may be regarded as idiopathic which means that there is no clear external trigger. However, genetic alterations and environmental factors play a role.

3.3.1 Genetic Susceptibility

Twin and family studies showed a strong genetic basis of the inflammatory bowel diseases. The coefficient of heritability for siblings of inflammatory bowel disease probands is 25–42 for Crohn's disease and 4–15 for ulcerative colitis, indicating that genetic alterations play a significantly more important role in CD than in UC. Vice versa, environmental factors seem to be more important in the pathogenesis of UC than in CD. Heritability estimates for Crohn's disease and ulcerative colitis from pooled twin studies are 0.75 and 0.67, respectively (Gordon et al. 2015).

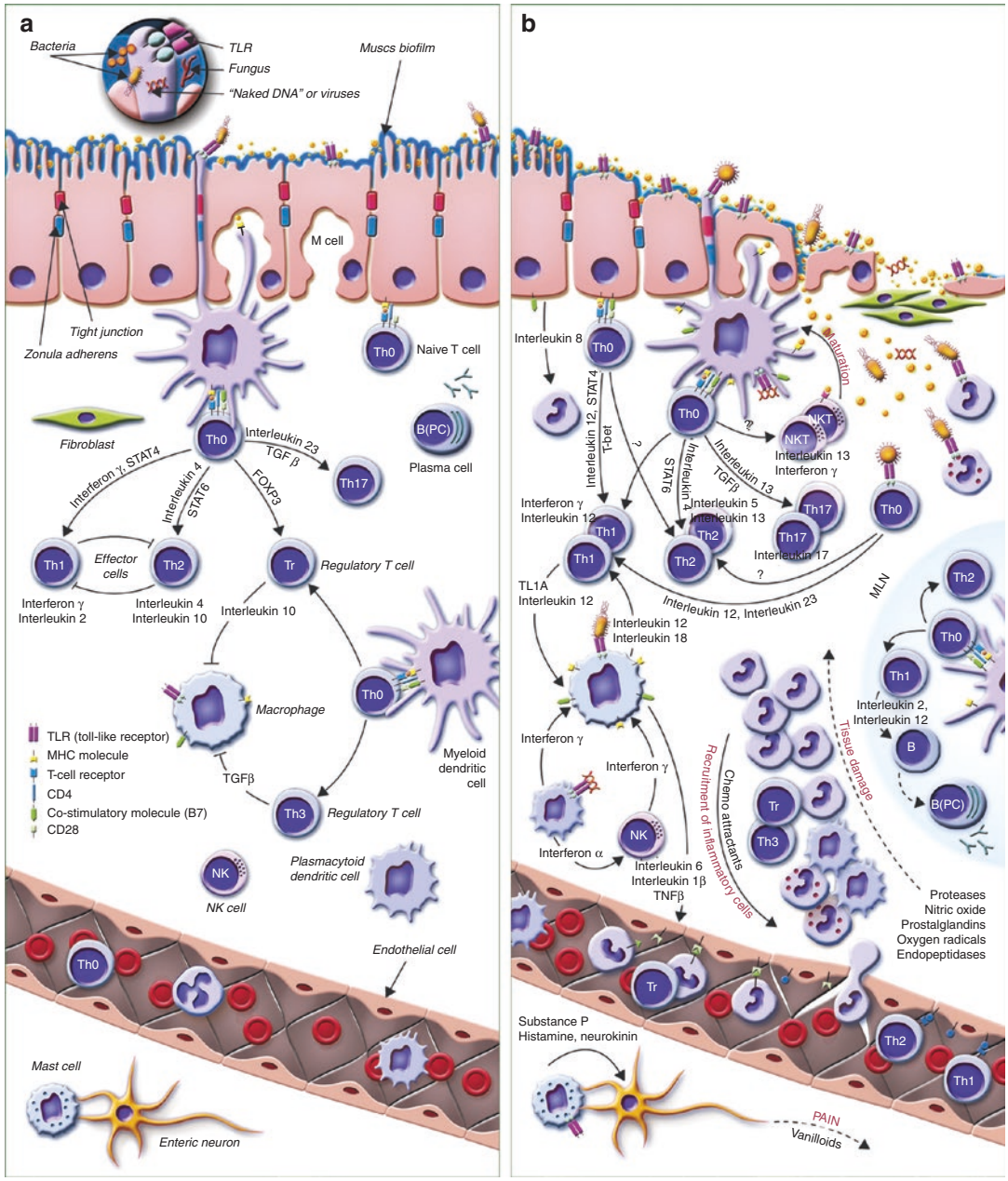

Fig. 3.1 Title intestinal immune system in healthy state (left) and IBD (right). (Reprinted from Baumgart and Carding (2007), with permission from Elsevier)

These early observations led the way to molecular genetics in IBD and culminated in the identification of nucleotide-binding oligomerization domain-containing protein 2 (NOD-2) gene as an IBD risk gene for CD. In the next years, genome-wide association studies have dramatically improved the resolution of the IBD genome and understanding of the pathogenesis of IBD. However, the complexity of the genetic puzzle in IBD seems more pronounced today than ever before (Ek et al. 2014). Recently, it has been highlighted that three

genetic markers, NOD-2, MHC, and MST1, are associated with distinct CD sites, supporting the concept that genetic variations may contribute to localize CD.

Genome-wide association studies have identified about 200 so-called "susceptibility genes" for IBD. Although most of them can be found in both major types of IBD, some of these susceptibility genes are specific for one of the major types. For example, alterations in the NOD-2 gene can be found in Crohn's disease, whereas patients with ulcerative colitis show alterations in genes responsible for the major histocompatibility complex class 2 region. Out of the gene mutations identified, many of the genetic alterations are associated with pathways that regulate the immune system. For example, mutations of the NOD-2 gene, observed in about 25% of the CD patients, impair the function of Paneth cells, that are responsible for the secretion of defensins (see Chap. 1). Interestingly, a large proportion of the IBD risk loci are also shared with other immune-mediated diseases, primary immunodeficiencies, and mycobacterial diseases, and none of these genetic alterations are specific for either CD or UC.

A family history can be found in up to 15% of affected patients. In first-grade relatives of patients with IBD, the risk of developing the disease is elevated by factor of approximately 10. In Crohn's disease, affected family members may show the same location and behavioral type (development of stenoses or fistulas). In children of affected persons, the risk is elevated; about 5% if one parent is affected and about 30% if both parents are affected. This is important in advising patients who are interested in becoming biological parents.

3.3.2 Environment

Environmental factors are thought to play a role in the development of IBD; however, their role is variable. There is no single external factor that initiates or perpetuates IBD, but environmental factors can trigger IBD. This observation is explained by the fact that the incidences of IBD have increased in the last decades. As the human genome has not changed in that period, the rising incidence of IBD must be due to changed environmental factors. Another indication is the fact that IBD becomes more common in previously less affected ethnic groups, such as Asians and Hispanics, and in immigrants from low incidence regions, after they have moved to areas with a traditionally high incidence.

This increased risk may be a due to *Western lifestyle*, improved sanitation (the so-called hygiene hypothesis), or consumption of "convenience food," that is, processed, fried, and sugary foods.

Smoking has a different effect on Crohn's disease than UC. The risk of developing Crohn's disease is elevated in smokers, and cessation of smoking can reduce the risk of a flare in persons with CD. By contrast, smoking may be protective against the development of UC and might reduce its severity. This observation has an important practical implication: patients presenting with symptoms of IBD or diagnosed with IBD should be questioned about their smoking habits, and patients with CD should strongly be advised to stop smoking.

Breastfeeding may provide protection against IBD for the breastfed child.

3.4 Clinical Manifestation

According to the traditional view, inflammatory bowel diseases are comprised of two major disorders: ulcerative colitis (UC) and Crohn's disease (CD), which have both distinct and overlapping pathologic and clinical characteristics. Recent research in the field of genetics however suggests the view of IBD as a continuum of disorders with three groups: ileal Crohn's disease, colonic Crohn's disease, and ulcerative colitis.

In some patients, a distinction between UC and Crohn's disease cannot be made even after taking into account the history, endoscopic appearance, histopathology of multiple mucosal biopsies, and appropriate imaging procedures. This condition is called *"inflammatory bowel disease unclassified (IBDU)."*

The term *indeterminate colitis* is reserved for pathologists to describe a colectomy specimen with overlapping features of UC and Crohn's disease. *Microscopic colitis* with its two types,

collagenous and lymphocytic, is another chronic inflammatory disease but is beyond the scope of this book.

IBD are lifelong diseases characterized by relapsing and remitting episodes of inflammation. Phases of activity are called "flares" and may be followed by periods of no activity, called "remission." A forecast of flare is not possible at the moment.

The natural history and clinical course are heterogeneous: while a significant rate of patients will have a relatively mild course (up to 50% of patients with ulcerative colitis and 30% with Crohn's disease), others may require surgery or immunosuppressive therapy. On the other side, up to 20% of patients with ulcerative colitis need colectomy for medically refractory disease, and about 50% of patients with Crohn's disease need surgery within 10 years of diagnosis. For patients with ulcerative colitis, extension of disease is the most important prognostic factor. The risk of colectomy is about 20% if the whole colon is affected and only 5% if the disease is confined to the rectum.

For patients with Crohn's disease, an unfavorable prognosis is associated with the following features: young age at initial diagnosis, localization in both small bowel and colon, perianal disease, or the necessity of steroids on first flare. CD is associated with only a modest decrease in overall life expectancy. Patients with ulcerative colitis may have a slightly higher overall mortality compared to the general population.

3.4.1 Crohn's Disease (CD)

Crohn's disease is characterized by transmural inflammation and can affect the complete intestinal tract from mouth to anus. The transmural inflammatory nature may lead to an augmentation of connective tissue with fibrosis and strictures and to obstructive clinical presentations. In addition the transmural inflammation can lead to small perforations and fistulae as well as formation of abscesses. CD is not limited to the lumen of the gut: "fat wrapping" and mesenteric thickening have been part of the first report by Crohn in 1932. Recently the role of the mesenteric organ in the disease process has been emphasized.

Crohn's disease may involve any segment of the gastrointestinal tract from the mouth to the perianal area. The distribution often is not continuous: there may be normal areas between affected areas, a phenomenon called *skip lesions*.

The anatomical location seems to be stable and may be genetically determined. The most commonly affected area is the ileum and proximal colon (see Fig. 3.2).

Distribution:

- Eighty percent small bowel involvement
- Fifty percent ileocolitis
- Twenty percent limited to the colon (sparing of the rectum in contrast to UC)

Approximately one third of patients have perianal disease.

Recently, a concept of CD as a progressive disease has emerged. Based on the hypothesis that inflammation may be present even in periods of clinical remission, there may be an accumulation of hits leading to progressive and irreversible structural damage and complications.

As mentioned above, isolated colonic Crohn's and Crohn's located in the ileocoecal region are considered as distinct entities according to recent genetic studies. It may be difficult to distinguish from ulcerative colitis.

3.4.1.1 Symptoms and Signs

Clinical symptoms indicating CD often precede the diagnosis and are mostly unspecific: abdominal pain, fever, weight loss, or, in children, growth retardation may be caused by obstruction. Whereas abdominal pain is more common in CD, bleeding is more frequent in ulcerative colitis (Table 3.1). Perianal disease includes fissures, fistulae, abscesses, and stenosis. Symptoms can vary from anal pain and purulent discharge to bleeding and incontinence and can be associated with significant morbidity and impaired quality of life.

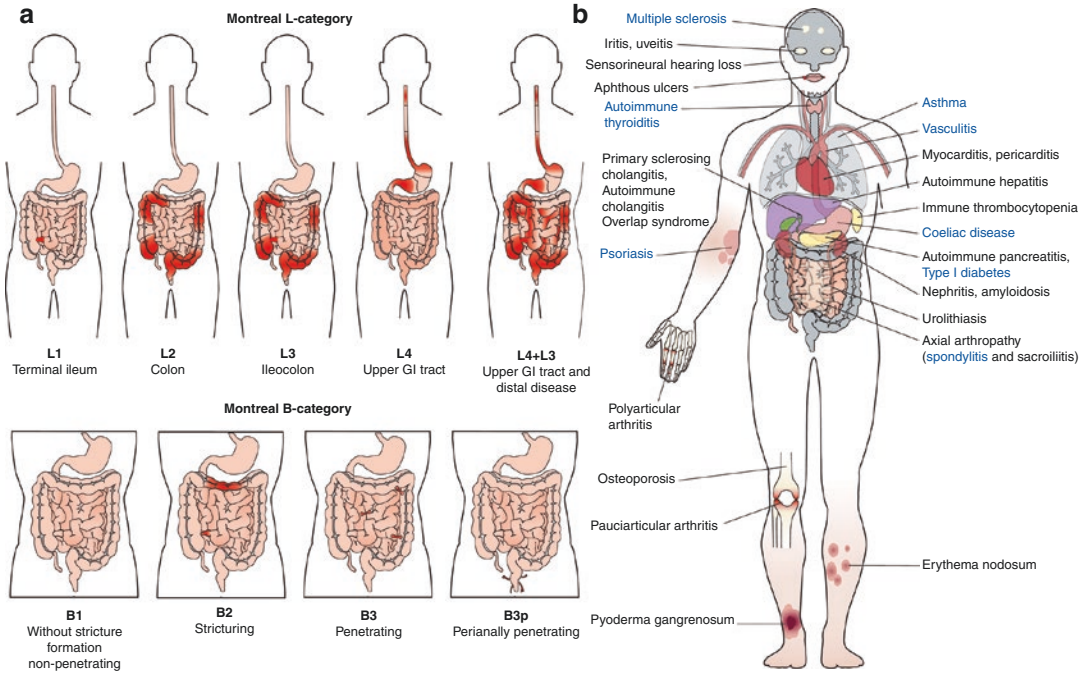

Fig. 3.2 Localization of Crohn's disease. (Reprinted from Baumgart and Sandborn (2012), with permission from Elsevier)

Clinical phenotypes may be classified according to the Montreal classification.

3.4.1.2 Complications of Crohn's Disease

Stenosis of the intestinal lumen may result from inflammation or fibrosis and lead to symptoms of intestinal obstruction.

Fistula is defined as a communication between epithelial-lined organs. Its existence may precede diagnosis. Risk may be as high as 50% over 20 years. Examples include entero-enteric fistulae, entero-vesical fistulae, enterovaginal fistulae, and enterocutanous fistulae.

Abscess is defined as a localized collection of pus. It may present with fever, abdominal pain, and tenderness.

Bile acid malabsorption occurs when more than 50 cm of the terminal ileum is involved or removed. Bile salts are normally reabsorbed in this area. If this process is disturbed, they can reach the colon where they induce diarrhea.

Disease of the terminal ileum may also lead to *vitamin B12 deficiency* with anemia and irreversible neurologic complications.

Surgical removal of large parts of the small bowel may result in *short bowel syndrome*, a severe malabsorptive condition which usually requires parenteral nutrition.

3.4.2 Ulcerative Colitis

In ulcerative colitis the inflammation is limited to the mucosal layer, and it is confined to the colon. Usually it involves the rectum and typically extends in a proximal and continuous fashion to involve other portions of the colon.

The extent of disease can be described in the following ways (see Fig. 3.3):

- Ulcerative proctitis: limited to the rectum
- Ulcerative proctosigmoiditis: limited to the rectum and sigmoid colon (not involving the descending colon)
- Left-sided or distal ulcerative colitis: disease that extends beyond the rectum and as far proximally as the splenic flexure
- Pancolitis: throughout the colon to the cecum

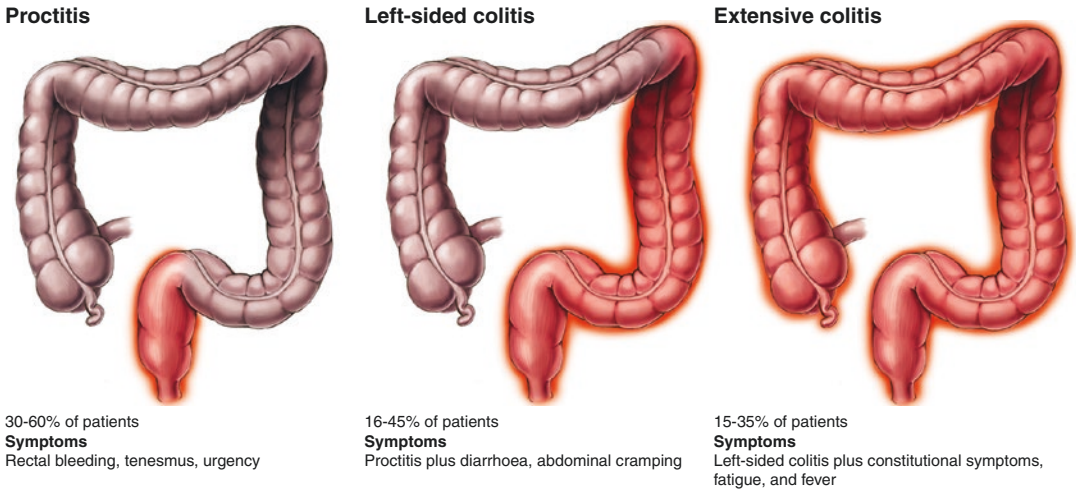

Fig. 3.3 Ulcerative colitis phenotypes by Montreal classification. (Reprinted from Ungaro et al. (2017), with permission from Elsevier)

Sometimes, in addition, the term "extensive colitis" is used, describing extension proximal to the splenic flexure but sparing the cecum.

Extent of the disease is of great importance for prognosis, risk assessment, use of diagnostic tools, and treatment including the choice of delivery systems for medications (i.e., suppositories, enema).

3.4.2.1 Symptoms and Signs

More than 90% of patients with active UC report having rectal bleeding (Table 3.1). Associated symptoms generally reflect the severity of mucosal disease and may differ according to disease extent. A decrease in stool consistency for more than 6 weeks is nearly always present. Patients with active disease complain of rectal urgency, tenesmus, mucopurulent exudate, nocturnal defecation, and crampy abdominal pain. Patients with proctitis usually present with rectal bleeding, urgency, tenesmus, and some occasionally with severe constipation. A fulminant course could include acute bleeding or toxic megacolon. Anemia may exist due to visible or invisible blood loss with resulting iron-deficiency.

Patients with CD and UC have an increased risk for developing *colorectal cancer* (CRC). However, the overall incidence of IBD-associated CRC has been diminishing in recent decades in Western countries. Risk factors to develop in CD and UC are longer disease duration, extent of inflammation, a positive familial history of CRC, coexistent primary sclerosing cholangitis, and the degree of inflammation (Kim and Chang 2014).

Table 3.1 Clinical manifestations of CD and UC

	CD	UC
Bleeding	+	+++
Diarrhoea	++	+++
Abdominal pain	++	+
Fistulae	+	–

3.5 Extraintestinal Manifestations (EIM)

While the gut is the main place of disease, the disease process is not confined to the intestinal tract but can affect other organ systems. These are called extraintestinal manifestations.

The pathophysiology of these EIMs is not fully understood. The frequency may be as high as 50% during the course of the disease. Most EIMs are thought to correlate with intestinal disease activity (erythema nodosum, arthritis), whereas others do not (PSC, axial arthropathy). EIM may be the main clinical symptom and can precede abdominal complaints.

3.5.1 Joint Disease

There may be involvement of peripheral joints, especially the large joints. In contrast to rheumatoid arthritis usually there is no synovial destruction. Other manifestations may be axial arthritis, sacroiliitis, or ankylosing spondylitis (these are associated with a HLA-B27-positive phenotype).

3.5.2 Skin

Erythema nodosum (EN) presents as red or violet subcutaneous nodules of a few centimeters size. They are tender and raised and typically located over the anterior tibial area. EN is the most common dermatologic manifestation and occurs in approximately 10%.

Other dermatological manifestations include pyoderma gangrenosum and Sweet's syndrome (acute febrile neutrophilic dermatosis).

Psoriasis may be associated with IBD but is not considered as an EIM.

3.5.3 Eye

Several ocular diseases may be associated with inflammatory bowel disease (IBD), some of which require urgent evaluation by an ophthalmologist. The most common may be *episcleritis* (an inflammation of the episclera) which does not lead to complications. However *scleritis* is a severe ocular disorder that can impair vision. It manifests with severe pain. Other examples include uveitis and iritis.

3.5.4 Primary Sclerosing Cholangitis (PSC)

PSC is a chronic progressive inflammation of the bile duct and is characterized by inflammation, fibrosis, and strictures. It may affect approximately 5% of patients with ulcerative colitis. Patients may be asymptomatic with just laboratory alterations in liver enzymes or present with fatigue, pruritus, and jaundice later in the course of disease. It can lead to cirrhosis and possibly require liver transplantation.

3.5.5 Other Manifestations

Patients with IBD, especially with Crohn's disease, are prone to formation of *kidney stones*. Calcium oxalate stones can result from steatorrhea and diarrhea. Uric acid stones can result from dehydration and metabolic acidosis.

Pulmonary involvement is rare and may include airway inflammation, parenchymal lung disease, and serositis. Apart from that, thromboembolic disease and drug-induced lung toxicity may occur.

Bone loss and osteoporosis may result from impaired vitamin D and calcium absorption or glucocorticoid use.

Patients with IBD are at an increased risk for *venous and arterial thromboembolism* as a result of hypercoagulability.

Anemia is present in many patients. It may result from a deficiency of nutrients like iron (due to blood loss and/or diminished absorption) or vitamin B12. Another form of anemia is anemia of chronic disease (for more information on EIM, see Chap. 19).

3.6 Summary/Conclusion

CD and UC are chronic relapsing diseases characterized by, but not limited to, intestinal inflammation. It is thought that IBD results from an aberrant and continuing immune response to the microbes in the gut, catalyzed by the genetic susceptibility of the individual. Although the etiology of IBD remains largely unknown, it involves a complex interaction between the genetic, environmental, or microbial factors and the immune responses. Although hundreds of susceptibility gene loci have been identified for IBD, genetic factors account for only a portion of overall disease variance, and microbial, immunological, and environmental factors interact with genetic elements in the pathogenesis of IBD.

Crohn's Disase can affect any part of the gastrointestinal tract, from the mouth to the anus (skip lesions), although more than 50% start in the terminal ileum. UC, in contrast, is restricted to the colon and begins in >95% (in the rectum).

This chapter represents an abstract on the theory of pathogenesis of IBD at the beginning of the twenty-first century. There seems to be a complex interplay of the components mentioned above. While some of the pathways are well understood, there is debate among researchers as to which of these pathways the primary event is and which is secondary. Physicians may have varying opinions on these topics. Since medicine is an ever-changing science, concepts may change in the future under the light of new research findings.

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Part II

Diagnosis, Assessment and Monitoring

Clinical Assessment

4

Helen Ludlow

Abstract

Clinical assessment of the patient with a known diagnosis of IBD has a primary and ongoing role throughout their disease management. The aspects of assessment will vary according to individual patients, taking into account the length of time since diagnosis and their current disease state. Some departments will routinely measure and record disease assessment scores such as the Harvey Bradshaw Index (HBI) or Ulcerative Colitis Disease Activity Index (UCDAI), and these can be helpful in detecting improvement or deterioration in disease activity.

The first and perhaps the most important aspect of any clinical assessment is the medical history. This should be in depth at the first consultation and then is usually briefer at subsequent assessments, to determine any changes in health status since the last appointment. A physical clinical examination may then follow, and it is helpful to choose a structured approach that will ensure a thorough clinical assessment.

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4.1 Introduction

This chapter will take you through a step-by-step guide of how to achieve both an in-depth assessment, a brief assessment, and the use of disease activity scores. It is important to ensure that any required training is undertaken prior to performing competent clinical patient assessment. There are often courses available for this purpose.

4.2 Taking an In-Depth Medical History

A thorough medical history is an important part of diagnosing, staging and assessing the patient. It can be used to identify extra-intestinal manifestations of IBD and can help identify clinical changes in the condition. The following is a summary of how to take a thorough clinical history:

- *General demographics*: Name, date of birth and preferred language. Ascertain if an interpreter is required.
- *Presenting condition*: What are the current symptoms? This may include mode of presentation, such as via the endoscopy unit or accident and emergency.
- *Background history to presenting condition*: Summary of IBD history to date.
- *Past medical history*:
  - Previous abdominal surgery

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  - Other autoimmune conditions, such as thyroid, diabetes and arthritis
  - Diseases which may complicate IBD treatment such as diabetes (steroids may increase blood sugars)
  - Mobility-limiting problems which may affect IBD treatment administration such as enema use
  - Clotting disorders which may indicate an increased risk of pulmonary emboli
  - Mouth ulcers
  - General medical history, e.g. cardiac, kidney, liver, neurological or endocrine disease
- *Extra-intestinal symptoms*:
  - Skin lesions—consider pyoderma gangrenosum or erythema nodosum.
  - Joint problems.
  - Eye problems, particularly painful red sclera and blurred vision may indicate uveitis—an ophthalmological emergency.
- *Medication history*:
  - Blood-thinning agents, e.g. warfarin and rivaroxaban
  - Drugs which may exacerbate IBD, e.g. non-steroidal anti-inflammatory drugs (NSAIDs)
  - Recent antibiotic use which increases the chance of a GI infection such as *C. difficile*
  - Proton pump inhibitors, which may cause diarrhoea
  - Drugs with constipating effects such as codeine
  - Drugs that may interact with IBD medication, e.g. allopurinol
  - History of recreational drug use
  - Over-the-counter drug use
  - Alternative medicinal use
- *Allergies/intolerances*:
  - Reactions to antibiotics, in case needed to treat infections
  - Reactions to aspirin which may result in reactions to 5-aminosalicylates
  - History of intolerances to IBD drugs for, e.g. pancreatitis with azathioprine
- *Vaccination history*:
  - Including childhood, travel and occupation health vaccinations
  - History of chicken pox
- *Family history*:
  - Family history of IBD
  - Family history of cancers, particularly colorectal
- *Social history*:
  - Smoking is known to increase the severity of CD and decrease the severity of UC, and is also associated with many other health risks (patients often present with a new diagnosis of UC after smoking cessation)
  - Alcohol intake, noting that excessive alcohol can result in diarrhoea and an increase in liver function blood results

4.3 Physical Examination

For the purposes of this section, only relevant systems will be discussed, including abdominal and general physical examination. It is important to link the details identified when taking the medical history and physical examination to note any impact that an existing disease may have on the patient (Box 4.1). Your history taking will guide you if any additional system examinations are required. It is good practice to offer a chaperone during the examination and to record if this is accepted or declined.

Box 4.1
Example:
Lung or joint problems may affect the patient's ability to manage their daily activities of living, which may further impact upon IBD disease management.

- *General appearance/presentation*:
  - Are there any obvious signs of confusion, distress, lack of self-care or depression?
  - Are there obvious signs of pain, respiratory problems or other physical illness?
  - Record the weight—is there evidence of gain or loss? Note the body mass index (BMI) (Box 4.2).

Box 4.2
Weight loss in particular is a red flag sign and can be quite sensitive in indicating deterioration of IBD or underlying malignancy. It is good practice to record the patient's weight at every hospital visit/intervention.

- A set of clinical observations—temperature, blood pressure, pulse and respiratory count—will be helpful if the patient is complaining of severe bowel symptoms (Box 4.3).

Box 4.3
Tachycardia, hypotension and raised temperature are all potential signs of severe IBD and should be discussed along with other examination findings with the patient's medical team.

- *Examine the hands*:
  - Look at the palms—is there evidence of:
    Palmar erythema—can be seen in chronic disease including liver disease and often in pregnancy
    Dupuytren's contracture—flexion of the finger tendons
    Liver flap—difficulty holding the hands out with wrists bend and fingers apart may be a sign of hepatic encephalopathy
  - Look at the fingers—is there evidence of:
    Nicotine stains
    Clubbing—nail deformity with loss of nail bed angle, can be associated with many chronic diseases, including IBD
    Leukonychia—whitening of the nail bed, seen in malabsorption of nutrients
    Koilonychia—inverted spooning of the nails, seen in iron deficiency anaemia and malabsorption
    Nail splinter haemorrhage—can be a sign of endocarditis

- *Examine the neck/face*:
  - Inspect the neck for abnormalities including lumps/swellings or lymph node enlargement—supraclavicular nodes enlargement may indicate GI malignancy/disease.
  - Pale conjunctiva is not an accurate sign of anaemia but is usually present if severely iron deficient.
  - Painful red eyes should be assessed urgently by an ophthalmologist—uveitis may present with active IBD and can cause permanent eye damage if not treated promptly.
  - Mouth ulcers—these may be general mouth ulcers if unwell or granulomatosis if related to more severe IBD.
  - Orofacial granulomatosis may present as large ulcers in and around the mouth and may indicate active IBD or as a stand-alone condition.
- *Examine the abdomen*:
- There are helpful books available that describe abdominal examination in depth (Shakespeare et al. 2017).

Look at the Abdomen

- Look for evidence of scars from previous surgery/skin abnormalities (bruises, rash, etc.) and distension.
- Visualise the four quadrants of the abdomen—right upper quadrant (RUQ), left upper quadrant (LUQ), right lower quadrant (RLQ) and left lower quadrant (LLQ) (see Fig. 4.1). Examine systematically to ensure a full examination. Identify pain early on (by verbal announcement, facial expression or guarding), and if present begin your examination in the area with least pain. Stand on the patient's right side with them lying supine in front of you.

Percuss the Abdomen

- Percuss the abdomen beginning in the centre down towards the lower quadrants—listen for tympany (like a hollow drum) over air-filled structures (bowel, stomach) and dullness over solid organs (liver, a full bladder/bowel). Note position of percussion sound change (Box 4.4).

Box 4.4
Unusual or unexpected sounds may indicate the presence of leaked intestinal gas (tympanic) or liquid (dullness) such as ascites.

Palpate the Abdomen

- Palpate the abdomen—moving around all four quadrants, first in a gentle motion to identify the presence of pain and then more firmly to identify organ structure and any abnormalities (see Fig. 4.1).

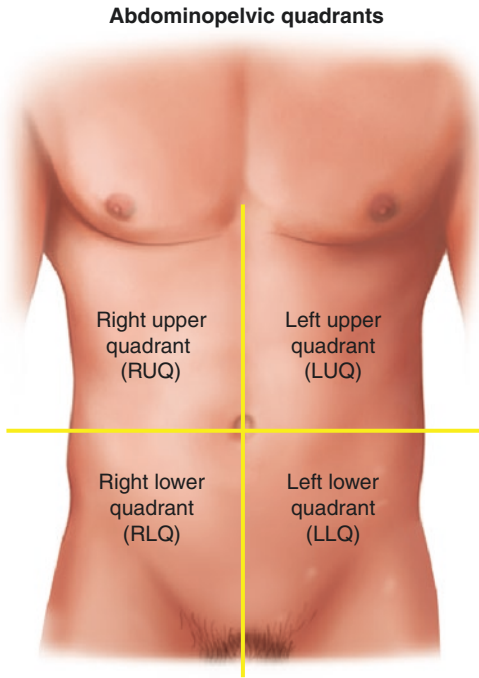

Fig. 4.1 The abdomen

- Assess the liver (Box 4.5).
- Assess the spleen (Box 4.6).
- Assess the kidneys (Box 4.7).
- Assess for ascites:
- The fluid thrill test
- The shifting dullness test (Box 4.8)

Box 4.5
An enlarged liver may indicate acute or chronic liver disease such as alcoholic liver disease or autoimmune hepatitis, malignancy and other liver problems.

Box 4.6
An enlarged spleen may indicate various haematological conditions, infection or portal hypertension.

Box 4.7
Enlarged kidneys are usually only palpable in the presence of disease such as polycystic kidney disease.

Box 4.8
The presence of fluid may indicate ascites due to acute or chronic liver failure, cardiac failure or malignancy.

Auscultate the Abdomen

- Auscultate with a stethoscope to listen for presence of bowel sounds—particularly relevant if bowel obstruction is a possibility. Listen to the aortic vessel arteries for clear, regular strong sounds (Box 4.9).

Box 4.9
Absence of bowel sounds may indicate paralytic ileus or perforation. High-pitched sounds may indicate intestinal obstruction. Abnormal atrial sounds may indicate cardiac conditions or aneurysms.

Digital Rectal Examination

Your hospital may have a policy regarding specific training to perform this examination, and you should only do so if necessary and considered competent to do so. It is good practice to always offer for a chaperone to be present and to record this in the notes.

Note any abnormal findings from the physical assessment in the patients' notes, and seek further medical advice if you are unsure.

4.4 Taking a Brief Assessment

It may be helpful to use a similar step-by-step process for a brief assessment as with a more in-depth assessment. This will help to ensure that you include important aspects and will promote a systematic consultation. A similar approach can also be used when undertaking a telephone assessment (see also Chap. 47). You may find it helpful to design your own list of questions to cover.

Below is an example of what you might wish to include in your brief assessment:

- Any weight loss/gain and any changes in appetite? If face-to-face consultation, you

can also check for any obvious changes in appearance, such as dramatic alteration in weight and general self-presentation as discussed earlier in this chapter.

- Since the last consultation:
  - General health, including any skin or eye problems.
  - Medication changes.
  - Have they experienced any flare-ups, and if so how were they managed (such as medication changes, steroids, etc.)?
- How is the patient currently?
  - Do they have any gastrointestinal symptoms?
  - Clarify medication dosages and concordance.
  - Are there recent investigations to discuss such as blood tests/endoscopy?
  - Do they have any concerns or questions they want to discuss?
  - Check if they are adherent to their medication and discuss any problems they may have.
  - Do they need a new prescription?
- Consider for the coming year:
  - Do they need further investigations such as blood tests/surveillance endoscopy/bone scans?
  - If on immunosuppression treatments, are they up-to-date with flu and pneumonia vaccinations?

Trials

It may be helpful to keep a list handy of any trials that your hospital is participating in. Then you will have a quick and easy reminder to look for potential participants.

4.5 Disease Assessment Tools

The increased use of biological agents has encouraged healthcare professionals and patients to aim for disease remission. By using assessment tools, it is possible to achieve quantitative evidence of current disease state as well as identifying changes in the patient's condition, particularly if used at each visit. There are many different scoring systems available, so it is important to ensure that everyone in your team is using the same scores, to prevent confusion and promote ease of use. Many of the tools look at similar markers, including clinical, endoscopic, histological, radiological, biomarkers and quality of life (QOL). Patient's own opinion on their health status is also taken into account, which has been shown to improve both long-term outcomes and patient care (de Jong et al. 2018). However, it is important that tools are not used without other means of assessment to ensure a full picture as well as mitigate for the well-known risks of inter-user variability (Walsh et al. 2016).

Below are two examples of commonly used activity scores—the Simple Clinical Colitis Activity Index (SCCAI; Table 4.1) (Box 4.10) for ulcerative colitis and the Harvey Bradshaw Index (HBI; Table 4.2) for Crohn's disease. It may be helpful to have your own copies of the tools, or those you wish to use, to be available for use in your clinical practice.

Table 4.1 Simple Clinical Colitis Activity Index (Walmsley et al. 1980)

Symptom	Score
Bowel frequency (day)	
1–3	0
4–6	1
7–9	2
>9	3
Bowel frequency (night)	
1–3	1
4–6	2
Urgency of defecation	
Hurry	1
Immediately	2
Incontinence	3
Blood in stool	
Trace	1
Occasionally frank	2
Usually frank	3
General well-being	
Very well	0
Slightly below par	1
Poor	2
Very poor	3
Terrible	4
General extra-colonic features	Score 1 for each
Total	Remission: <1
	Active disease: >5

Box 4.10

Example of background history:

2001: diagnosis of distal UC via colonoscopy → settled well on a course of oral steroids and commenced on oral mesalazine

2003: flare-up with blood diarrhoea and urgency → settled with maximised dose of oral and rectal mesalazine

2004 onwards: occasional mild flare-up → settled well with maximised dose of oral and rectal mesalazine

Table 4.2 Harvey Bradshaw Index (Harvey and Bradshaw 1980)

General well-being (yesterday)	
Very well	0
Slightly below par	1
Poor	2
Very poor	3
Terrible	4
Abdominal pain (yesterday)	
None	0
Mild	1
Moderate	2
Severe	3
Number of liquid or soft stools per day (yesterday)	0
	1
	2
	3
	4
	5
	6
	7
	>8
Abdominal mass	
None	0
Dubious	1
Definite	2
Definite and tender	3
Complications	*Score 1 for all that apply*
Arthralgia	
Uveitis	
Erythema nodosum	
Aphthous ulcers	
Pyoderma gangrenosum	
Anal fissure	
New fistula	
Total	Remission: <5
	Mild disease: 5–7
	Moderate disease: 8–16
	Severe disease: >16

4.6 Summary

Taking a thorough medical history, a physical examination and using disease activity scores are all important aspects of the clinic assessment of a patient with IBD. Brief assessments may take place at follow-up clinic appointments or telephone consultations, and the assessment process can be individualised for each patient encounter.

Ensure that your assessment is recorded accurately in the patient notes, and discuss any aspect that you are unsure about with the patients' medical team or more senior nursing colleague.

Recording of disease measurements such as the Harvey Bradshaw Index (HBI) or Simple Clinical Colitis Activity Index (SCCAI) can also be helpful to provide additional information for quantifying and monitoring changes to the patient's condition over a period of time.

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Endoscopy

5

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Abstract

Ileocolonoscopy is at present an essential tool for diagnosis of inflammatory bowel disease (IBD), disease assessment for prognostic purposes and therapeutic interventions. Severe endoscopic lesions are associated with higher risk since most severe endoscopic findings are associated with an increased rate of surgery and poor outcome in both Crohn's disease and ulcerative colitis. Patients with an improvement of mucosal lesions after treatment have a good prognosis and no or slow disease progression.

Capsule endoscopy is a complimentary technique to visualize small bowel lesions. It has limited but extremely valuable indications in inflammatory bowel disease diagnosis and assessment. Upper GI endoscopy is less commonly used in the standard diagnostic workup of adult inflammatory bowel disease. However, it can be used to supplement other diagnostic techniques in selected cases.

Classification of disease activity according to endoscopic scores is essential for clinical trials as they contribute to a more objective disease assessment and allow for subsequent evaluation and grading of disease variation. The most commonly used scoring systems are Mayo endoscopic subscore and UCEIS (ulcerative colitis endoscopic index of severity) for ulcerative colitis, Rutgeerts' score for postsurgical Crohn's disease and CDEIS (Crohn's disease endoscopic index of severity) and SES-CD (simplified endoscopic score for Crohn's disease) for the assessment of ileocolonic Crohn's disease. However, there are some limitations that have to be considered when using endoscopic scores.

Patients affected by IBD may require special nursing care as they are likely to require several endoscopic examinations during their lifetime which may result in higher anxiety. This care extends to endoscopic-specific counselling as well as bowel-cleansing prescription and sedation planning.

5.1 Introduction

Endoscopic techniques are essential tools in the management of IBD for:

- Diagnosis
- Prognostic classification
- Disease monitoring
- Therapeutic interventions and cancer surveillance

The endoscopic techniques routinely used are ileocolonoscopy (virtually always needed), upper

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GI endoscopy (restricted to selected patients) and small bowel endoscopy and capsule or device-assisted enteroscopy (limited to very select patients) (Annese et al. 2013).

5.2 Practical Aspects

Suspected or known IBD patients require the same bowel cleansing, sedation and procedural skills as for the general population. However, some suggestions can be made to achieve the best results in IBD patients.

5.2.1 Bowel Cleansing

Adequate bowel cleansing is essential for proper visualization and decreased risk of missed lesions. When a proctosigmoidoscopy is planned (e.g. to monitor treatment response in ulcerative colitis), a cleaning enema in the morning is sufficient to achieve adequate bowel cleansing. For capsule endoscopy, fasting for a minimum of 12 h before the procedure is essential. Any necessary medication should be taken with water before the exam and during the first 4 h of recording. After that, the patient can eat and drink freely. In these cases, there is no evidence that bowel cleansing increases diagnostic yields; however, most centres still use a reduced macrogol-based bowel cleansing (e.g. 1–2 L macrogol solution) the day before the capsule endoscopy.

Although there is no specific literature for ileocolonoscopy, macrogol-based bowel cleansing is preferred over sodium phosphate-based regimens due to less irritation to the colonic walls. However, the low-volume and split administration of the sodium phosphate regimens remains the preferred option to maximize patient adherence and enhance cleansing results.

5.2.2 Sedation

Each country and individual medical clinic may have different standards with respect to sedation for endoscopy. In addition to these standards, it is advisable to take specific care in sedation when dealing with IBD patients.

To ensure patient comfort, many physicians are likely to prescribe deep sedation (e.g. with propofol) administered by either anaesthesiologists or gastroenterologists according to local regulations. If deep sedation is not available or if there is a patient preference against deep sedation, conscious sedation might be considered, even if less effective and possibly higher risk.

Deep sedation should be the standard when operative procedures are planned (e.g. stricture balloon dilation, anal stenosis dilation, device-assisted enteroscopy) since they are more likely to last longer and generate more intense pain.

5.2.3 Specific Issues with IBD Endoscopy

When severe clinical activity occurs, endoscopy might be required in order to check the severity of endoscopic lesions (deep ulcerations) and tissue samples obtained in order to confirm diagnosis and exclude superinfections, e.g. *Clostridium* or cytomegalovirus. In these cases, full bowel cleansing and extensive exploration of the colon and ileum are unnecessary and potentially harmful due to higher risk of bowel perforation. Additionally, electrolyte depletion which could occur with some bowel cleansing may be even more harmful; therefore no bowel cleansing or only a water enema before the procedure is suggested. Colonoscopy in this situation should be restricted to rectosigmoid evaluation with minimal or no air insufflation, avoiding any attempt to proceed more proximally.

5.3 IBD Diagnosis

IBD diagnosis is not the result of a single test, but it requires integration of:

- Clinical signs (e.g. diarrhoea, abdominal pain, blood in stool, weight loss, etc.)
- Laboratory findings (anaemia, elevation of inflammatory tests, deficiency in iron or vitamins, etc.)

- Endoscopic findings
- Pathological findings

Even in cases when endoscopy alone is not sufficient to reach a proper IBD diagnosis, it is still extremely valuable.

First, endoscopic features of IBD are quite specific; in most cases, a reliable classification of IBD into Crohn's disease (CD) and ulcerative colitis (UC) is possible. A series of endoscopic features that can help to differentiate CD and UC are listed in Table 5.1.

Secondly, ileocolonoscopy reaches the areas where CD and UC are most commonly found, allowing bioptic sampling in the ileum as well as different locations within the colon and in the rectum. This supplies histopathological findings for a final diagnosis.

According to ECCO diagnostic guidelines (Gomollòn et al. 2017; Magro et al. 2017), when there is a strong suspicion of IBD with negative ileocolonoscopy and imaging results, small bowel endoscopy should be considered. Its extremely high sensitivity offers an added valuable technique for confirming or reliably ruling out an IBD diagnosis.

The main limitation of the least invasive technique, capsule endoscopy (CE), is the inability to provide bioptic samples to support the diagnosis. Moreover, caution should be applied since CE can result in the complication of capsule retention and, rarely, bowel obstruction. The procedure should not be carried out if stenotic symptoms are present; although relevant small bowel stenoses may be missed by imaging techniques, a preliminary imaging of the small bowel is usually required.

Device-assisted enteroscopy (DAE, e.g. single- or double-balloon enteroscopy) can be considered as an alternative to CE. It is more invasive and less commonly available but allows the advantage of bioptic sampling.

In Fig. 5.1 are some endoscopic features of CD and UC.

Table 5.1 Endoscopic features more common in Crohn's disease as compared to ulcerative colitis, leading to accurate inflammatory bowel disease subtype diagnosis in close to 90% cases (Pera et al. 1987)

Endoscopic features making Crohn's disease more likely	Endoscopic features making ulcerative colitis more likely
Discontinuous lesions	Continuous involvement from rectum backward
Cobblestone appearance	Mucosal granularity
Aphthoid ulcers	Vascular pattern faded/ disappeared
Rectal sparing	Rectal involvement
Anal lesions	Erosions
Ileal involvement	Micro-ulceration
Serpiginous or linear ulcers	Clear demarcation of affected/healthy mucosa

5.4 IBD Prognostic Classification

Not all IBD patients share the same progressively disabling course, and some endoscopic features are shown to correlate with more unfavourable disease course. Presently, only ileocolonoscopic findings are relevant in establishing differences in clinical outcomes. Indeed, the presence or absence of upper GI IBD lesions seems to have no prognostic value for the disease course.

5.4.1 Severe Mucosal Lesions Are Linked to Poorer Disease Outcomes

It has been demonstrated in both CD and UC that patients displaying more severe endoscopic features share the highest risks of subsequent surgical needs due to unresponsiveness to medical treatments:

- CD patients with more severe endoscopic lesions (deep ulcers) spanning over large proportions of an ileocolonic segment (>30% of the surface of a segment) are 5 times more likely to undergo surgery than patients without such severe endoscopic characteristics.
- UC patients with more severe endoscopic features (deep ulcers, large mucosal abrasions, well-like ulcers) undergo proctocolectomy roughly 40 times more often than patients without the same endoscopic characteristics.

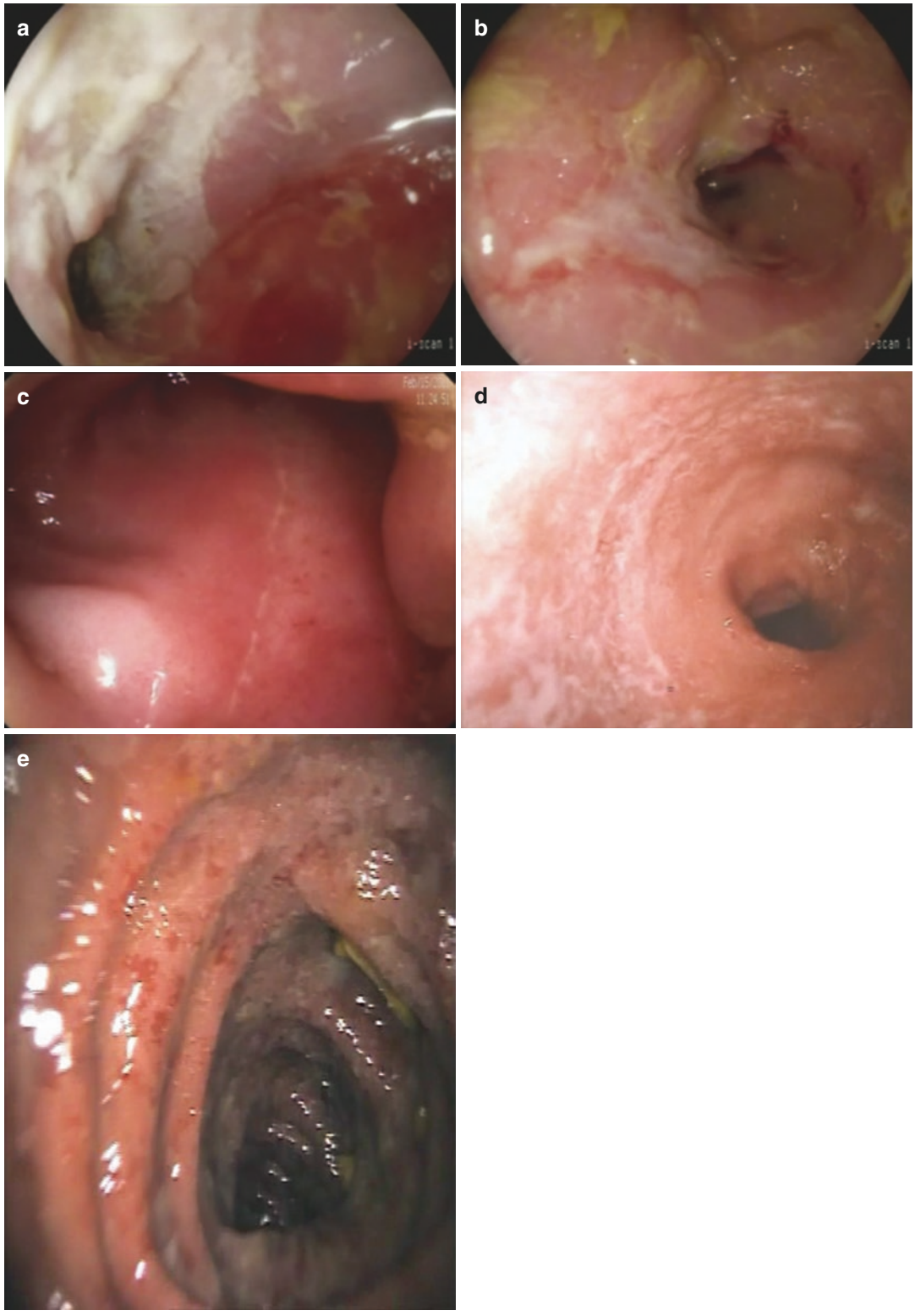

Fig. 5.1 Examples of endoscopic features of Crohn's disease (CD) and ulcerative colitis (UC) at ileocolonoscopy. (**a**) CD with ulcerated stenosis; (**b**) CD with irregular-shaped ulcer; (**c**) CD with fissure ulcer in area of near-normal mucosa; (**d**) UC with clear demarcation of affected area; (**e**) UC with erosions and continuous involvement

5.4.2 Healing of Endoscopic Lesions Is Associated with Better Disease Outcomes

Both in CD and UC, it has been shown that patients displaying substantial improvement of endoscopic features have a better disease outcome than patients without mucosal healing:

- The 10-year rate of surgery due to ineffectiveness of medical treatments is roughly 3 times lower in patients reaching endoscopic healing 1 year after IBD diagnosis; figures are similar both in CD and UC.
- The 5-year rate of adverse outcomes (colectomy, need for immunosuppressive treatments, hospitalization) is roughly 6 times lower in UC patients reaching not only clinical remission but also mucosal healing after a first steroid course when compared to patients reaching clinical but not endoscopic remission.
- The 2-year rate of remission of steroid and/or infliximab in patients reaching full endoscopic normalization after 2 years of treatment was roughly 7 times higher than patients not reaching the same levels of normalization.
- According to two recent meta-analyses, mucosal healing assessed at endoscopy regardless of biologic or nonbiologic treatments correlated with:
  - In CD (12 studies and 673 patients considered): 3 times higher clinical remission, 2 times higher surgery-free course and 14 times higher long-term mucosal healing (Shah et al. 2016a).
  - In UC (13 studies and 2073 patients considered): 5 times higher clinical remission, 4 times higher colectomy-free course, 10 times higher long-term steroid-free remission and 8 times higher long-term mucosa healing (Shah et al. 2016b).

5.5 IBD Monitoring with Endoscopy

The use of IBD-specific, robust endoscopic scores to determine disease activity is needed to objectively determine the impact of therapeutic interventions on mucosal healing. Such endoscopic scores of activity are available for UC and CD; CE diagnostic scores for Crohn's disease can also be used in order to quantify disease activity in the follow-up, but their role in the follow-up of IBD patients remains to be better defined.

5.5.1 UC Endoscopic Activity Scores

Several endoscopic scores of activity have been proposed and used for UC, either as pure endoscopic instruments or within an integrated clinical activity score. At present the two mostly used in clinical trials and practice are the Mayo endoscopic subscore (MES) and the ulcerative colitis endoscopic index of severity (UCEIS). Both scores require at least a sigmoidoscopy for their calculation, and, conventionally, worsened endoscopic features lead to a higher score. Main characteristics of the two scoring systems are listed in (Schroeder et al. 1987; Travis et al. 2013) Table 5.2.

5.5.2 CD Endoscopic Activity Scores

For CD, other endoscopic scores were developed and validated for varying disease subsets:

- The Rutgeerts' score is relevant to early (6 months to 1 year) postsurgical evaluation after ileocecal resection due to its prognostic impact in this clinical scenario (Rutgeerts et al. 1990).
- The Crohn's disease endoscopic index of severity (CDEIS) (Mary & Modigliani 1989) and the simplified endoscopic score for Crohn's disease (SES-CD) are robust alternative scores to measure Crohn's disease endoscopic activity (Daperno et al. 2004).

The Rutgeerts' score requires a full ileocolonoscopy reaching the ileocolonic anastomosis and passing into the neoterminal ileum for several centimetres if possible. It is scored taking only these two landmarks into consideration. The worst endoscopic lesions observed determine the score. Rutgeerts' score was shown to have a

Table 5.2 Operative characteristics of the Mayo endoscopic subscore (MES) and of the ulcerative colitis endoscopic index of severity (UCEIS) with advantages and disadvantages (Travis et al. 2013)

	MES	UCEIS
Score modalities	*0 (remission)*: normal or healed mucosa *1 (mild)*: faded vascular pattern, mild friability, erythema *2 (moderate)*: absent vascular pattern, marked friability, erosions *3 (severe)*: spontaneous bleeding, large ulcers	*Vascular pattern*: 0 (normal), 1 (patchy obliterated), 2 (obliterated) *Bleeding*: 0 (none), 1 (mucosal), 2 (luminal mild), 3 (luminal moderate-to-severe) *Erosions and ulcers*: 0 (none), 1 (erosions), 2 (superficial ulcers), 3 (deep ulcers)
Score range	0–3	0–8
Formally validated?	No	Yes
Interobserver reproducibility?	Fair	Medium-fair
Cut-off for remission/activity	Not validated, but commonly used in trials: 0 (full endoscopic remission) 0–1 (endoscopic remission)	Not validated
Complexity	Easy	Medium
Used in central review?	Yes	Yes
Prognostic relevance?	Yes	Not yet shown

relevant impact on disease prognosis over the 5-year horizon:

- Patients with i0–i1 recurrence share minimal risks of clinical relapse, roughly 0–5%.
- Patients with i2 recurrence have substantial risks of clinical relapse, around 25%.
- Patients with i3–i4 recurrence share extremely high risks of clinical relapse, roughly 60–100%.

These data have been replicated in recent studies.

The CDEIS and SES-CD also require a full ileocolonoscopy in order to be calculated. They are substantially more complex, but for both of the scores, prognostic relevance has been demonstrated. These two scores require the categorization of different variables in each ileocolonic segment in order to reach the final score.

Characteristics of Rutgeerts' score, CDEIS and of SES-CD are listed in Table 5.3.

5.5.3 IBD Endoscopic Scores Reproducibility

Endoscopic scores were used in clinical trials and in routine practice in order to reduce overestimation of clinical symptoms. In both ulcerative colitis and in Crohn's disease, however, it was shown that when scores were used in clinical trials, physicians tended to overestimate endoscopic activity, as compared to off-site (so-called central) reviewers blinded to patients conditions and not related to their management.

Moreover, all endoscopic indices are based on interpretation of images and therefore are intrinsically at risk of disagreement in scoring when physicians share neither a common training nor common scoring rules. Several studies demonstrated that interobserver agreement might be suboptimal for virtually each scoring system used for recording IBD endoscopic activity.

It has been recently demonstrated that formal training dedicated to IBD endoscopic scores might substantially improve the interobserver agreement leading to better quality in endoscopic activity scoring (Daperno et al. 2017).

5.6 Endoscopy for Therapeutic Intervention and Cancer Surveillance

Endoscopic examination and particularly ileocolonoscopy might act as a means to delivering therapeutic interventions. They are also essential in carrying out cancer surveillance programmes on IBD patients.

Table 5.3 Operative characteristics of the Rutgeerts' score (Rutgeerts), Crohn's disease endoscopic index of severity (CDEIS) and the simplified endoscopic score for Crohn's disease (SES-CD) with advantages and disadvantages (Daperno et al. 2004)

	Rutgeerts	CDEIS	SES-CD
Applicability	Postsurgical setting, ileocecal resection	Every Crohn's disease	Every Crohn's disease
Score modalities	*i0*: no lesion in neoterminal ileum *i1*: ≤5 aphthoid lesions in the ileum *i2*: >5 aphthoid lesions in the ileum with normal mucosa interposed or lesions/ulcers (<1 cm) confined to anastomosis *i3*: diffuse aphthous ileitis with extensively inflamed mucosa *i4*: diffuse inflammation with large ulcers, nodules and/or stenoses	*Deep ulcerations* (0 = no, 12 = yes) *Superficial ulcerations* (0 = no, 6 = yes) *Surface involved by disease* (range 0–10 referred to 0–100%) *Surface involved by ulcerations* (range 0–10 referred to 0–100%) *Number of segments explored* (range 0–5) *Ulcerated stenosis* (0 = no, 3 = yes) *Non-ulcerated stenosis* (0 = no, 3 = yes)	*Presence and size of ulcers* (0 = none, 1 = aphthoid ulcers <0.5 cm, 2 = large ulcers 0.5–2 cm, 3 = very large ulcers >2 cm) *Ulcerated surface* (0 = none, 1 = <10%, 2 = 10–30%, 3 = <30%) *Affected surface* (0 = none, 1 = <50%, 2 = 50–75%, 3 = <75%) *Narrowings* (0 = none, 1 = single passable, 2 = multiple passable, 3 = not passable stenosis)
Score range	i0–i4	0–44	0–56
Formally validated?	No	Yes	Yes
Interobserver reproducibility?	Fair	Good	Good
Cut-off for remission/ activity	Not validated, but commonly used in trials: i0–i1 (no recurrence) i2 (mild/substantial recurrence) i3–i4 (advanced recurrence)	Not validated	Not validated
Complexity	Easy	High	High
Used in central review?	Yes	Yes	Yes
Prognostic relevance?	Yes	Yes	Yes

5.6.1 Therapeutic Interventions

Endoscopy offers therapeutic capabilities mainly for:

- Stenosis conservative management
- Precancerous lesions treatment

5.6.1.1 Stenosis Management

Crohn's disease is often complicated by bowel (colonic) stenoses, which eventually become a surgical indication when leading to bowel obstruction.

Bowel stenoses are usually classified as:

- Primary stenoses (occurring due to stenosing CD progression, usually >5 cm long)
- Postsurgical stenoses (occurring at the anastomotic site, usually <5 cm long)

Due to the shorter stricture, postsurgical stenoses are more commonly treated endoscopically. Available endoscopic techniques for the treatment of CD bowel stenoses are:

- *Balloon dilation*, using endoscopic balloon catheters, which was reported to be effective 70–90% in the short-term, with complications and perforations as low as 6 and 3%, respectively. Important points to be aware of are:
  - Endoscopic balloon dilation leads to temporary postponing of the required surgery, but up to 75% of patients undergo surgery within 5 years.
  - Rates of technical success and of complications were not significantly different when comparing primary and postsurgical stenoses dilation, but a propensity bias in stenoses selection for balloon dilation

should be considered when analysing literature results.
  - Balloon dilation is at present a standard option at least in European countries, supported by more than 2600 dilation procedures reported in a recent meta-analysis.
- *Self-expanding metallic stent (SEMS) placement* might be an alternative tool to conservatively treat symptomatic CD stenoses. Be aware that:
  - There are significantly fewer reports than balloon dilation.
  - Present techniques and devices require removal of the stents after a period of 1–4 weeks.
  - Complications in expert hands were shown to be close to those reported for endoscopic balloon dilation.
  - Stent impaction is a specific adverse outcome to be considered when choosing this therapeutic option.
- *Biodegradable stent placement* was seldom reported; their effectiveness and safety require more data before becoming part of the therapeutic armamentarium.

5.6.1.2 Precancerous Lesions Treatment

The use of advanced endoscopic therapeutic techniques to treat sporadic precancerous lesions of the colon has been reported in the care of IBD.

The two main techniques considered are:

- *Endoscopic mucosal resection (EMR)*, more commonly performed in western countries, less time-consuming, allows more precise histopathological analyses, but not as complete as surgical specimen or specimen from submucosal dissection.
- *Submucosal endoscopic dissection (ESD)*, a technique where submucosal dissection is performed using a special electrosurgical knife. ESD achieves a higher en bloc resection rate resulting in more accurate histopathological assessment and enhanced curability. However, careful patient selection and thorough patient education should be carried out, as technical success in removing a dysplastic lesion does not prevent progression of synchronous or metachronous lesions in the remaining colon.

5.6.2 Cancer Surveillance

IBD patients have a slightly increased risk of colorectal cancer than the general population. Although this excess risk was resized in recent years and now appears to be minimal, specific surveillance programmes are advised for IBD patients.

Ileocolonoscopy, performed with high-definition equipment and supported by indigo carmine dye spray chromoendoscopy to enhance surface contrast, is the standard-of-care surveillance technique for colonic IBD patients.

A first screening colonoscopy should be offered an estimated 8 years after the onset of colitic symptoms for all patients. This is to reassess disease extent both microscopically and endoscopically, screen for early dysplasia and exclude chronic active endoscopic activity.

However, since colorectal cancer risks are significantly different in IBD patient subpopulations, subsequent surveillance programmes vary according to individual colorectal cancer risks:

- *High-risk features*: stricture or dysplasia detected within the past 5 years, primary sclerosing cholangitis, extensive colitis with severe active inflammation or a family history of colorectal cancer in a first-degree relative at less than 50 years should have next surveillance colonoscopy scheduled for 1 year.
- *Intermediate-risk features*: extensive colitis with mild or moderate active inflammation, postinflammatory polyps or a family history of colorectal cancer in a first-degree relative at 50 years and above should have next surveillance colonoscopy scheduled for 2–3 years.
- *Low-risk features*: patients with neither intermediate- nor high-risk features should have next surveillance colonoscopy scheduled for 5 years.

CD patients with extensive colitis need be considered for surveillance purposes similar to UC patients.

5.7 Capsule Endoscopy

CE is an endoscopic technique developed in the past 15–20 years and consists of:

- Small dedicated wireless capsule endoscopic cameras which are swallowed and pass through the entire small bowel
- Image acquisition either through wireless transmittal to a recorder or stored in the capsule
- Subsequent offline evaluation of the images

The technique was developed and validated for investigation of obscure gastrointestinal bleeding, but the chance to explore the small bowel led to its application in IBD diagnosis and monitoring.

CE is minimally invasive, but patients with known Crohn's disease have an increased risk of capsule retention and, very rarely, bowel obstruction. This should be extensively discussed and acknowledged with patients before the examination.

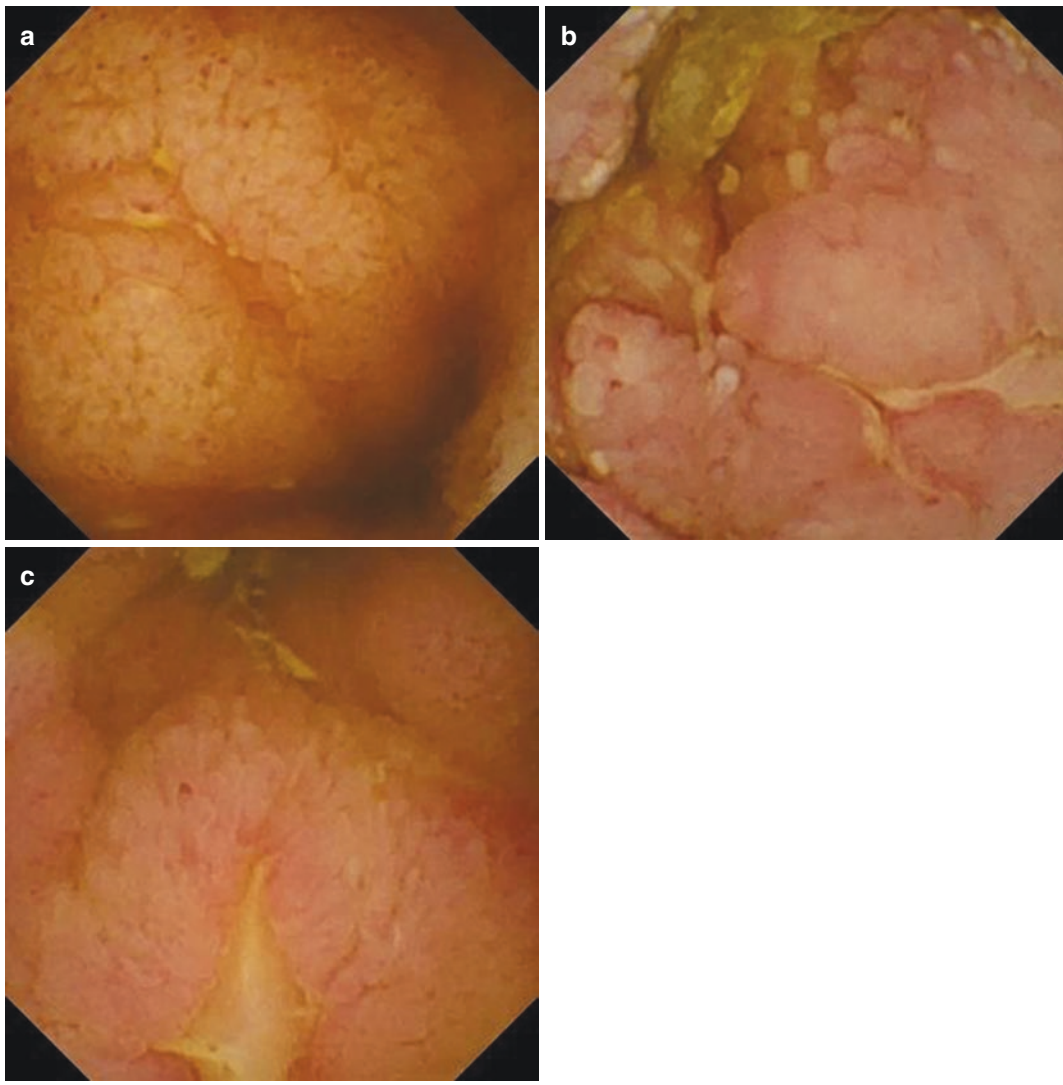

Fig. 5.2 Examples of endoscopic features of CD at capsule endoscopy. (**a**) Diffuse oedema with small ulcers; (**b**) larger ulcers and more severe mucosal oedema; (**c**) irregular-shaped ulcer

CE is extremely sensitive (which results in few false negatives) but low in specificity (which results in more false positives). Consequently, a negative examination is extremely valuable in cases with unspecific ulcerations and high clinical suspicion. Even in patients with erosions and ulcerations due to the use of NSAIDs, CE can rule out CD with a high degree of certainty.

Figure 5.2 lists some examples of CD visible in capsule endoscopy.

5.8 Summary

Nursing is crucial to ensure adequate bowel cleansing, patients' adherence to pre- and post-procedure prescriptions and assisting patients during endoscopic procedures. A highly trained IBD nurse could possibly be expected to carry out diagnostic endoscopy in select populations depending on the policies of the individual medical centres and country of residence. Moreover, a dedicated IBD nurse can contribute to patient confidence by supporting patients with an advanced focus on issues related to their disease which includes all aspects of endoscopy.

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Laboratory Findings

6

Catherine Colman, Marlene Stone, and Alain Bitton

Abstract

Diagnosing and treating inflammatory bowel disease (IBD) is a challenging process. Several criteria are required for a definite diagnosis. These include clinical presentation, endoscopic appearance, histological findings, as well as biochemical and laboratory investigations (ECCO, J Crohns Colitis 11(1):3–25, 2017; Vermiere et al., Gut 55:426–431, 2006). Laboratory investigations are noninvasive and usually accessible and inexpensive and an integral part of diagnosis and overall IBD management. They are essential in detecting infection and inflammation, in assessing malabsorption and nutritional deficiencies, and in monitoring the response to therapy. Considering the relapsing and remitting course of IBD, certain investigations or laboratory markers are available that can help guide detection for early intervention, which can lead to improved outcomes. Both serum and fecal markers are used routinely in IBD clinical practice. The most widely studied and used markers in IBD are C-reactive protein (CRP) and fecal calprotectin (FC). Several laboratory markers have been described in the literature but are not routinely used in clinical practice either because they are not readily available or have not gained favor. These include serum amyloid, alpha-1 antitrypsin, orosomucoid, and interleukin 6. Other essential laboratory markers in the management of IBD are also reviewed.

6.1 Introduction

Laboratory investigations are noninvasive and an integral part of diagnosis and overall management of inflammatory bowel disease (IBD). They are essential in detecting infection and inflammation, in assessing malabsorption and nutritional deficiencies, and in monitoring the response to therapy. Laboratory markers that are essential throughout the trajectory of disease, from diagnosis to relapse and to ongoing monitoring, will be reviewed (Table 6.1).

6.2 Initial Laboratory Investigations: Suspected IBD

When evaluating a patient who presents with symptoms of suspected IBD, initial laboratory investigations should include complete blood count (CBC), liver profile, electrolytes, albumin,

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Table 6.1 Laboratory investigations in IBD

Routine investigations		Markers of IBD activity
• Complete blood count	• Folate	• C-reactive protein
• Albumin	• Iron studies	• Fecal calprotectin • Fecal lactoferrin
• Liver profile	• Vitamin B12	• Platelets
• Electrolytes	• Clostridium difficile	• Ferritin
• Renal profile	• Stool culture and sensitivity • Stool ova and parasite	• Fecal leukocytes

iron studies, ferritin, renal function, vitamin B12, and C-reactive protein (CRP) or erythrocyte sedimentation rate (ESR) (Papay et al. 2013; Batres and Baldassano 2003). Stool microbiological testing for clostridium difficile or other pathogens is important in order to rule out intestinal infection (Fig. 6.1).

CRP is a marker that may have a role in the initial workup but is not specific for IBD. It is an acute phase protein produced by hepatocytes in response to cellular injury. CRP testing is inexpensive and both widely and readily available. It has a short half-life (19 h) (Vermiere et al. 2006) and can help differentiate functional from inflammatory disease. It is important to note that there is a cohort of IBD patients who are nonproducers of CRP and will not have elevations despite active disease. In UC inflammation is limited to the mucosa, and despite mucosal damage, serum CRP levels often remain low, whereas in CD, a transmural disease, values are often higher. Because of this, CRP appears to be more useful in CD than in UC, with up to 50% of UC patients having normal levels during active disease (Kopylov et al. 2014). Infection and other autoimmune disorders may alter CRP values, so this must also be considered when using it in clinical practice (Kopylov et al. 2014).

Fecal calprotectin (FC) is a calcium- and zinc-binding protein derived from neutrophils and monocytes (Vermiere et al. 2006; Kopylov et al. 2014; Däbritz et al. 2014; Bressler et al. 2015). It is released from inflamed gastrointestinal tissue and picked up in the stool. FC can be used to differentiate inflammatory from functional (noninflammatory) conditions such as irritable bowel syndrome (IBS) (Däbritz et al. 2014). However, its specificity for differentiating IBD from infection of the gut is low (Kopylov et al. 2014).

Ferritin and platelet counts may be elevated in acute inflammatory conditions such as IBD, whereas iron, folate, B12, and albumin deficiencies may signal poor nutritional status due to lack of absorption or gut losses due to inflammation.

Laboratory markers in suspected IBD are used to help with the differential diagnosis of IBD. Physicians aim to rule out infectious and functional etiologies with the help of laboratory markers, but a definitive diagnosis will require endoscopic and histologic confirmation.

6.3 Laboratory Markers: Assessment of IBD Relapse

Patients in remission may experience a recurrence of symptoms of their IBD suddenly or over a period of time before presenting to clinic. A thorough history is always the starting point, followed by appropriate laboratory markers to help determine the cause. Intestinal infection should always be considered either as the cause of worsening symptoms or as a trigger of IBD relapse (Fig. 6.2).

Fecal calprotectin (FC) is an important biomarker for assessing relapse. It can differentiate between active and quiescent disease and correlates with the degree of mucosal inflammation (Papay et al. 2013). Levels of FC are sensitive and specific to intestinal inflammation. A recent meta-analysis reported a pooled sensitivity and specificity of 49 and 92% for detecting endoscopic activity in IBD (Mosli et al. 2015). In some units, FC kits are available for point-of-care testing. Take-home kits are also available in some locations for patients to measure their FC levels at home (Kopylov et al. 2014). There is an ongoing discussion among IBD specialists as to the ideal "cutoff" values for fecal calprotectin in Crohn's disease and ulcerative colitis, with acknowledgment that variation also exists between assays (Chang et al. 2015). It is generally accepted however that an ELISA value of >200 (mcg/g) signifies active inflammation (Kopylov et al. 2014).

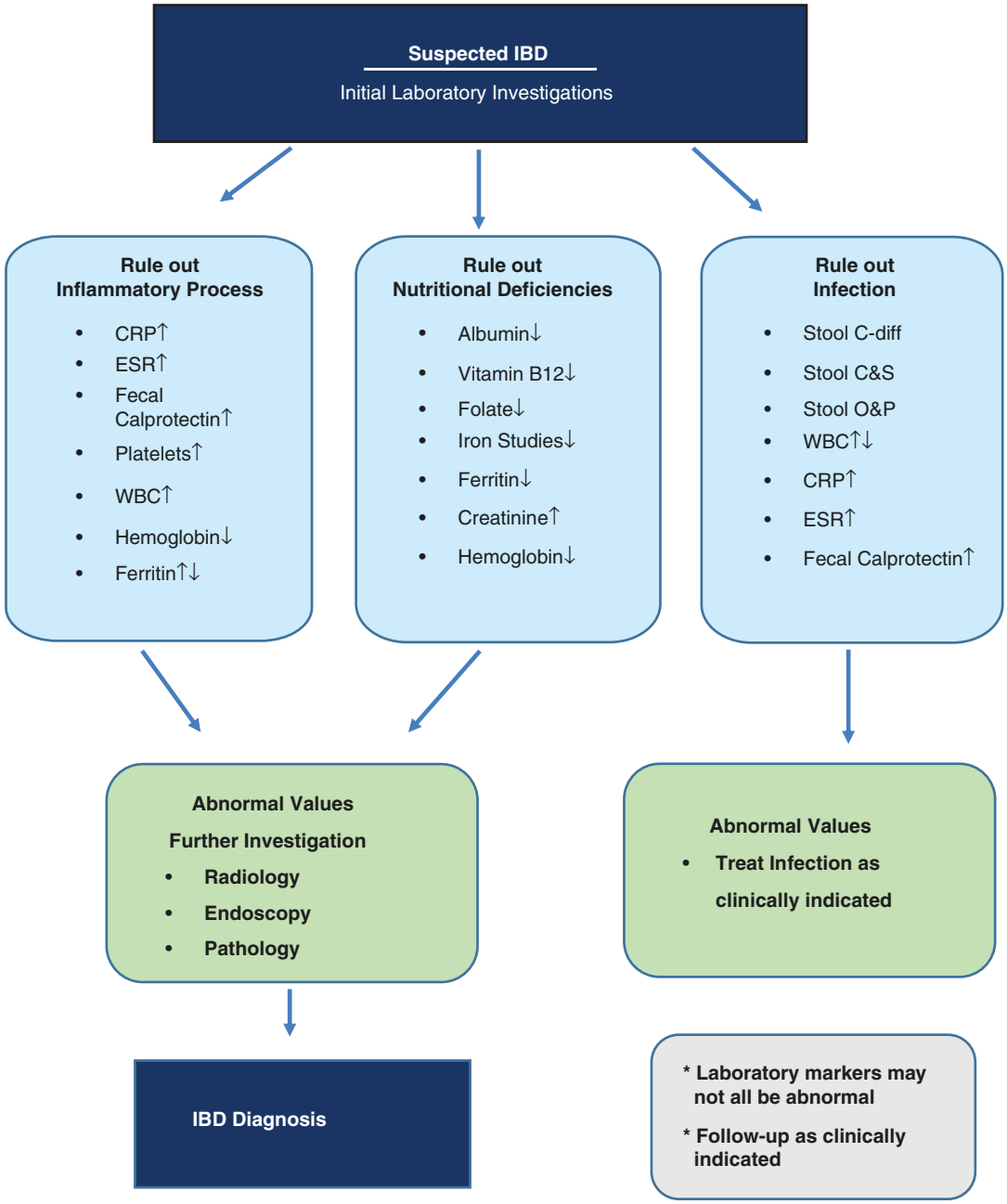

Fig. 6.1 Suspected IBD

6.4 Laboratory Markers: Monitoring IBD (Fig. 6.3)

There exists best practice in IBD consensus statements. For example, the European Crohn's and Colitis Organization (ECCO), among others, has consensus guidelines which recommend regular serum and fecal marker follow-up to monitor and possibly predict IBD flares (ECCO 2017).

Considering its short half-life, C-reactive protein (CRP) is an ideal marker to use to assess response to treatment. A decrease or normalization of CRP levels indicates response to treatment. CRP can also be useful as a predictor of

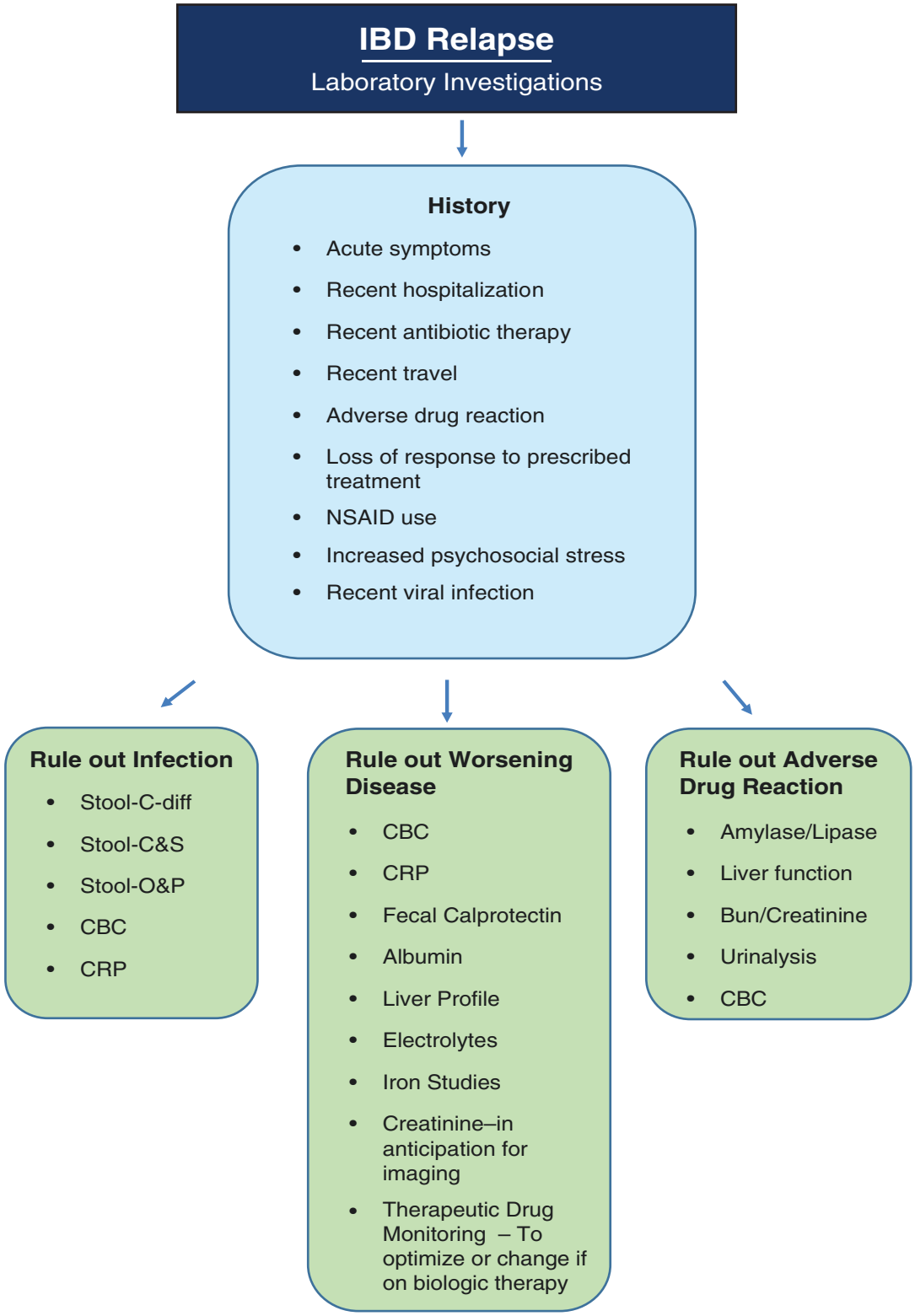

Fig. 6.2 The bubble worsening of disease

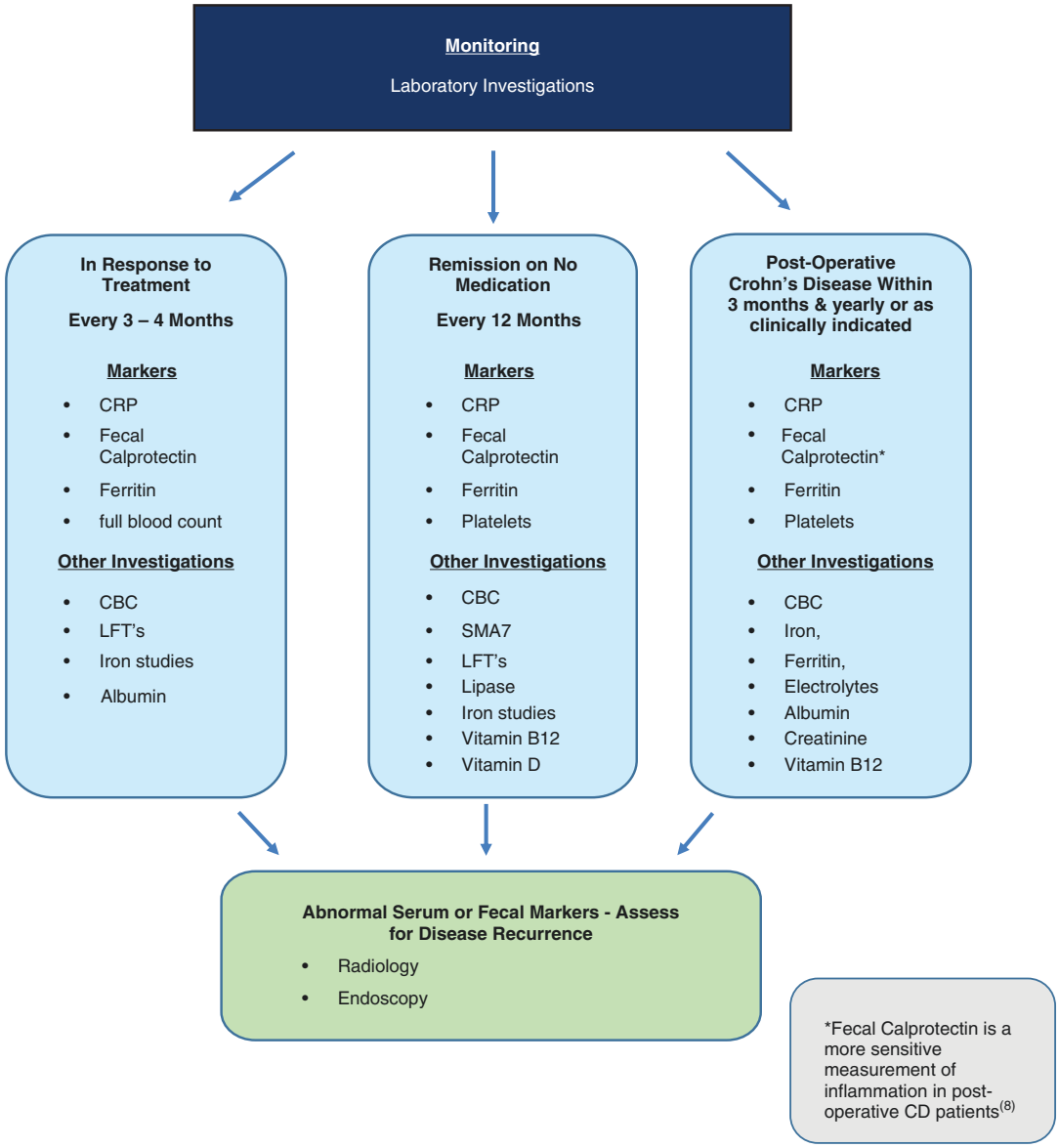

Fig. 6.3 Monitoring Laboratory Investigations

disease relapse. In a recent study, levels of CRP in Crohn's disease were shown to rise 4–6 months prior to a relapse, suggesting that routine measurement of CRP may be useful in the prediction of relapse in patients in clinical remission (Chang et al. 2015). Considering CRP is more reliable in cases of transmural inflammation, CRP may not be the most reliable biomarker for predicting CD recurrence postoperatively (Chang et al. 2015). For UC patients with normal CRP levels, it is important to consider that endoscopic disease may still be present (Chang et al. 2015). Elevation in CRP correlates with clinical relapse and is also seen in patients who lose response to treatment (Chang et al. 2015).

Fecal calprotectin (FC) can also be used as a monitoring tool to assess response to treatment. Normalization of FC level is a good indicator of improved or resolved intestinal inflammation (Papay et al. 2013). Elevated FC levels in an

asymptomatic patient can predict relapse within a 3-month period. It can be particularly useful in patients who lose response to biologics in order to objectively confirm the loss of response before adjusting therapy. The frequency of FC measurement in patients in stable clinical remission should be every 3–4 months. FC is also a more reliable indicator than CRP for monitoring postoperative recurrence (Chang et al. 2015). There is evidence that levels should return to normal at 8 weeks postoperatively (Vermiere et al. 2006; Kopylov et al. 2014; Däbritz et al. 2014; Bressler et al. 2015).

6.5 Serum Laboratory Markers: Importance in IBD

6.5.1 C-Reactive Protein (CRP)

- Increased in suspected IBD and relapse.
- Useful in monitoring disease in remission or impending relapse.
- Useful in monitoring response to therapy.
- Only 60% of individuals mount a CRP response.

6.5.2 Erythrocyte Sedimentation Rate (ESR)

- An acute phase reactant elevated in response to systemic inflammation.
- Nonspecific for intestinal inflammation (Däbritz et al. 2014).
- ESR is slow to both rise and decrease once an event is over, making it less useful and less relied upon than CRP in clinical practice (Vermiere et al. 2006).

6.5.3 Ferritin

- Acute phase reactant
- Reflects iron stores
- May be decreased or increase in active IBD

6.5.4 Platelets

- Thrombocytosis is associated with disease activity (Voudoukis et al. 2014).
- Platelet activation—increased risk of thrombotic events in the IBD population (Batres and Baldassano 2003; Voudoukis et al. 2014).

6.6 Fecal Laboratory Markers: Importance in IBD

6.6.1 Fecal Calprotectin (FC)

- Surrogate marker of gut inflammation.
- Can help differentiate functional versus inflammatory conditions.
- Increased in suspected IBD and relapse.
- Useful in monitoring disease in remission or impending relapse.
- Sensitivity and specificity depend on cutoffs.
- Despite stability there is day-to-day variability in FC.
- Serial measurements of FC can be more useful than a single measurement (Kopylov et al. 2014).
- NSAID's and PPI's can elevate FC levels (Bressler et al. 2015).

6.6.2 Fecal Lactoferrin (FL)

- Surrogate marker of gut inflammation
- Not readily or widely used
- An iron-binding protein released from neutrophils of the gut mucosa
- Correlates well with inflammation endoscopically and clinically (Papay et al. 2013)
- FL less widely accepted and less studied than FC as a marker in IBD (Papay et al. 2013; Vermiere et al. 2006; Kopylov et al. 2014; Bressler et al. 2015)

6.6.3 Fecal Leukocytes

- Present in bacterial infection, parasitic (amebiasis) invasion, or inflammation (Walk-in-Lab n.d.)
- Can assist in the differential diagnosis in those with diarrhea (Walk-in-Lab n.d.)
- Detected with methylene blue staining

6.7 Other Laboratory Investigations: Importance in IBD

6.7.1 Complete Blood Count (CBC)

- An indicator of general health status.
- Insight to possible infection, anemia, and inflammation.
- Anemia can signal active disease in otherwise asymptomatic patients.
- Leukocytosis—a response to inflammation, infection, and/or steroid use.
- Leukopenia—viral illness and medications, i.e., thiopurines and methotrexate.

6.7.2 Albumin

- Serum colloid protein lowered in inflammation and infection.
- Hypoalbuminemia is associated with chronic disease, infection, inflammation, and nutritional status (Qin et al. 2016).

6.7.3 Renal Profile

- Creatinine (Cr)—high levels indicate altered filtration and/or dehydration.
- Medications such as methotrexate and 5-aminosalicylates may result in interstitial nephritis.
- Blood urea nitrogen (BUN)—elevations reflect decreased GFR and dehydration (Mayo Clinic n.d.).

6.7.4 Liver Profile

- Hepatobiliary extraintestinal manifestations are associated with or common in IBD, e.g., fatty liver and primary sclerosing cholangitis.
- Drug-induced liver toxicity, i.e., sulfasalazine, methotrexate, thiopurines, and anti-TNF.
- Assess liver profile every 4 months or as clinically indicated (UpToDate n.d.-a).

6.7.5 Vitamin B12

- Increased risk of developing B12 deficiency in Crohn's disease (CD).
- Risk factors—ileal disease, resection of the TI, bacterial overgrowth, and gastritis (UpToDate n.d.-b).
- With deficiency, increased risk of developing megaloblastic anemia and dysfunction of the nervous system with symptoms such as numbness, paresthesia, gait disturbances, or memory impairment.
- B12 levels should be monitored in all patients with ileal CD and in those who have undergone an ileal resection (UpToDate n.d.-b).
- IF If vitamin B12 is low, methylmalonic acid [MMA] and homocysteine [Hcy] should be performed in order to confirm true B12 deficiency.

6.8 Conclusion

Inflammatory bowel disease is a systemic, immune-mediated lifelong disease that requires a comprehensive approach to management. Laboratory markers are essential throughout the trajectory of the disease, from diagnosis to relapse and to ongoing monitoring. Fecal calprotectin and C-reactive protein are the most widely used markers in the management of IBD. Considering elevations in these markers can present months prior to the onset of symptoms, routine testing could potentially alter the course of the disease. The cost versus benefits of this type of management have yet to be determined, but the possibility of improving the

natural course of IBD is exciting for those involved in the care of this increasing and challenging population.

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Radiology

7

Christian Maaser and Kerri Novak

Abstract

It is well known and recognized that relying solely on the clinical symptoms at initial diagnosis as well as during the cause of the disease in the symptomatic and also asymptomatic patients bares the danger of under- as well as overtreating as symptoms often do not reflect the current disease status. Therefore, at different time points of the disease, specific attention must be given to various imaging modalities to optimize the IBD treatment. The following chapter will focus on the different imaging options and suggest algorithms on when to apply which method.

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7.1 Introduction

Why do we need imaging other than endoscopy for managing our IBD patients?

Why is imaging in the management of inflammatory bowel disease important?

Although endoscopy is considered the gold standard modality for both, initial diagnosis of inflammatory bowel disease (IBD) as well as follow-up evaluation, endoscopic examinations have a number of important limitations that limit patient acceptance and repeatability. In addition to the need for patient bowel preparation and fasting, even for sigmoidoscopy, endoscopy is invasive and has associated risks. In most countries, patients prefer to be sedated, given associated discomfort. There is patient absence from work with associated costs, as well as the significant expense associated with the procedure itself. These factors limit the feasibility and patient acceptance of recurring use of the examination for patients with IBD, which is necessary given the chronic nature of the condition.

While ulcerative colitis is a disease mostly restricted to the colon (usually non-stricturing in nature as it is restricted to the mucosal or innermost lining of the colon), Crohn's disease is a transmural disease (affecting all layers of the small or large bowel). Given the transmural and progressive nature of CD, damage secondary to recurrent inflammation is commonly seen, such as narrowing or stricturing. Crohn's disease also

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often involves the small bowel (~80%); thus, the disease may not be easily reached with conventional endoscopy given its proximal location or in the presence of strictures which limits progression of the examination. This results in incomplete understanding of the extent of disease when evaluation is limited to endoscopy. Crohn's disease damage can also manifest as penetrating complications, seen as fistula(e) or tracts forming between bowel loops and other organs. These may only be visible if the extramural aspects, outside the wall of the bowel, are evaluated. Therefore, cross-sectional imaging is essential to detect the extent and severity of the disease including complications and extramural disease as outlined (Novak and Panaccione n.d.).

Increasing attention is being given to the need to objectively evaluate patients with IBD, because clinical symptoms such as abdominal pain and diarrhea do not always correlate well with the disease activity (Papay et al. 2013; Sandborn et al. 2014). Additional measures such as C-reactive protein or fecal calprotectin (fCal) are not sensitive indicators of disease activity in all patients (af Björkesten et al. 2012). Therefore, increasing use of accessible, repeatable imaging modalities such as ultrasound may be combined with the clinical assessment, including the patient's history of clinical symptoms in order to evaluate both the response to therapy and change in symptoms. Ultrasound is also potentially important in the follow-up of the asymptomatic patient to detect asymptomatic recurrence or loss of response of medical therapy and for evaluating possible extension of disease in the context of a flare, to best guide therapy, e.g., left-sided versus pancolitis.

7.2 Imaging Indications in IBD

There are a number of different circumstances where imaging in IBD is indicated. At the time of diagnosis, it is crucial to evaluate disease extent and severity as well as to exclude complications. Imaging is also important prior to the initiation of immune-modulating medications as well as to later evaluate response to treatment.

Imaging can be done invasively and noninvasively, e.g., with IUS or MRI, in addition to laboratory parameters such as calprotectin. In addition, regular, scheduled interval imaging is also important once a patient is in remission, to ensure continuous treatment success, esp. when calprotectin increases.

The type of diagnostics depends on the disease and location, e.g., IUS or sigmoidoscopy for UC and IUS, MRI, or colonoscopy for ileal CD depending on the local expertise. Imaging is also informative in the context of a disease flare, when complications are suspected, and for postoperative evaluation of recurrent disease, often combined with either, or both, noninvasive markers such as fecal calprotectin (fCal) or endoscopy. Finally, imaging is an important component of staging in the context of established or suspected malignancy.

Imaging Indications in IBD

- Initial diagnosis
- Response to treatment
- Routine follow-up of asymptomatic patient
- Suspected disease flare
- Suspected complications
- Postsurgical follow-up to detect recurrence
- Dysplasia/cancer

7.3 Cross-Sectional Imaging Modalities: Merits and Limitations

7.3.1 Radiography

7.3.1.1 Abdominal X-ray

Although abdominal plain films have a number of limitations, they are important as a useful, safe screening tool in the context of bowel obstruction or suspected perforation. Detection of both obstruction and perforation has limited sensitivity, however, as partial small bowel obstruction is common in CD and may not be overtly evident on plain films. In addition, the detection of perforation is dependent upon the amount of free air present. Thus microperforations, such as those more common in CD that are walled off by the surrounding mesentery, may be easily missed. A normal abdominal X-ray does not rule out a gross or microperforation in the context of high clinical suspicion.

7.3.1.2 Small Bowel Follow Through and Enteroclysis

Both of these methods, either per oral ingestion of barium or instilled by a nasogastric/jejunal tube, have been standard methods historically to detect signs of inflammation in the small bowel of patients with known or suspected Crohn's disease (CD). However, these are increasingly supplanted by other imaging modalities, namely, US, computed tomography (CT), and magnetic resonance (MR), which have better sensitivity in detecting disease (Solem et al. 2008). Small bowel follow through and enteroclysis are also challenging examinations for patients, given the need to prepare with either oral contrast or with nasojejunal tube, followed by air or methylcellulose in order to create a double contrast. Barium studies currently are largely limited to those examinations where strictures are known to exist and length/characterization is necessary.

In addition, we are increasingly aware of exposure to ionizing radiation which is needed for this technique and should be avoided, as well as the decreasing imaging expertise with a high operator dependence for this technique. Therefore, *this method should be avoided* unless other imaging methods are inaccessible or the intent is to characterize an established stricture. When applying this method, one should always consider if the results would influence further patient management. If the answer is no, this method should not be applied due to the disadvantages mentioned above.

7.4 Abdominal CT, Computed Enterography, and Enteroclysis

Computed tomography (CT) has evolved in the last few decades remarkably and exhibits high-resolution, high-quality images with rapid acquisition times and high patient tolerance (Panés et al. 2011). However, there are some important caveats: first and foremost, CT imparts significant radiation exposure, up to 15 mSV (Estay et al. 2015; Kroeker et al. 2011). In addition, the intravenous contrast agents used have been associated with allergy, renal failure, and adverse thyroid implications. Dedicated small bowel imaging using enterography (oral negative contrast ingestion, often polyethylene glycol or PEG, VoLumen, or methylcellulose) or via nasojejunal instillation (enteroclysis) is highly sensitive for the detection of inflammatory disease activity and complications. CT is often readily available, with better access in most centers compared to MRI and at lower cost. One of the most important indications for CT scans in many centers is urgent/emergency department assessment given suspicion of acute complications, including bowel obstruction, perforation, or abscess, although mounting evidence suggests comparable sensitivity and specificity to other, alternate, nonionizing radiation-based modalities such as IUS and MR. Therefore, *consideration of the radiation exposure associated with abdominal CT scan should motivate preference for IUS where available* as the first choice method, and an abdominal CT should only be performed if the abdominal ultrasound findings do not explain the clinical symptoms/suspected pathology. Abdominal abscesses can be drained using abdominal CT for guidance. However, where abdominal IUS is available, abscess detection and drainage are feasible and effective by IUS.

Specific preparations/considerations (Taylor et al. 2016):

- Acute use is not limited by the need for patient fasting.
- Given radiation pregnancy patients and children are ideally excluded.
- Given i.v. contrast, renal and thyroid function should be monitored.

7.5 Magnetic Resonance, Enterography, and Enteroclysis

Magnetic resonance enterography (MRE) and enteroclysis are nonionizing, cross-sectional imaging modalities for the small bowel, increasingly used internationally in the management of IBD (Allen and Leyendecker 2014; Ordás et al. 2014) (see Fig. 7.1). There is excellent soft tissue resolution. However, there is need for patient

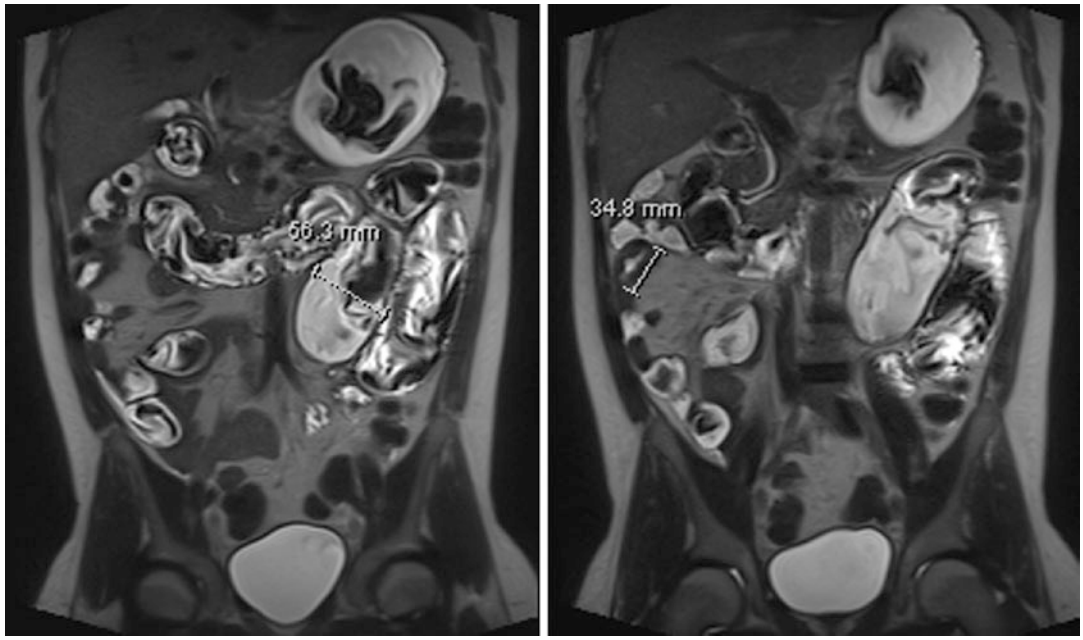


Fig. 7.1 These are two coronal images from same patient 27-year-old smoker, longstanding disease, given recurrent tooth abscess, off anti-TNF for 1 year. Longstanding fibrostenotic disease, one previous surgery (ileocecectomy)—followed by anti-TNF until last year. Lost to follow-up for more than 12 months. Presents with obstructive symptoms, 40 lbs of weight loss—admitted to hospital

preparation, similar to CT, with oral/nasojejunal contrast often needed to reduce small peristalsis with use of anti-motility agents (e.g., butylscopolamine/Buscopan®), and some centers use rectal contrast instillation (Ordás et al. 2014). Like CTE, MRE is very good for detecting complications and extramural findings (Al-Hawary et al. 2014).

Advantages of MRI:

- Lack of need for sedation for adults (though children may need sedation).
- Good soft tissue contrast with evaluation of structures beyond the mucosa.
- No radiation exposure.
- Standardized acquisition of images allows later evaluation by other specialists.
- Existence of validated scores for clinical studies (MaRIA Score, Lemann Score).
- Variability inter-rater consistency.

Disadvantages:

- High cost; as a result, limited access in many centers
- Need to reduce small bowel movement/peristalsis using medications (Buscopan®)
- Expertise dependent with interest in IBD
- Long acquisition times, so patients spend long time periods in the scanner (This may reduce tolerability.)

Limitations/exclusions:

- Contraindicated for patients with metal devices implanted.
- Severe claustrophobia.
- Children may need sedation.

Specific preparations (Taylor et al. 2016):

- *MR enterography*:
  - Fasting 4–6 h before examination.
  - Ingestion of usually >1000 mL oral contrast, mostly hyperosmolaric solution (CAVE: patients might get cramping and diarrhea) about 45–60 min prior to examination.
  - In most centers spasmolytic agent, e.g., butylscopolamine, is injected i.v.

- *MR enteroclysis:*
  - Nasojejunal tube needs to be placed under fluoroscopy before MR.
  - Oral contrast agent (same as for MR enterography) is applied via an automated pump or by hand.
- *MR enteroclysis vs. enterography:*
  - Pro: potentially better distension of the small bowel especially the proximal part.
  - Contra: nasojejunal tube placement requires radiation and usually causes patient discomfort.

Indications for MRI enterography/enteroclysis in Crohn's disease patients:

- Initial diagnosis of Crohn's disease, to detect small bowel involvement (Panes et al. 2013)
- Crohn's disease patients with strictures that cannot be passed by endoscopy
- Suspected complications, fistula, and abscess
- Consider for postoperative detection of disease recurrence

Due to expense and consequent lack of access, this method is not routinely used for follow-up to assess treatment response, though studies have demonstrated its potential for this indication (Quon et al. 2015). Furthermore, indications for the use of MRI in ulcerative colitis, as a colonic disease, are scarce. However it is potentially useful in cases of suspected complications.

7.6 Validated MRI Score: Magnetic Resonance Index of Activity (MaRIA)

The MaRIA score is a MRI score validated to measure response to therapy of the small bowel. It is currently mainly used in clinical trials and not for daily clinical routine due to the time intensity (Rimola et al. 2011):

MaRIA = (1.5 × wall thickness (mm)) + (0.002 × relative contrast enhancement) + (5 × edema) + (10 × ulcers)

7.7 Pelvic MR

Perianal fistula and perianal abscess are frequent complications of Crohn's disease, necessitating further pelvic imaging for the detection and planning of therapeutic options. Pelvic MR is considered the gold standard for the detection of perianal fistulas and abscesses. The acute presentation of abscesses usually requires immediate confirmation, imaging, and intervention (Villa et al. 2012). Given the potential for significant waiting times for MR examinations in most centers, other more accessible imaging methods such as perianal ultrasound (see below) can be useful for immediate detection.

Specific preparations/considerations:

- No specific preparation is usually required.
- Severe claustrophobia and metal devices implanted are contraindications.

7.8 Bowel Ultrasonography

Intestinal ultrasonography (IUS) is an inexpensive, noninvasive, safe nonionizing radiation method of assessing the small and large bowel, without specific preparation. In contrast to the other imaging methods outlined, IUS can be performed by the treating gastroenterologist during the clinical assessment, as it facilitates direct objective assessment (Novak et al. 2015). In addition, it has been shown in multiple evaluations to be comparable in accuracy to other imaging modalities, specifically CT and MR (Panés et al. 2011; Horsthuis et al. 2008; Greenup et al. 2016). Bowel pathology can be directly demonstrated to the patient, providing an opportunity for patient education, enhancing the patient's understanding of their disease, and increasing their understanding and engagement regarding treatment (Fig. 7.2).

Advantages of intestinal ultrasonography:

- Can be quick and easy
- Noninvasive, no preparation, no sedation required, and well tolerated
- May be broadly available in clinic, without significant wait times for assessment

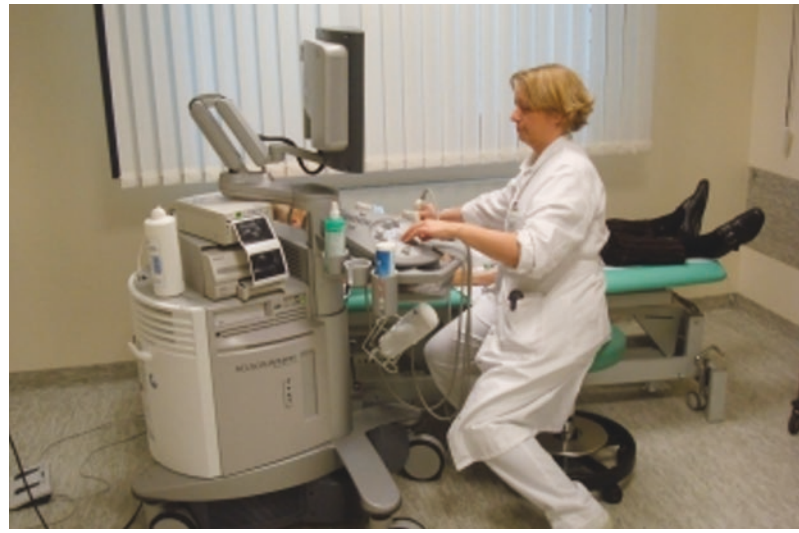


Fig. 7.2 Treating physician performing bowel ultrasound on a patient with IBD explaining the findings to the patient at the same time

- Inexpensive
- Opportunity for evaluation of real-time intestinal movement
- Provides cross-sectional, transmural, and extra-luminal evaluation
- Absence of radiation
- May be performed by treating gastroenterologist as part of routine assessment

Disadvantages:

- In contrast to MRI and CT, no standardized documentation.
- In many countries, it is currently not part of the gastroenterology training.
- No validated score for clinical trials yet.
- Limitations in anatomic resolution.

Limitations of intestinal ultrasonography:

- Increased abdominal girth/obese patients.
- Rectum and duodenal segments of the bowel may be limited.
- Retroperitoneal pathologies may be limited.

Specific preparations:

- In the majority of examinations, no preparation is required for bowel ultrasonography. As blood flow detected within the bowel wall is potentially influenced by the ingestion of food, some centers prefer a fasting of 4–8 h before intestinal ultrasound for standardization.
- *SICUS* (small intestine contrast ultrasonography): In some centers and for specific cases, e.g., to detect postoperative strictures and multiple strictures in the small bowel, an oral contrast agent is used, usually between 300 and 500 cc oral PEG (Pallotta et al. 2012; Calabrese et al. 2013). In those cases, an initial intestinal ultrasonography without oral contrast is performed, followed by oral contrast ingestion with reexamination 25–45 min later.
- *CEUS* (contrast enhanced ultrasonography): The application of intravenous contrast for the differentiation of, e.g., an abscess from a phlegmon requires an i.v. line, US contrast agent (e.g., SonoVue 1–5 mL), and 10 mL saline solution to flush the i.v. line. The US contrast consists of gas-filled lipid-layered bubbles that remain in the intravascular space and is therefore completely different from the contrast used for MRI or CT. US contrast does not impart the same allergy, renal, or thyroid implications.
- *Ultrasound-guided abscess drainage* in specialized centers: An abscess can be drained guided by ultrasonography, which requires specific puncture and drainage set.

Spasmolytic agents, as often applied for MR enteroclysis, *should not* be applied for intestinal ultrasound as this would take away one of the major advantages of intestinal ultrasonography: the evaluation of bowel movement.

Standard activity measures with ultrasound (Nylund et al. 2017):

- Bowel wall thickness (normal: colon <4 mm, small bowel <3 mm)
- Bowel wall stratification (normal starting from the luminal side: mucosa, submucosa, muscularis)
- Bowel wall blood perfusion detected by color Doppler (increased in the inflamed bowel, decreased in the fibrotic bowel)
- Bowel wall movement
- Mesenteric fatty proliferation of the mesenteric fat adjacent to the inflamed bowel segment
- Increased lymph nodes
- Complications: stricture, fistula, and abscess

Indications for intestinal ultrasound in IBD (Calabrese et al. 2016)*:*

- Initial diagnosis
- Response to treatment
- Follow-up of asymptomatic patient (Fig. 7.3a)
- Suspected disease flare (Fig. 7.3b)
- Suspected complications
- Postsurgical follow-up to detect recurrence

7.9 Perianal Ultrasonography

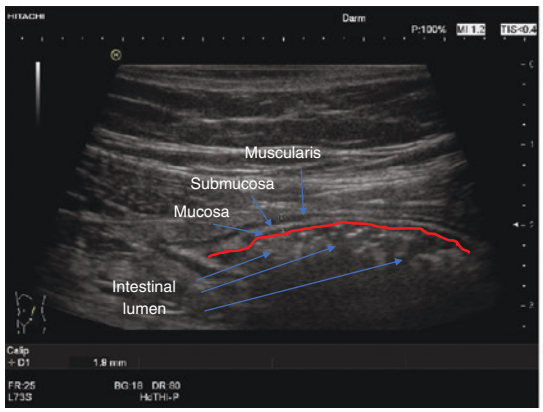
Perianal fistulae and abscesses are common as previously outlined. Perianal US is an accurate, useful, noninvasive method often available at the bedside for immediate use (Maconi et al. 2013). For this method the patient is turned on the side, and an ultrasound probe is placed on the painful perianal swelling to differentiate an inflammatory mass from an abscess. For perianal fistula detection, the probe is placed on an external opening if present. The imaging contrast can be enhanced by injecting contrast, e.g., mineral water with bubbles or H2O2 with an atraumatic needle into the external opening.

Specific preparations/considerations:

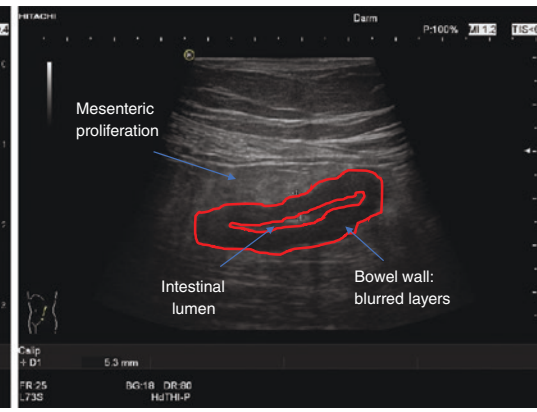
- None
- No contraindications

Indications:

- Perianal abscess (Fig. 7.4)
- Perianal fistula



Normal bowel wall sigmoid colon



Inflammed bowel wall sigmoid colon

Fig. 7.3 (**a**) Normal sigmoid colon (three layers from luminal side: mucosa, submucosa, muscularis; width < 3 mm) in a 24-year-old male patient with Crohn's colitis in remission. (**b**) Inflamed sigmoid (blurred wall layers, bowel wall width > 3 mm) with mesenteric fatty proliferation as a sign of inflammation in an 18-year-old female with segmental Crohn's colitis with an acute clinical flare

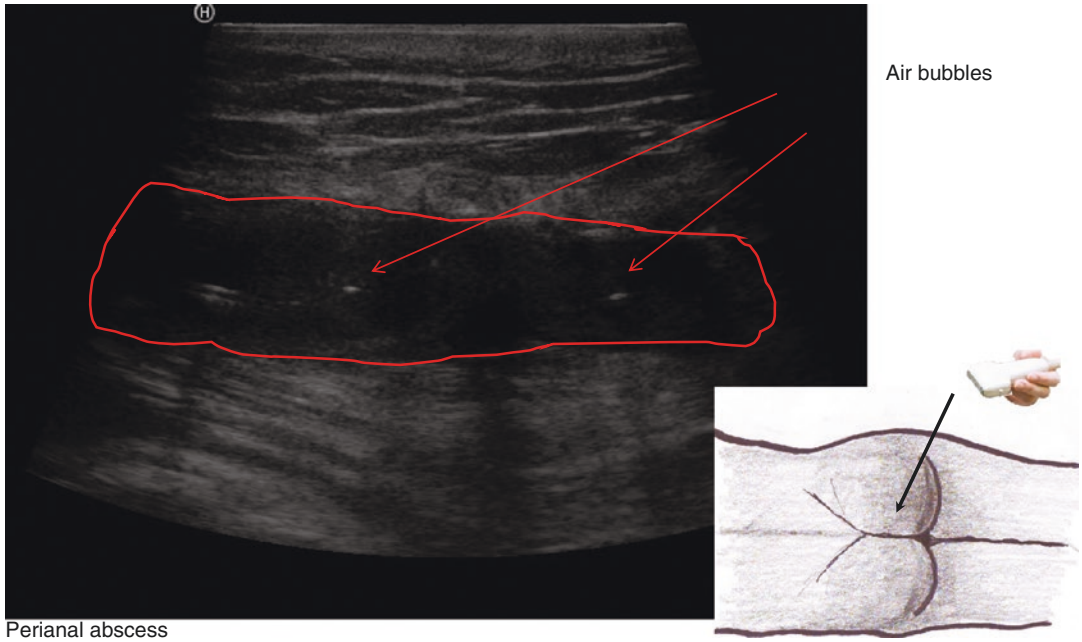


Fig. 7.4 A 21-year-old patient with Crohn's ileitis and perianal fistulas in the past, currently under anti-TNF therapy presenting with acute painful perianal swelling. Perianal ultrasonography confirmed the suspected diagnosis of a perianal abscess, and the patient was referred to the surgeon for same-day drainage

7.10 What Is the Best Imaging Modality?

There are distinct advantages and disadvantages to each and every modality outlined above, and where they demonstrate similar accuracy, additional considerations are important. Two of the most important factors in guiding imaging choice are patient preference, comfort, acceptance, and safety and secondly cost and availability. For these reasons, IUS is increasingly gaining attention as a preferred modality in the evaluation of IBD. In addition:

- Initial diagnosis: in the detection of disease extent and complications, CT/MR is important for the initial mapping of disease.
- Treatment response: repeatable, tolerable modality such as IUS is ideal.
- Suspected flare: easy repeatability, acceptable modality such as IUS is ideal.
- Follow-up of asymptomatic patient: a repeatable, acceptable modality such as IUS is ideal.
- Suspected complication: stricture, fistula, abscess, and ileus—depends upon availability, access, rapidity of need for assessment, urgency, and complexity (in cases of urgency, IUS first followed by CT where necessary, e.g., symptoms cannot be explained by IUS alone).
- Postoperative: for early detection of recurrence, easily accessible, repeatable, and tolerable modality such as IUS is preferred.

7.11 Summary

Cross-sectional imaging is an important component of disease assessment in the management of IBD and the associated complications, as well as for follow-up examinations. There are a number of available options, each with benefits and limitations. Intestinal US is safe and accurate, potentially applied at the bedside and easily repeated for interval assessment. Therefore, IUS is increasingly recognized as an ideal method for various indications in IBD patients. However, the choice

of method in most centers depends on local availability and expertise. Given increasing recognition of potential harm from ionizing radiation, minimizing patient exposure is important with preference for safer non-radiation-based modalities (Brenner et al. 2003).

Modality	Endoscopy	US	MRI	CT	Stool markers
Initial diagnosis	+	First choice	First choice	Second choice if endoscopic results are inconclusive and first choices not available	+
Treatment response	+ (Sigmoidoscopy in UC)	+ in CD, potentially in UC	(+)		+
Treatment failure	(+)	+	(+)		+
Intra-abdominal complication, e.g., abscess	–	First choice	First choice	Second choice if other imaging not available or inconclusive	–
Perianal abscess	–	Perianal US	Pelvic MRI if available in a timely manner	–	–
Suspicion of perianal fistula	Second choice	Potential option in experienced hands	First choice		
Postoperative recurrence in CD	+	+			+
Suspected pouchitis	+				+

7.12 Resources

- ECCO IBD Imaging guideline: www.ecco-ibd.eu → go to "Publications" → "published guidelines"
- ESGAR/ESPR consensus statement on the technical performance of cross-sectional small bowel and colonic imaging: Tylor SA et al. Eur Radiol 2017
- Intestinal Bowel Ultrasound Group: www.ibus-group.org
- EFSUMB Educational Portal: www.efsumb.org

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Histopathology

8

Paula Borralho Nunes

Abstract

The diagnosis of IBD requires a multidisciplinary approach involving a team of specialists that includes gastroenterologists, nurses, radiologists and pathologists.

The histologic examination of endoscopic biopsies or resection specimens is a crucial element in the diagnostic workup of a patient with suspected IBD and assists in making a final diagnosis, differentiating between UC and CD and other forms of colitis.

An adequate number of biopsies and a careful handling of the tissue are essential for an accurate diagnosis.

8.1 Introduction

The correct diagnosis of IBD requires a multidisciplinary approach involving a team of specialists, where nurses also have a very important role. The diagnosis should be established by a combination of medical history, clinical evaluation, laboratory data (including negative stool examinations for infectious agents) and typical radiologic, endoscopic and histologic findings (Magro et al. 2013). In patients with suspected IBD, it is crucial to perform a histologic examination before initiation of treatment: pathologists can find alterations consistent with IBD and in some cases rule out other conditions that may mimic IBD clinically, namely, infectious colitis (e.g. tuberculosis, parasitic diseases). Also during follow-up pathological evaluation can diagnose complications such as opportunistic infections and dysplasia.

8.2 Approach to Histologic Diagnosis

The initial histologic diagnosis is usually based on the analysis of biopsies, and an adequate sampling is crucial. For a reliable diagnosis of inflammatory bowel disease, ileocolonoscopy rather than rectoscopy should be performed as the accuracy increases significantly when serial biopsies are taken (Dejaco et al. 2003). Adequate sampling

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also gives an indication of the "geographical" distribution of the lesions along the gut, which is important for a correct diagnosis. A minimum of two biopsies from at least five sites along the colon, including the rectum, and the terminal ileum should be obtained in the initial workup of suspected IBD, even if not endoscopically affected, as histological inflammation can be present without macroscopical alterations. The exception to the rule is in patients presenting with fulminant colitis, when only one or two biopsies are indicated.

Esophagogastroduodenoscopy is also included in the initial diagnostic workup when IBD is suspected in the upper GI tract (with two or more biopsies from the oesophagus, stomach and duodenum) (Levine et al. 2014). In fact, specific typical features including the isolated detection of granuloma are found only in upper GI biopsies in a significant proportion of cases (particularly in the context of CD).

Multiple biopsies are also indicated when the patient is screened for dysplasia (intraepithelial neoplasia) or when other complications are suspected (i.e. opportunistic infection).

The careful handling and fixation of the tissue is critical, as dried or crushed material is inappropriate for histologic examination. Biopsies should be immediately fixed in a formaldehyde-based fixative or another solution that guaranties the optimum quality of the tissue. Nurses are fundamental to guarantee this goal, as their collaboration during endoscopic examination may prevent artefacts that render the histologic diagnosis difficult or even impossible. The samples should be stored and transported in separate vials as this is essential to map and grade the distribution and degree of inflammation in different colonic segments and in the terminal ileum. Orientation of the samples using filter paper or acetate (submucosal side down) before fixation may yield better results, allowing a better assessment of architectural abnormalities.

The biopsy samples should be accompanied by clinical information including endoscopic findings as well as the age of the patient, symptoms and duration of symptoms, duration and type of treatment, comorbidities and travel history.

8.2.1 Histologic Features Used for the Diagnosis of IBD

IBD is a chronic inflammatory destructive process that produces characteristic morphologic changes in the histology of the bowel. These characteristic changes can help to establish the diagnosis of IBD, to define IBD as UC or CD (Table 8.1) and to aid in assessing activity of disease (particularly in UC). Moreover, histology can assist in the diagnosis of complications such as opportunistic infections, dysplasia or neoplasia.

However, there are no pathognomonic histologic features of IBD. In many cases, especially CD, the samples show only signs of chronic disease and "non-specific" inflammatory infiltrate (that will vary according to disease severity and activity). It is relatively rare to find typical non-caseating granulomas in biopsy samples from patients with CD (especially in adults), and the majority of biopsies will not include aphthoid ulcers. Many characteristic features of CD are beyond the reach of biopsies.

These facts should not delay the diagnosis, which requires a multidisciplinary approach, and should never be made based on histology alone.

Table 8.1 Microscopic features useful for the diagnosis of IBD

	Ulcerative colitis	Crohn's disease
Architectural irregularity	Diffuse (continuous)	Focal (discontinuous)
Chronic inflammation	Diffuse (continuous), decrease proximally	Focal (discontinuous)
Localization	Mucosa	Transmural
Crypt abscesses	Common	Uncommon
Mucin depletion	Pronounced	Mild
Neuronal hyperplasia	Rare	Common
Paneth cell metaplasia	Present	Uncommon
Pyloric gland metaplasia	Rare	Present
Granuloma (not related to crypt rupture)	Absent	May be present
Terminal ileum involvement	Absent	May be present

The pathologist should be aware that in many cases the findings seen in IBD are in fact non-specific but avoid terms like "non-specific colitis" and try to decide if the biopsies are consistent with IBD. For this purpose, pathologists need adequate sampling and clinical information. On the other end, gastroenterologists have also to be aware of the limitations of histologic examination, provide all the important clinical data to the pathologist and then decide on the basis of all the information gathered, not delaying therapy in order to repeat histology.

Ideally, all IBD cases but particularly the more doubtful ones should be discussed in a multidisciplinary meeting, which should also include the pathologist.

8.2.1.1 Ulcerative Colitis

UC is a chronic inflammatory process which is continuous and limited to the mucosa. Typically, the mucosa shows diffuse and continuous chronic inflammation involving the rectum and spreading proximally without skip areas of normal mucosa. The transition between the involved and the normal mucosa is sharp in UC. Macroscopically, the mucosa has a friable granular appearance and shows superficial ulcers. In severe disease these ulcers may undermine the adjacent mucosa, finally resulting in denudation of the mucosal surface or penetration deep through the muscularis mucosae (Geboes et al. 1999; Sanders 1998). Microscopically, distorted crypt architecture with crypt distortion, branching and atrophy and an irregular villous architecture are typical of UC (Fig. 8.1) and more frequent than in CD (Seldenrijk et al. 1991). Normal colorectal crypts are straight and parallel and extend from immediately above the muscularis mucosae to the surface, while crypt distortion implies non-parallel, variable diameter or cystically dilated crypts as opposed to the normal "test-tube rack" appearance. Crypt branching represents growth or regeneration after injury and is increased in frequency in IBD (Jenkins et al. 1997). The inflammatory infiltrate is composed of lymphocytes, plasma cells, eosinophils and neutrophils when

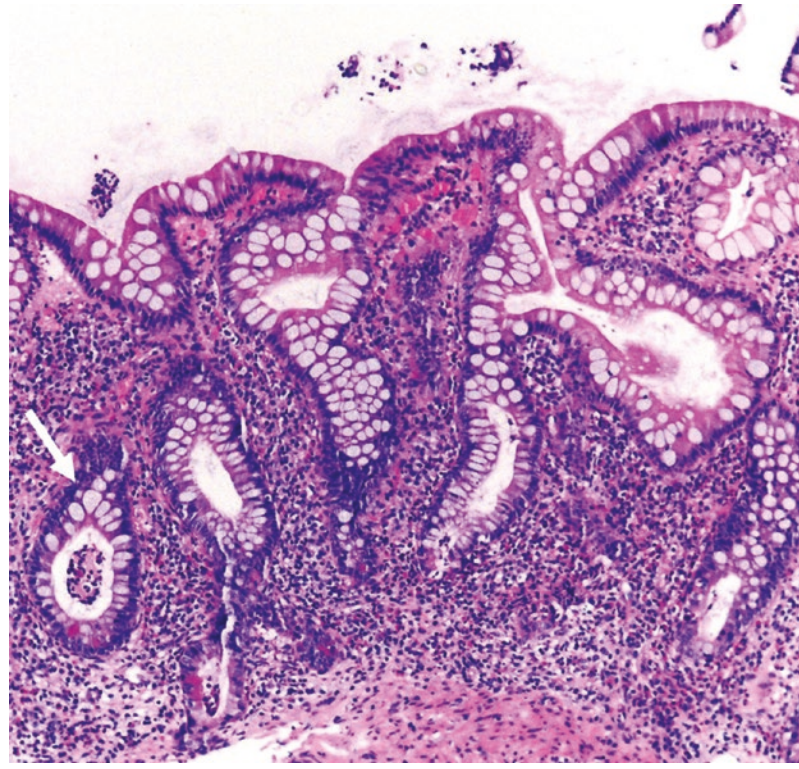

Fig. 8.1 Colonic biopsy showing characteristic aspects of ulcerative colitis: crypt distortion and branching, mixed inflammatory i nfiltrate that is restricted to mucosa and crypt abscesses (arrow)

active. Neutrophils cause cryptitis (defined as the presence of neutrophils within crypt epithelium) and crypt abscesses (defined as the presence of neutrophils within crypt lumina). Plasma cells are predominantly observed between the base of the crypts and the muscularis mucosae (basal plasmacytosis), usually intermingled with eosinophils. This feature is very helpful in the differentiation between a first attack of UC and infectious colitis (where basal plasmacytosis is very rare) but not CD, where it can also be found with similar frequency (Surawicz et al. 1994). Preserved crypt architecture and the absence of a transmucosal inflammatory cell infiltrate do not rule out ulcerative colitis at an early stage, as these features take some time to develop. Basal plasmacytosis is the earliest diagnostic feature with the highest predictive value for the diagnosis of ulcerative colitis [ECCO-ESP statement 10] (Magro et al. 2013). Features of chronicity also include Paneth cell metaplasia (especially in left-sided colitis), presence of inflammatory pseudopolyps and hypertrophy of the muscularis mucosae. The inflammation may cause mucin depletion of the epithelium, and depending on the degree of inflammatory activity, the surface may become eroded or even ulcerated. The activity of the disease is directly related to the presence of neutrophils in the chorion and permeating the epithelium (cryptitis and crypt abscesses). Granulomas are not found in biopsies of patients with UC, except those that are related to foreign bodies, ruptured crypts and mucin (cryptolytic granulomas) (Mahadeva et al. 2002).

The morphologic features may change according to disease duration, patient age and treatment. In fact, paediatric UC can show rectal sparing and patchiness (Washington et al. 2002), and treatment may induce complete restoration of the architectural distortion with decrease of the intensity of inflammation, skip lesions or rectal sparing (Odze et al. 1993).

8.2.1.2 Crohn's Disease

CD may affect any part of the gastrointestinal tract from the mouth to the anus. Most commonly, the disease affects the terminal ileum (Fig. 8.2a), often in association with the right colon.

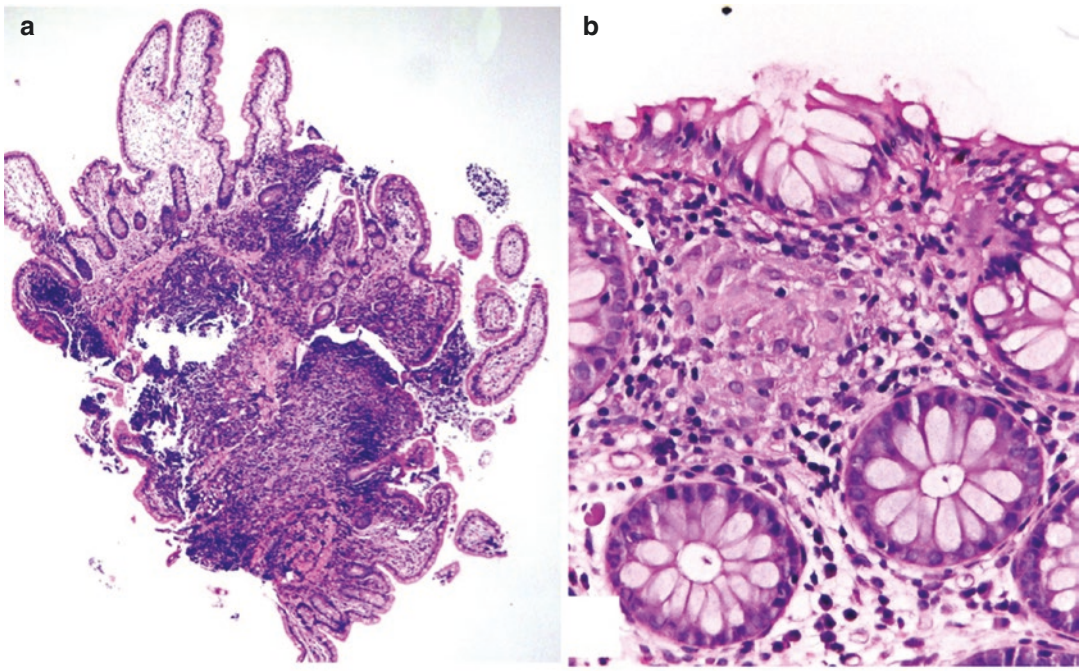

Fig. 8.2 Typical features of Crohn's disease: ileal involvement (**a**), with architectural distortion and inflammation, not limited to mucosae and a small granuloma (collection of epithelioid histiocytes) in the chorion of colonic biopsy (**b**)

Classically, CD shows a discontinuous pattern of inflammation. Diseased segments are frequently separated by areas of uninvolved, i.e. normal bowel ("skip lesions"). Some of the typical features of CD, like the transmural character of the disease as well as fistulae, can only be identified in surgical specimens. Likewise, the histologic involvement of small bowel beyond terminal ileum is usually not accessible to biopsies.

Macroscopically, the earliest grossly visible mucosal lesions of CD are small aphthous ulcers that typically develop over lymphoid follicles. As the aphthous ulcers enlarge, they coalesce to large deep serpiginous or linear ulcers with overhanging oedematous mucosal edges. Islands of oedematous, non-ulcerated mucosa, separated by deep ulcers, may give rise to the classic cobblestone appearance. The generally accepted microscopic features which allow a diagnosis of CD in the colon (on endoscopic biopsies) include focal (discontinuous) chronic inflammation, focal crypt irregularity and granulomas (not related to crypt injury). Focal (discontinuous) chronic inflammation means a variable increase in lamina propria cellularity (lymphocytes and plasma cells) across the biopsy specimen and not confined to the superficial zone. The granuloma in CD is defined as a collection of epithelioid histiocytes (monocyte/macrophage cells) without necrosis (Fig. 8.2b). Multinucleated giant cells are not characteristic but may be present (Jenkins et al. 1997). Only granulomas in the lamina propria, not related to crypt injury, may be regarded as a corroborating feature of CD. In fact, granulomas are not pathognomonic of CD. Non-caseating granulomas, small collections of epithelioid histiocytes and giant cells or isolated giant cells can be observed in infectious colitis (e.g. *Yersinia pseudotuberculosis* and *Treponema* sp.), and caseating granulomas are highly suggestive of *Mycobacterium* sp. infection and must not be regarded as evidence for CD. The same histologic features and described for colon and, an irregular villous architecture, are accepted as typical of CD in biopsy samples from the ileum. If the ileitis is in continuity with colitis, the diagnostic value of this feature should be used with caution (ECCO-ESP statement 22) (Magro et al. 2013).

Besides granulomas, additional features which have been found to be useful are pyloric gland metaplasia in ileal biopsies, aphthoid ulcers, nerve fibre hyperplasia (usually only accessible in surgical specimens), increased intraepithelial lymphocytes and a proximal location of ulceration and architectural distortion. Pyloric gland metaplasia is a feature indicative of chronic mucosal inflammation, commonly related to mucosal ulceration and repair that can be observed in 2–27% of ileal biopsies from patients with CD and is common in ileal resections, but not specific for CD (Buisine et al. 2001).

Despite detailed histologic criteria used to differentiate Crohn's colitis from ulcerative colitis in colonoscopic biopsies, no single pathognomonic lesion has been identified, and accurate discrimination between the two diseases is not yet optimal among expert gastrointestinal pathologists (ECCO-ESP statement 23) (Magro et al. 2013). Pseudovillous appearance of the colorectal surface is more consistent with a diagnosis of UC, while granulomas and focal architectural abnormalities favour CD. The absence of features that are highly suggestive or diagnostic of UC, such as diffuse crypt irregularity, reduced crypt numbers and numerous crypt abscesses, can also orient towards a diagnosis of CD.

8.2.1.3 Indeterminate and Unclassified IBD

Labels such as "indeterminate" colitis", "uncertain colitis", "inflammatory bowel disease unclassified (IBDU)", "CIBD-unclassified" and "chronic idiopathic inflammatory bowel disease NOS (not otherwise specified)" are used in the literature for patients presenting with chronic colitis without a definitive diagnosis.

The term indeterminate colitis (IC) was first introduced in a series of surgical specimens where urgent surgery had been performed, to describe the ones with "overlapping features" and "data, insufficient to make a decision" (Kent et al. 1970; Price 1978). This designation should be used only for a subgroup of cases that are difficult to classify, mainly from patients presenting with clinically severe disease and by definition in resection specimens (Lee et al. 1979). The pathological diagnosis

of indeterminate colitis relies on the presence of "overlapping features" or the absence of a "clear diagnostic pattern". It is not a real "positive" diagnosis and should not be used in biopsy samples lacking features that can clarify the diagnosis. However, the term has been misused since then, and the tendency to use the term IC for patients who seem to have IBD but cannot be readily called UC or CD became common, particularly in the paediatric gastroenterology literature, because 4–23% of new-onset cases in children present with an equivocal diagnosis. Sixty percent of such cases are ultimately reclassified as UC or CD.

The diagnosis of indeterminate colitis should be avoided when evaluating endoscopic preoperative biopsies, because of the high potential for diagnostic error. The term inflammatory bowel disease unclassified (IBDU) should instead be used for patients with chronic colitis who clearly have inflammatory bowel disease based on the clinical history, but macroscopy and/or endoscopic biopsies show no definitive features of ulcerative colitis or Crohn's disease (ECCO-ESP statement 27). Both IC and IBDU are "temporary diagnoses". Diagnostic uncertainty occurs more often in children but can also be observed in adults where confounding morphologic changes without a definite classification may be present as part of the natural history of ulcerative colitis or secondary to treatment.

8.3 The Role of Histology on the Diagnosis of IBD Complications

8.3.1 Infectious Colitis Related to Inflammatory Bowel Disease

Infections may be involved in triggering the onset of inflammatory bowel disease. Moreover, they can be responsible for complications such as abscesses and have been linked with onset of the disease and relapse of symptoms. Intestinal super infections may trigger flares of disease and complicate the clinical picture (Bossuyt et al. 2009). Of greatest concern in IBD patients are *Clostridium difficile* (*C. difficile*), cytomegalovirus (CMV) and fungal infections, including histoplasmosis and coccidioidomycosis. However, histology doesn't always help, this being true particularly for superinfections caused by *Clostridium difficile*. In the case of *C. difficile*, evidence continues to accumulate in support of the view that, especially in IBD, *C. difficile* infection presents in a nonclassical fashion (Rodemann et al. 2007). This can show a variety of microscopic patterns including oedema, overt active colitis without architectural abnormalities and pseudomembranous colitis. In IBD, the absence of pseudomembranes makes it very difficult for the pathologist to make a correct diagnosis that in most cases will depend on other laboratory tests (Bossuyt et al. 2009).

In CMV infection, H&E typically reveals enlarged (cytomegalic) cells with large eosinophilic nuclear inclusions, usually surrounded by a clear halo, and smaller cytoplasmic inclusions. IHC improves histologic sensitivity and specificity and should always be performed if CMV is suspected (Ayre et al. 2009). It involves identification of the CMV early and late antigen using monoclonal antibodies, thus identifying more infected cells. Quantitative PCR of colonic tissue can also be used to detect viral DNA in the colon, although the significance of a positive result in the absence of other histologic signs of infections remains unclear (Kuwabara et al. 2007).

8.3.2 Dysplasia and Cancer in IBD

Colorectal cancer risk in IBD is associated with disease duration and disease extent and raises at a rate of approximately 0.5–1% per year after a total duration of colitis of 8–10 years (Itzkowitz 1997). In UC the highest cancer risk is observed in extensive colitis, whereas no or only moderate risk is found in ulcerative proctitis or left-sided disease. Additional risk factors include primary sclerosing cholangitis (PSC), early age of onset of colitis, severity of microscopic inflammation, the presence of pseudopolyps and a family history of CRC. Patients with CD also carry an increased risk of both colorectal and small bowel adenocarcinomas (Palascak-Juif et al. 2005). The most important risk factors for the development of colorectal cancer are young age at onset, long disease duration and extensive large bowel involvement (pancolitis), indicating a cumulative effect of colonic inflammation (dysplasia–carci-

noma sequence), as known from patients with UC. Dysplasia (intraepithelial neoplasia) represents the best and most reliable marker of malignancy risk in patients with ulcerative colitis (ECCO-ESP statement 17). Colitis-associated dysplasia develops only in areas with chronic inflammation and can be divided into four morphologic categories: negative (regenerating epithelium), indefinite, positive for low-grade dysplasia, and positive high-grade dysplasia. Endoscopy with biopsy is used for secondary prevention and the detection of dysplasia in UC and may similarly be used in patients with CD depending on the extent of colon involvement.

Macroscopically, there are two patterns of dysplasia in UC: flat and elevated lesions. Flat dysplasia is defined as a lesion, the thickness of which is less than two times that of normal mucosa. It is a lesion not endoscopically visible, which carries a high risk for CRC (Muto et al. 1985).

Histology has a very important role in the detection of dysplasia and IBD-associated carcinoma. The microscopic features that are used for diagnosis of dysplasia are analogous to those characterizing neoplastic growth in general, including both architectural and cytological abnormalities. Architectural abnormalities are crowding of glands, thickening of the mucosa and lengthening and distortion of the crypts with excessive budding and increased size. Surface and crypts are lined by tall, high columnar cells in which there is some mucus differentiation. Mucin tends to be in columnar cells rather than in the usual goblet cells. Nuclear changes are morphologically similar to those seen in tubular adenomas in non-IBD patients: hyperchromatic and enlarged nuclei, with nuclear crowding and frequent overlapping. The nuclei are also typically stratified. Mitotic figures may be present in the upper part of the crypts and even in the surface (Riddell et al. 1983).

Interobserver agreement is poor, particularly for low-grade and indefinite dysplasia. Adjunctive methods like immunostaining for P53 (a tumour suppressor gene that appears as a key factor in the initial steps of IBD-associated colorectal carcinogenesis) and alpha-methyl-CoA racemase have been shown to be sensitive and highly specific for dysplasia in IBD (Gerrits et al. 2011; van Schaik et al. 2012). However, a small proportion of regenerating, non-dysplastic cases may also be positive (Marx et al. 2009). Confirmation of dysplasia by an independent expert GI pathologist is recommended and probably still the best method to improve diagnostic accuracy.

Summary The correct diagnosis of IBD requires a multidisciplinary approach where histology plays an essential part. However, histology has some limitations that should be well known. Adequate sampling and a careful handling and fixation of the tissue are critical, and optimum quality has to be guaranteed by quick immersion in fixative.

- In UC the mucosa shows diffuse and continuous destructive chronic inflammation (including lymphocytes, plasma cells, eosinophils and neutrophils) with crypt distortion, which involves the rectum and spreads proximally. Cryptitis and crypt abscesses are characteristic of active disease, and basal plasmacytosis is the earliest diagnostic feature, helping in the differentiation from acute colitis.
- CD shows a discontinuous pattern of inflammation that may affect any segment of the digestive tract with focal (discontinuous) chronic inflammation, focal architectural irregularity and granulomas (not related to crypt injury). The lesions are not limited to the mucosa as in UC and may affect the entire thickness of the gut wall.
- Despite detailed histologic criteria used to differentiate Crohn's colitis from ulcerative colitis in colonoscopic biopsies, no single pathognomonic lesion has been identified, and accurate discrimination between the two diseases is not always possible. The term inflammatory bowel disease unclassified (IBDU) should be used in these situations.
- Infections have an important role, triggering the onset of IBD, triggering flares of disease and complicating the clinical picture. Histology may be very useful in the diagnosis of CMV infection but not *C. difficile*.
- Histology has a very important role in the detection of dysplasia and IBD-associated carcinoma. Criteria for diagnosing dysplasia are well defined, and immunohistochemistry may be useful in difficult cases, although confirmation of dysplasia by an independent expert GI pathologist is recommended.

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Differential Diagnosis

9

Manuela Franke-Vögtlin and Stephan Vavricka

Abstract

Although often clinical symptoms and first investigations arouse the suspicion of inflammatory bowel disease (IBD), clinical features, such as diarrhea, abdominal pain, or rectal bleeding, are not specific for either CD or UC. As no single diagnostic criterion proves IBD, and several other diseases can mimic CD or UC, accurate patient profiling, including patient history, endoscopy, lab investigations, ultrasound, and MRI is needed to make the final diagnosis.

Differential diagnosis varies with the type of symptoms, site of involvement, and the duration of symptoms and includes, e.g. irritable bowel syndrome, colon cancer, celiac disease, and infection disorders, but also rare diseases such as auto-immune enteropathy.

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9.1 Introduction

Inflammatory bowel diseases (IBD) are characterized by a chronic inflammatory reaction of the gastrointestinal tract and beyond. The inflammatory reaction is a nonspecific response of the bowel to diverse attacks on its integrity and can be triggered by many different causes. At the first manifestation of an IBD, however, it is not always easy to distinguish between Crohn's colitis (CD) and ulcerative colitis (UC). To date, there is no test that serves as a gold standard for the diagnosis of the IBD. Therefore, a confirmation of the diagnosis of CD/UC remains a major clinical challenge.

If a patient presents with symptoms that are suggestive of an IBD, the patient history is very important and should include a detailed history of the symptoms, personal and family history, travel history, smoking status, and medication intake (especially NSAIDs, ergotamine, digoxin, and penicillamines). Symptoms such as abdominal pain, chronic diarrhea, rectal bleeding, and family history of IBD and iron-deficiency anemia are suspicious of IBD. However, often the clinical situation is less typical. The immense range of differential diagnoses varies with the type of symptoms, site of involvement, and the chronicity.

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9.2 Differential Diagnosis According to the Type of Symptoms

A summary of possible differential diagnosis of IBD patients is given in Tables 9.1 and 9.2.

Table 9.1 Differential diagnosis of ileitis

Infection	Yersinia enterocolitica
	Yersinia pseudotuberculosis
	Mycobacterium tuberculosis
	Mycobacterium avium-intracellulare complex
	Typhlitis
	Histoplasma capsulatum
	Salmonella
	Cryptococcosis
	Anisakiasis
	Actinomycosis israelii
Inflammation	Appendicitis, Appendiceal abscess
	Cecal diverticulitis
Gynecologic	Pelvic inflammatory disease
	Tuboovarian abscess
	Ovarian cyst or tumor
	Endometriosis
	Ovarian torsion
	Ectopic pregnancy
Neoplasm	Cecal or small bowel (ileal) adenocarcinoma
	Lymphoma
	Lymphosarcoma
	Carcinoid tumor
	Metastatic cancer
Drug-related	Nonsteroidal antiinflammatory drug-related ulcer or stricture
	Ischemic: oral contraceptives, ergotamine, digoxin, diuretics, antihypertensives
Vascular	Ischemia
	Vasculitides: Polyarteritis nodosa, Churg-Strauss syndrome, Takayasu's arteritis, Wegener's granulomatosis, lymphomatoid granulomatosis, giant cell arteritis, rheumatoid arthritis vasculitis, thromboangiitis obliterans, Henoch-Schönlein purpura
	Systemic lupus erythematosus
	Behçet's syndrome
Infiltrative	Eosinophilic gastroenteritis
	Amyloidosis
Lymphoid nodular hyperplasia	
Torsion of the appendiceal epiploica	
Ileitis associated with spondyloarthropathy	
Backwash ileitis in ulcerative colitis	
Radiation enteritis	
Bacterial overgrowth	

Early symptoms are often mild and nonspecific and abdominal problems are frequently misinterpreted as *irritable bowel syndrome* (IBS). There are no typical symptoms with which a distinction between functional vs. organic disorder can be made without a doubt. In patients with diarrhea, a number of different causes must be ruled out by the combination of patient history,

Table 9.2 Differential diagnosis of colitis and proctitis

Colitis
Ulcerative colitis
Crohn's colitis
Indeterminate colitis
Acute self-limited colitis
Segmental colitis associated with diverticular disease
Diverticulitis
Infections
Cytomegalovirus
Shigella
Campylobacter
Clostridium difficile
Salmonella
Aeromonas (Plesiomonas), Amebiasis
Enterohemorrhagic Escherichia coli (EHEC)
Mycobacterium tuberculosis
Yersinia enterocolitica
Schistosomiasis
Strongyloides
Ischemic colitis
Behcet's disease
Microscopic colitis
Collagenous colitis
Lymphocytic colitis
Radiation colitis
Diversion colitis
Chronic granulomatous disease
Graft-vs.-host disease
Gastrointestinal sarcoidosis
Eosinophilic gastroenteritis
Drug-related (NSAIDs, gold, penicillamine)
Proctitis
Prolapse
Solitary rectal ulcer
Trauma
Chemical injury
Infection
Herpes simplex type II
Neisseria gonorrhoeae
Syphilis (Treponema pallidum)
Lymphogranuloma venereum
Chlamydia trachomatis
Whipworm infestation
Ulcerative proctitis
Crohn's proctitis

clinical examination, laboratory, endoscopy, histology, and potentially radiology. Chronic abdominal pain with alternation of bowel habits (diarrhea and constipation) indicates an IBS while nocturnal diarrhea (esp. when with blood or pus), fever, and weight loss are rarely functional and are suspicious of different organic disorders such as IBD, infectious and neoplastic diseases. The stool marker *calprotectin* is useful to distinguish functional (normal values) versus organic disorder. However, this inflammation parameter can also increase with infections, NSAID therapy, and neoplasms. In addition, *lactose intolerance* presents itself with symptoms of abdominal discomfort and diarrhea in combination with flatulence typically after ingestion of milk-containing products. On a lactose eliminating diet, the symptoms resolve completely which helps to distinguish it from other causes.

Elevated bowel frequency and loosening stool consistency are the most common symptoms of IBD. *Acute diarrhea* can also be seen in *ischemic colitis* or *infectious* enterocolitis but in these cases there are no antecedent changes in the intestinal habits in the patient history. A detailed history of the onset and frequency of symptoms is therefore important for the interpretation of the histological findings in order to distinguish between IBD and other intestinal inflammations. In addition to the patient history and calprotectin, further *stool analyzes* are recommended to exclude Salmonella, Shigella, Campylobacter, EHEC, Yersinia, and parasites. Clostridium difficile toxin should be measured particularly in cases with previous antibiotic therapy; microbiological analysis from intestinal biopsies can also be helpful since, for example, CMV can mimic CD in immunocompromised patients. With elderly patients chronic diarrhea is suspicious of *microscopic colitis* (mean age of diagnosis 65 years) and should be excluded histologically. Furthermore, *laxative abuses* must be considered and should be included in the patient history.

Abdominal pain is the second most common symptom of IBD. Many patients with ileocecal *CD* report pain in the *right lower abdomen*, which is often increased after eating. Other pain localizations indicate different areas of inflammation. Patients suffering from *UC* report mostly localized cramping in the *left lower abdomen* that increases before defecation and improves thereafter. Tenesmus (a distressing but ineffectual urge to evacuate the rectum) indicates *proctitis*. *Sexually transmitted diseases* including herpes virus, Neisseria gonorrhoeae, Chlamydia trachomatis, and syphilis must also be considered in patients who suffer from tenesmus. If tenesmus is associated with hematochezia, a *rectal prolapse* should be ruled out.

Blood and mucus discharge is suggestive of a UC or some *infectious colitis* such as EHEC and Entamoeba. Rectal bleeding due to bowel *endometriosis* is rare; in these cases, patients often report changes in bowel habit, and bowel cramping which may be cyclic. Other reasons for rectal bleeding include *hemorrhoidal disease, diverticular bleeding,* and *ischemic colitis*.

Weight loss can be caused by eating disorders like *bulimia or anorexia nervosa* (often in combination with vomitus) and must always be considered since IBD is frequently diagnosed in young adult patients. With elderly patients, *malignancy* is a more frequent cause of weight loss.

9.3 Differential Diagnosis Depending on the Localization of the Inflammatory Changes

Ileitis In addition to many other diseases, Crohn's disease causes pain in the right abdomen, with or without diarrhea. In many cases, imaging assays such as ultrasound or CT can identify or exclude *appendicitis* or *gynecological diseases* as a cause. CT can also detect thickening of the ileum, lymphadenopathy, fistulae, or stricture. However, the CT findings alone should never lead to the diagnosis of Crohn's disease since it is not pathognomonic. *Medications* (oral anticonceptives, ergotamines, digoxin, and NSAID), the *Henoch-Schönlein purpura* (immunoglobulin A vasculitis), and infections can cause the same clinical manifestation. *Infectious diseases* with acute ileitis resembling CD can be due to *Yersinia*, tuberculosis, and amebiasis.

Proctitis Not only CD and UC but also a *rectal prolapse* or *sexually transmitted diseases* such as herpes virus, Neisseria gonorrhoeae, Chlamydia trachomatis, and syphilis can cause proctitis.

Colitis Many *infectious agents* can cause acute self-limited colitis (ASLC) which usually heals within 2 weeks but, in some cases, can last over 6 weeks. Ruling out infectious colitis with stool samples is essential; however, due to a low sensitivity of those tests, a negative culture result still does not exclude an infection. If no pathogen can be detected, the histological findings are even more important. An *ischemic colitis* leads to symptoms and histological changes which can mimic IBD colitis, particularly UC; this typically occurs in elderly patients with cardiovascular risk factors or atrial fibrillation. *Microscopic colitis* can lead to chronic diarrhea especially in elderly patients with an inconspicuous endoscopic image. The diagnosis is made via histological examination. The distinction between *diverticulitis* and a segmental CD is often difficult because strictures, fistulae, and abscesses may occur in both entities. Crohn's colitis should always be considered a differential diagnosis in the evaluation of ulcerative colitis since the therapy strategy differs. *Suspicious of CD* are sparing of the rectum, ileitis, perianal disease, fistulas, absence of bleeding, and histological findings like granulomas and focality of inflammation. An MRI of the small bowel or a capsule endoscopy can help to detect further lesions of the small bowel and a gastroscopy for upper intestinal involvement of CD.

Extraintestinal Manifestations Extraintestinal manifestations may indicate an IBD but are not pathognomonic. Aphthous/ulcerous stomatitis is also seen in patients with Behçet's syndrome where oral aphthae recur at least three times in one year in combination with other features like recurrent genital aphthae, eye and skin lesions, and a positive pathergy test. Further extraintestinal manifestations include peripheral arthritis; ankylosing spondylitis/axial arthropathies can occur also with other causes like rheumatological diseases. Skin lesions such as erythema nodosum, pyoderma gangrenosum, or papulonecrotic skin lesions are also not pathognomonic. For example, pyoderma gangrenosum, a neutrophilic dermatosis with painful inflammatory skin ulcers, is also associated with hematologic disorders and arthritis. Erythema nodosum can be seen in patients with malignancies (lymphoma), vasculitis, medications (oral contraceptives), or sarcoidosis.

9.4 Summary

Inflammatory bowel diseases (IBD) are characterized by a chronic inflammatory reaction of the gastrointestinal tract similar to those that are triggered by many different causes. The immense range of differential diagnoses varies with the type of symptoms, site of involvement, and the duration of symptoms. Therefore, a detailed patient history is essential. In combination with the clinical examination, laboratory, endoscopy, histology, and potentially radiology, a number of different causes must be excluded before the diagnosis of an IBD can be made.

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Part III

Managing IBD

Medical Management 1: General

10

Andreas Sturm

Abstract

In inflammatory bowel disease (IBD), no single cause initiates or triggers the disease. So far, medical treatment of ulcerative colitis (UC) and Crohn's disease (CD) has been aimed at decreasing the frequency and intensity of flares and limiting comorbidities and their consequences such as strictures, fistulae or cancer. Life-long therapy is usually required as there is to date no cure for IBD.

The goal in the treatment of IBD is to reach deep remission, meaning long-lasting clinical well-being combined with normal endoscopic (mucosal), biochemical (calprotectin and CRP) and histological findings. This status is currently considered to be necessary to alter disease course in IBD patients. Along with clinical reported outcomes (ClinRO), patient-reported outcome measures (PROMs) are gaining more and more weight in the judgement of remission. PROMs are validated and standardized questionnaires intended for completion by the patient to measure their perceptions of their own health condition or treatment. PROMs are aimed to allow decision-making at the level of individual patients.

As the causes of UC and CD are multifactorial, numerous and varying therapeutic strategies are needed to establish a sufficient treatment regime in IBD. However, as disease and patient expectations change over time, treatment often needs to be modified to meet the treatment goals required to optimize the disease outcome.

10.1 Introduction

Crohn's disease and ulcerative colitis are chronic, disabling diseases which not only have a significant impact on the daily life of our patients but could also lower life span due to several possible complications (Cosnes et al. 2011). This usually requires life-long therapy in both diseases, particularly because there is to date no cure for IBD. However, some patients can gain long-term drug-free remission after surgery.

Disease burden and the natural history of IBD are determined by the occurrence of inflammatory lesions, the manifestation and severity of symptoms, the development of complications and the need for surgery, disability and mortality (Latella and Papi 2012).

The therapeutic goal in the treatment of IBD is to reach long-lasting, sustained remission and prevent complications. Although remission is defined by many scores, the easiest definition consists of the absence of clinical IBD-related complaints.

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This symptom-free time, known as "sustained clinical remission", must last as long as possible. In most studies, clinical remission in Crohn's disease (CD) is defined as a Crohn's Disease Activity Index <150. In UC, the most often used score is the Mayo Score Clinical Score or Disease Activity Index (DAI). This score defines complete response (remission) as complete resolution of (1) stool frequency (normal stool frequency), (2) rectal bleeding (no rectal bleeding), (3) patient's functional assessment score (generally well), (4) endoscopy findings (normal) and (5) a PGA (Physician's Global Assessment) score of 0 (Bernstein 2015).

10.2 Background of Treatment

For decades, clinical remission was the ultimate goal both clinically and scientifically. It has more recently become clear that clinical remission needs to be accompanied by mucosal healing in order to prevent long-term complications such as the need for surgery (Fig. 10.1). Mucosal healing leads to an improved outcome of both UC and CD as evidenced by less need for surgery, use of immunosuppressants or hospital stay. However, there is no validated definition of what constitutes mucosal healing in IBD (Peyrin-Biroulet et al. 2011).

An International Organisation of IBD (IOIBD) task force proposed defining mucosal healing in UC as the absence of friability, blood, erosions, and ulcers in all visualized segments of gut mucosa (Vuitton et al. 2017). Similarly, for Crohn's disease, the IOIBD put forward a consensus definition of mucosal healing that includes the absence of ulcers. Simply stated, the absence of ulcerations and erosions should indicate mucosal healing (Bryant et al. 2014). Although it seems obvious that decreased visible mucosal inflammation would indicate better control of the disease, it has not yet been determined what minimum degree of endoscopic improvement is associated with improved clinical outcomes.

Clinical remission combined with endoscopic or mucosal remission and biomarker remission (calprotectin and CRP normal) is called deep remission, a status which is currently considered to be necessary to alter disease course in IBD patients. In the near future, the concept of deep remission might include transmural healing in CD and histologic healing in UC (Pineton de Chambrun et al. 2016).

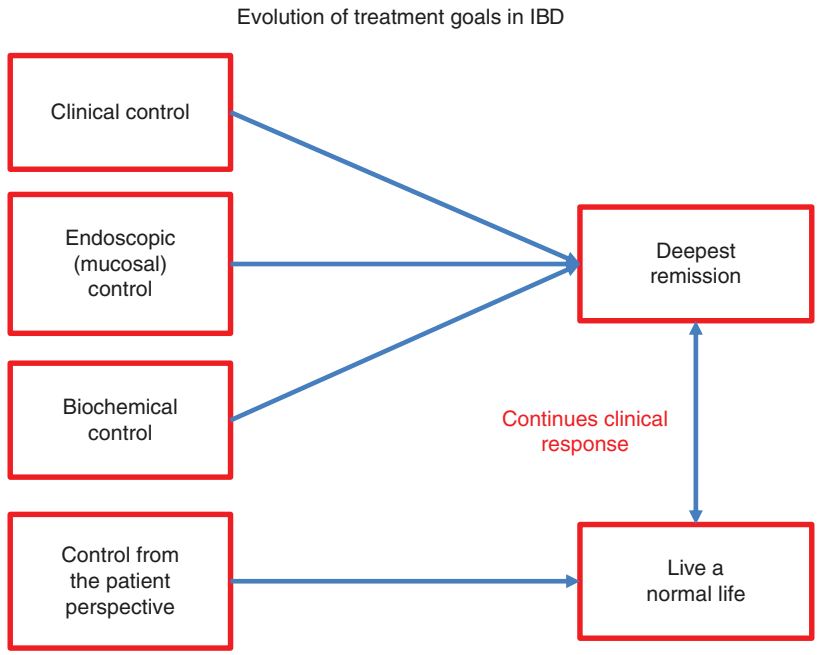

Fig. 10.1 Evolution of treatment goals in IBD

Healing of the bowel mucosa is not a predictor of remission after discontinuation of drug treatment. Being chronic diseases, both UC and CD will most likely reoccur if medical therapy is stopped even if deep sustained remission has been reached. This applies to both steroids and azathioprine (Doherty et al. 2018). Healing of the mucosa will, at best, be associated with a modest prolongation of the symptom-free interval in comparison with the non-healed bowel, but eventually the disease will resume its course. Strikingly, endoscopy upon relapse in patients who achieved mucosal healing with biological treatment shows exactly the same pattern and location of the disease as before mucosal healing. This strongly suggests that the "basic disease mechanism in the mucosa" does not disappear with healing of the ulcers and that the intraluminal trigger ends up damaging the mucosa again in a "predisposed manner" (Rutgeerts et al. 2007).

In addition to clinical remission defined by scores, endoscopic or biochemical remission, patient-reported outcomes are important psychometric instruments created and defined by patients to quantify symptoms (Kim et al. 2018). As patient satisfaction is one of the most important outcomes in IBD treatment, a combination of goals including not only the objective evaluation of inflammation by endoscopy and calprotectin but also patient-reported outcomes seems to be the most clinically and scientifically meaningful target of medical treatment. Unlike composite indices, response definitions based on endoscopic and biochemical markers as well as patient-reported outcomes can be readily applied in practice.

This convergence of outcome assessment in clinical trials and practice could expedite implementation of "treat-to-target" algorithms, in which therapy is progressively intensified until a specific treatment goal is reached. This approach could improve patient care by reducing rates of disease-related complications, surgery and hospitalization (Peyrin-Biroulet et al. 2015).

IBD are heterogeneous diseases, and there is not one single cause which initiates or exacerbates CD or UC. Often, multiple and varying therapeutic strategies are needed to identify a sufficient treatment regime in IBD. These treatments will often need to be adapted to reflect changes in the course of IBD due to complications such as intestinal resection changing the response to drugs. It is important to keep in mind that the patient's individual treatment and therapeutic needs often change over time.

Medical therapy often causes adverse side effects which lead to its own complications and negatively affect disease prognosis. Immunomodulators commonly used in IBD and which are associated with an increased risk of infections include corticosteroids, thiopurines, methotrexate, calcineurin inhibitors, anti-TNF agents, anti-integrins, anti-cytokines (Rahier et al. 2014) or JAK-kinase inhibitors. Despite different mechanisms of action, any of those drugs can lead to varying types of infection. No strict correlation between a specific immunomodulator drug and a certain type of infection has been observed. Moreover, as these drugs are commonly prescribed together, adverse events might amplify.

In clinical trials, a distinction is made between an adverse event and a serious adverse event. Generally, any event which causes death, permanent damage and birth defects or requires hospitalization is considered a serious adverse event.

The patient must be aware of risk-benefit ratios and willing to accept the possibility of any unavoidable side effects (Bewtra et al. 2015). As patient advocate, it is a crucial mission of the IBD nurse to know the pros and cons of medical therapy in order to communicate both effectively and compassionately with the patient.

There are probably four types of mistakes in defining the treatment strategy for a IBD patient:

- Under treatment of a patient who will develop disabling, complicated or severe disease
- Suboptimal use of steroids and immunosuppressants
- Continue ineffective medication
- Overtreatment of a patient with a benign disease course

However, the disease course changes over time and not only the will responsiveness towards medical treatment vary over time,

comorbidities and age increase the risk of adverse effects. However, IBD patients are willing to accept the known risks associated with IBD therapies while demanding substantial treatment benefit to make this trade-off (Bewtra et al. 2015; Siegel 2009).

10.3 Overview

- UC and CD are chronic, potentially disabling diseases. Both diseases cannot be cured, and thus, life-long therapy is needed in most patients.
- The therapeutic aim in UD and CD is to limit inflammation, achieve long-term clinical remission, prevent steroids, heal the mucosa, and guarantee a high quality of life.
- Continuous remission, both on the clinical and mucosal level, without the use of steroids, is needed to change the course of the disease and prevent complications.
- There are crucial mistakes in IBD medical therapy including the undertreatment of a patient who will develop disabling, complicated or severe disease or overtreatment of a patient with a benign disease course which might cause potential adverse events.

10.4 Summary

IBD affects a broad spectrum of physical, psychological, familial and social dimensions of life. The treatment aims consist of a long-term, deep, steroid-free remission including a symptom-free life, mucosal healing and normalization of inflammation and malabsorption markers, leading to the ultimate goal in IBD treatment: improving and normalizing the quality of life of our patients. This ambitious goal can be difficult in clinical practice, especially in patients with long-standing disease. The goal of the patient and healthcare professional needs to be re-evaluated over time in order to adapt the therapeutic approach to the course of a changing disease.

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Medical Management 2: Conventional

11

Torsten Kucharzik and Anil Kumar Asthana

Abstract

Treatment algorithms of Crohn's disease (CD) and ulcerative colitis (UC) share a lot of similarities. However, despite a variety of common therapeutic pathways, there are a few differences between both diseases that require different treatment approaches. There is no standardized definition on conventional therapy in IBD. In the following chapter steroids and mesalamine are defined as conventional therapy in IBD. The gold standard in the treatment of mild to moderate active ulcerative colitis is mesalamine. Mesalamine also plays an important role in maintenance treatment of UC. Topical application should always be considered as with topical application, much higher concentration of mesalamine could be obtained within the mucosa compared to the oral application. Mesalamine is less frequently used in patients with Crohn's disease. Budesonide is used as standard treatment for mild to moderate Crohn's disease with ileocecal involvement. Budesonide MMX exerts a continuous release within the whole colon and can be used in UC patients refractory to mesalamine. Conventional steroids are the method of choice in severe UC and CD. Long term steroid use should be avoided in patients with IBD. Mesalamine and steroids have no role in maintenance therapy of CD. If maintenance therapy appears to be useful in CD patients, immunosuppressive drugs or biologicals should be used. In the following chapter, we will present a therapeutic algorithm on how to use conventional drugs in patients with ulcerative colitis and Crohn's disease.

11.1 Introduction

Treatment algorithms of Crohn's disease and ulcerative colitis share a lot of similarities. However, despite a variety of common therapeutic pathways, there are a few differences between both diseases that require different treatment approaches. In the next chapter, we will therefore discuss conventional therapy of ulcerative colitis and Crohn's disease separately.

There is no standardized definition on conventional therapy in IBD. Probably everyone would agree that steroids and mesalamine belong to the conventional treatment options in IBD. As azathioprine and methotrexate are commonly used

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as immunosuppressive agents in IBD, they are discussed in a separate chapter.

Steroids belong to the oldest treatment options in patients with IBD. Although they may cause a lot of side effects and have therefore been criticized over the last couple of years, they still belong to the main pillars of treatment in ulcerative colitis as well as in Crohn's disease patients. The introduction of steroids in the treatment of IBD has dramatically reduced the mortality of IBD in the last century and can therefore be determined as most innovative therapy in IBD patients. Different treatment options for systemic and topical treatment of steroids are currently available which will be discussed in the following. Besides steroids, mesalamine and mesalamine derivatives belong to the main columns of treatment in IBD patients. They are still frequently used in patients with ulcerative colitis because of its high efficacy and because of only little side effects. Mesalamine is less frequently used in patients with Crohn's disease.

Before treatment in individual patients with active IBD is initiated, different parameters have to be evaluated. First of all the disease activity has to be determined. In particular the identification of a severe disease flare in distinction to bacterial or viral infection is important. Second, it is important to determine the extension of disease because it directly influences the use of local therapeutic strategies. Third, the course of disease is important as it directly affects the long-term therapeutic strategy. The course of disease is determined by different factors including the frequency of flares, premedication, extraintestinal manifestation, or comorbidities.

In the following chapter, we will present a therapeutic algorithm on how to use conventional drugs in patients with ulcerative colitis and Crohn's disease. Pharmacological aspects of the relevant drugs including potential side effects will be discussed at the beginning. After discussing the treatment of the acute flare of both diseases, maintenance therapy of ulcerative colitis and Crohn's disease with conventional therapeutics will be addressed.

11.2 Substances and Pharmacology

11.2.1 Mesalamine

Mesalamine or 5-aminosalicylate (5-ASA) derivatives are now used for more than 30 years with good evidence for treatment in patients with ulcerative colitis for induction of remission and for maintenance of remission. Sulfasalazine has been employed as initial drug which is a combination of 5-ASA with a sulfonamide. Because of side effects of the sulfonamide component, the anti-inflammatory part of the molecule-5-ASA has been mainly used during the last decades. As 5-ASA and mesalamine are synonyms, we harmonize the terms and use mesalamine in this chapter from now on. Mesalamine is orally applied and usually absorbed within the jejunum. As mesalamine is usually used for inflammation within the colon, the local concentration should be high which can't be achieved during main resorption within the jejunum. Therefore, a couple of derivates have been developed which guarantee a mesalamine-independent distribution of the drug within the terminal ileum and the colon. The most commonly Eudragit-covered pH-dependent products (such as Claversal©, Salofalk©, and Asacol©) induce equal distribution of mesalamine within the lower GI tract. Micropellets with a semipermeable membrane covered with ethylcellulose distribute mesalamine continuously within the whole small bowel (Pentasa©). In contrast, multimatrix systems (MMX, Mezavant©) distribute the drug continuously within the ileum and the whole large bowel (Mezavant©). For topical application of mesalamine, for instance, for treatment of distal colitis or proctitis enema, foam or suppositories are available. With the topical application, about 100 times higher concentration of mesalamine could be obtained within the mucosa compared to the oral application. Rectal application of enemas can approach the left hepatic flexure. Mesalamine foam may be distributed within the rectum and sigmoid colon. Suppositories can only distribute the drug within the distal rectum (Nielsen and Munck 2007).

The inflammatory effect of mesalamine is mainly based on prevention of synthesis of prostaglandins and leukotrienes. Various inflammatory mediators as well as free radicals are inhibited through different inflammatory signal transduction pathways within the mucosa (Nielsen and Munck 2007). Even though the positive effect of mesalamine in IBD patients depends on the local distribution within the colon with high mucosal concentrations, more than 50% of the orally applied and 25% of the topically applied dose of mesalamine will be absorbed. For these reasons, there is always a relevant amount of mesalamine which is systemically absorbed independent of the galenics of the drug and which may cause side effects. The side effects of sulfasalazine are high and documented in up to 45% of patients. Intolerance to sulfasalazine occurs frequently. In contrast to sulfasalazine, mesalamine is much better tolerated by the patients. For the use of mesalamine, side effects are only documented in up to 15% of patients, most of them being mild.

General side effects of mesalamine are rare and may include:

- Headache
- Abdominal discomfort
- Diarrhea
- Myalgias
- Arthralgias

Some of the more severe potential side effects that rarely occur include:

- Perimyocarditis
- Pancreatitis
- Interstitial nephritis

Even though all of these side effects are rare, they can occur even after long-term application of mesalamine. Because of the occurrence of interstitial nephritis, repetitive controls of lab parameters including urinalysis are suggested every 6 months.

From the current data, it is likely that mesalamine can be safely used during pregnancy and lactation even though any kind of drug should be used with caution in this situation (Nielsen and Munck 2007).

In particular in ulcerative colitis, mesalamine treatment is based on a high number of prospective controlled trials for induction as well as for maintenance of remission (Ford et al. 2011). Mesalamine in ulcerative colitis can be applied by oral substances as well as by topical application. The oral application of sulfasalazine is as effective as mesalamine. Within the orally applied mesalamine substances, the effect appears to be independent of the different galenics.

11.3 Corticosteroids

Corticosteroids cover the groups of glucocorticosteroids and mineralocorticosteroids. After being evaluated almost 80 years ago, glucocorticosteroids have been used in several diseases since that time including Crohn's disease and ulcerative colitis because of its anti-inflammatory action (Barnes 2011). We may differentiate between intravenous, orally, and topically applied derivatives of corticosteroids. With the oral application, we can distinguish between the classic or systemically available corticosteroids and the locally released budesonide which can be released in the ileum and the right colon or within the whole colon as an MMX preparation. For topical use enemas and foams are available which are mainly used for the treatment of left-sided or distal manifestations in the colon. Systemically available corticosteroids such as prednisolone could also be used as intravenous monotherapy during severe disease courses. Glucocorticosteroids have a very high bioavailability when applied orally. Budesonide has a high hepatic first pass effect which reduces the systemic availability to about 15%. This high first pass effect can reduce side effects as blood levels and systemic tissue levels are minimized even though tissue concentration within the bowel is high. With launching of budesonide MMX (Cortiment©) in 2015 in several countries for oral therapy of mild to moderate ulcerative colitis, there is now an orally applied glucocorticosteroid available which has the advantage of low systemic side effects in combi-

nation with a release within the whole colon. The multimatrix structure of this agent is responsible for the pH-dependent continuous release of the drug within the whole colon (Travis et al. 2014).

There are different anti-inflammatory strategies on the level of transcriptional level as well as an inhibition of enzyme activity at translational level with regard to the effect of corticosteroids (Becker 2013). The nonselective mechanism might explain the strong and anti-inflammatory effect as well as the frequently occurring side effects of this drug.

Main side effects of glucocorticosteroids include:

- Osteoporosis
- Steroid-induced diabetes mellitus
- Myopathy
- Steroid acne and glaucoma
- Cataract and peptic ulcer
- Arterial hypertension
- Psychiatric complications
- Infections

The immunosuppressive nature of steroids is responsible for the increased risk of infections which has been shown in several trials and registers. There is a clear dose response with regard to the side effects which may occur even with low concentrations. Because of the frequent side effects of the drug, the length of therapy should be reduced to 3 months. Even though there is no clear cut-off dose with regard to the side effects, it is likely that a daily concentration of more than 15–20 mg prednisolone equivalent might be associated with an increased risk of infections as well as postoperative complications. Because of potential adrenal insufficiency after treatment of more than 14 days, systemically acting steroids should not be disrupted immediately after a period of 14 days of treatment. Because of severe suppression of the immune system when applying ≥20 mg prednisolone equivalent life vaccine have to be avoided in this situation before a 4-week period after stopping prednisolone therapy. Systemically acting glucocorticosteroids should also be used with caution during pregnancy and during lactation, even though these drugs may be used, if clinically indicated.

Glucocorticosteroids are not useful in maintaining remission. Despite useful effects in active ulcerative colitis and Crohn's disease, steroids have no role in maintenance of remission in both diseases because of its side effects and because of being not efficient. Dosage is related to the route of application. Systemically acting corticosteroids are usually applied at a dose of 1 mg prednisolone equivalent per kg per day or 60 mg/day. On the long term, more than half of the patients benefit from induction therapy with glucocorticosteroids. After 1 year of treatment, more than 25% of the patients still require steroids and are steroid dependent.

A trained nurse should be aware of the potential side effects of corticosteroids as well as mesalamine and should directly ask the patient during taking the history whether such side effects may have occurred in the past. It is also important for the IBD nurse to ask on how long steroids have been already taken and at which dosage. This information is crucial to get an idea about potential long-term side effects of steroids and to decide whether a patient has a steroid-dependent or steroid-refractory course of disease.

11.4 Conventional Treatment of Ulcerative Colitis

11.4.1 Proctitis

Even though the course of disease of ulcerative proctitis is usually milder compared to the extended form of the disease, the manifestation can still be severe and sometimes challenging. Local therapy has the main impact in proctitis with mild to moderate disease activity. The primary choice for treatment of mild to moderate active proctitis is mesalamine applied as suppository. Meta-analyses have shown that induction of remission by mesalamine is quite efficient and clearly superior compared to placebo (Marshall et al. 2010; Wang et al. 2016a). The daily dose of 1 g mesalamine as suppository applies the maximum effect. Dose escalation with more than 1 g/day does not show any better effect. As the

twice-daily application of mesalamine is not better than the once-daily application, the once-daily application should be applied because of better compliance (Andus et al. 2010). In comparison with topically applied steroids, mesalamine appears to work better with regard to induction of remission. Oral application alone or in combination with local mesalamine administration is not better than local therapy alone. Just in case of a non-response of mesalamine, topical steroids should be added. Combined therapy of mesalamine plus corticosteroids is more effective than monotherapy with mesalamine. As corticosteroids are currently unavailable as suppositories, individual preparation of budesonide or beclomethasone suppositories may be useful. Only if combined local administration of local therapy with mesalamine plus topical steroids does not induce remission in ulcerative proctitis, therapeutic escalation to systemic steroids should be considered.

11.4.2 Distal Colitis

In contrast to proctitis, suppositories alone are usually not sufficient to treat distal colitis. Because of an extended distribution of the drug, enemas and foam have to be applied in distal colitis. Treatment of choice in distal colitis with mild to moderate disease activity is mesalamine (Cohen et al. 2000). During the first 8 weeks after treatment, initiation remission rates of 40–80% can be expected. Efficacy of topical application of mesalamine in distal colitis in comparison to placebo has been shown in several studies. The best effect may be achieved with a combination therapy of oral and local application of mesalamine (Safdi et al. 1997). In case of non-compliance or if rectal application is not applicable for any other reason, the oral formulation of mesalamine alone might be sufficient. Oral therapies with mesalamine should be performed with a dosage of ≥3 g/day and local application at a dosage of ≥1 g/day. Once-daily application should be preferred compared to a divided dosage. In case of contraindications for mesalamine or if mesalamine is not effective steroid containing enemas or foam (e.g., budesonide, beclomethasone, or hydrocortisone) should be applied topically. From the current data, it is likely that local steroids and mesalamine have a comparable efficacy. As budesonide MMX in combination with mesalamine is superior to mesalamine monotherapy for induction of remission, addition of budesonide MMX might be an alternative in patients with mesalamine non-response. In particular in patients with a non-compliance for the rectal application of mesalamine, budesonide MMX may be an alternative.

11.4.3 Extensive Colitis

The gold standard in the treatment of ulcerative pancolitis is mesalamine which should usually be given orally at a dosage of ≥3 g/day. It has been shown that mesalamine is more effective than placebo for induction of remission (Wang et al. 2016a; Harbord et al. 2017). Mesalamine should be preferred compared to sulfasalazine because it has less side effects. Even in extended colitis, it has been shown that a combination of orally and locally applied mesalamine is more effective than oral application only. Because of the same efficacy but higher compliance, once-daily application is preferred compared to the three-day application. In case of mesalamine non-response, corticosteroids should be used. The time point of adding steroids depends on the severity of disease. Higher disease activity of the colitis requires earlier use of steroids. Budesonide MMX exerts a continuous release within the whole colon and has been shown to have clinical efficacy in mild to moderate active ulcerative colitis (Travis et al. 2014). It should therefore be the preferred option in mild to moderate active ulcerative colitis because of less side effects compared to prednisolone. In case of budesonide MMX non-response or in patients with highly active disease, prednisolone should be preferred. The initial dose of prednisolone should not be lower than 0.5–1 mg/kg/day. There is no standardized dose de-escalation pattern for treatment with prednisolone. However, it is known that any exit earlier than 3 weeks is associated with more

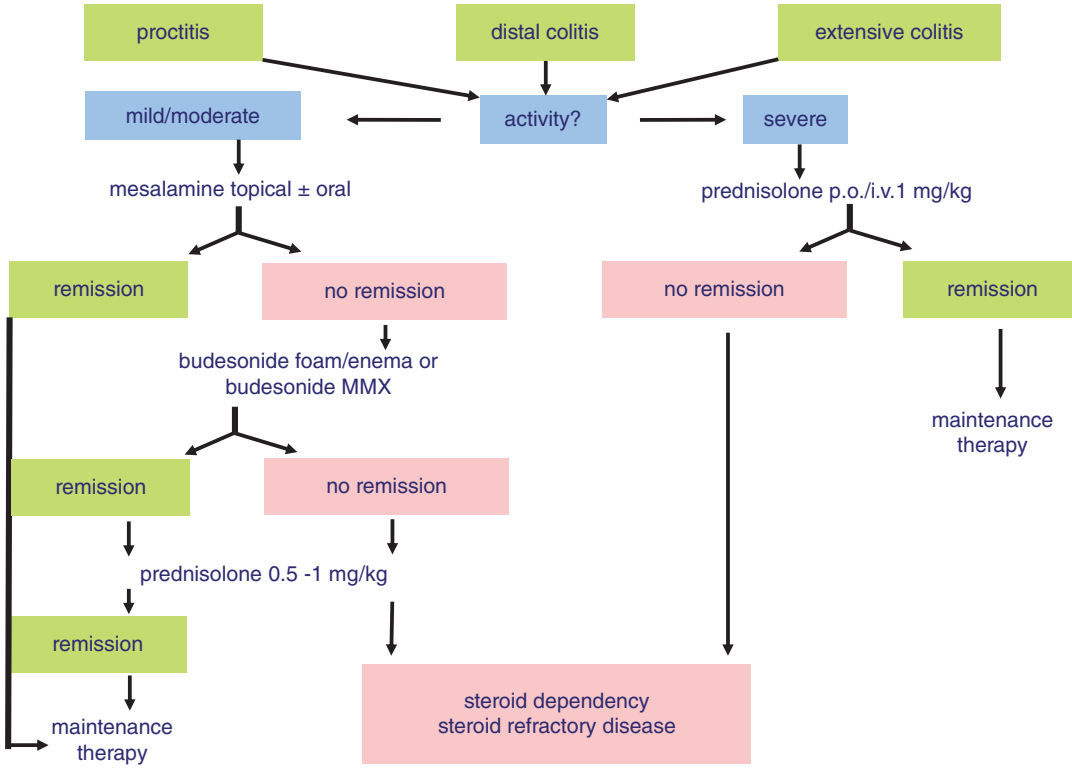

Fig. 11.1 Algorithm on conventional therapy in ulcerative colitis

frequent recurrences. Most physicians reduce prednisolone in 5–10 mg steps/weeks over a period of 2–3 months. An algorithm on how to use conventional therapy in patients with UC is shown in Fig. 11.1.

11.4.4 Severe Ulcerative Colitis

Treatment of severe ulcerative colitis is independent of the extension of the disease. Definition of severity of disease depends on the clinical course, even though indices for characterization of severity could also be used. In clinical practice, the Truelove and Witts score is used most frequently. As the course of severe ulcerative colitis is associated with high mortality, it is required to treat these patients as in-patients. Because of the benefit of interdisciplinary treatment, mortality of a severe disease course could be reduced to <1%. Prior to treatment, endoscopy should be performed in order to determine disease activity and specificity as well as to exclude infectious conditions which might be caused by CMV or by *Clostridium difficile*. In order to assess endoscopic disease activity usually no ileocolonoscopy is required. Rectosigmoidoscopy without bowel preparation is sufficient in this situation. Prednisolone should be applied at a dosage of 1 mg/kg/day or 60 mg/day. Higher dosages have not been proved to be more efficient. In contrast, lower doses are associated with less efficacy and increased mortality. If patients do not respond to oral treatment, i.v. application of steroids should be considered. A therapeutic response could be expected within 3 days. If there is no clinical and biochemical response within this period, further investigation is required. According to the ECCO guideline definition, steroid-dependent disease is defined if patients are unable to reduce steroids below the equivalent of prednisolone 10 mg/day (or budesonide below 3 mg/day) within 3 months after starting steroids, without recurrent active

disease, or if patients have a relapse within 3 months after stopping steroids (Gomollon et al. 2017). Steroid-refractory disease course is defined as active disease despite treatment with prednisolone up to 1 mg/kg/day for period of 4 weeks (Gomollon et al. 2017).

11.5 Maintenance of Remission in Ulcerative Colitis

More than 50% of patients with ulcerative colitis are relapsing within the first year after treatment of an acute flare. Maintenance treatment of ulcerative colitis after inducing remission is therefore required in patients with ulcerative colitis. The choice of treatment depends on several aspects, e.g., if the patient has been naïve for treatment, if the flare occurred under maintenance therapy, and if the patient had a steroid-refractory or steroid-dependent course of disease. It also depends on how the remission had been induced in this patient. After induction of remission with mesalamine, treatment should be extended over a period of another 2 years. Placebo-controlled trials and subsequent meta-analysis could clearly show that maintenance treatment with mesalamine is superior to placebo (Wang et al. 2016b). It is not quite clear if a maintenance period of longer than 2 years has a further benefit for the patients, e.g., for prevention of colitis carcinoma. Mesalamine maintenance therapy is also suggested if remission has been induced with steroids. The application form of mesalamine during maintenance treatment depends on the extension of the disease. Patients with proctitis should receive maintenance therapy with mesalamine suppositories. A single dose of 1 g every other day appears to be sufficient for maintenance therapy. In more extended forms of the disease, other applications with foam, enema, or tablets can be used. The minimal dosage of mesalamine being effective for maintenance treatment is 1.2 g/day. In case of intolerance to mesalamine, maintenance treatment with the probiotic *E. coli* Nissle might be used as an alternative as several controlled trials didn't show any inferiority compared to mesalamine for maintenance therapy of UC (Kruis et al. 2004).

Maintenance treatment with steroids is not suggested because of side effects that are associated with long-term use of steroids. In addition, budesonide has been shown to be not effective to maintain remission in IBD patients.

11.6 Crohn's Disease

11.6.1 Induction of Remission

The most frequent drugs that are used for induction of remission in patients with Crohn's disease are glucocorticosteroids, budesonide, and mesalamine.

CD patients with ileocecal manifestation and mild to moderate disease course are usually treated with budesonide at a dose of 9 mg/day. Side effects are less frequent under treatment with budesonide compared to corticosteroids. After a treatment period of 8–10 weeks, remission can be expected in 50–70% (Seow et al. 2008).

In case of manifestations extending the terminal ileum and the right colon, glucocorticosteroids should primarily be used at a dose of 1 mg/kg body weight/d. Induction of remission under these circumstances can be expected in 60–92% after 6 weeks (Benchimol et al. 2008) (Fig. 11.2).

The use of mesalamine in Crohn's disease patients is controversial, even though it is still frequently used for induction of remission in mildly active CD. Sulfasalazine can be effectively used in patients with Crohn's colitis. As side effects occur frequently during the use in CD, sulfasalazine is only rarely used in this situation. Another potential indication of sulfasalazine includes extraintestinal joint manifestation in CD such as arthralgia or arthritis.

The beneficial effect of mesalamine in CD patients is only minimal in meta-analysis. Therefore, it is not frequently used in Crohn's disease (Lim et al. 2016). However, the problem with these meta-analyses is that different formulas of mesalamine including pH-dependent and pH-independent forms of release are mixed in the

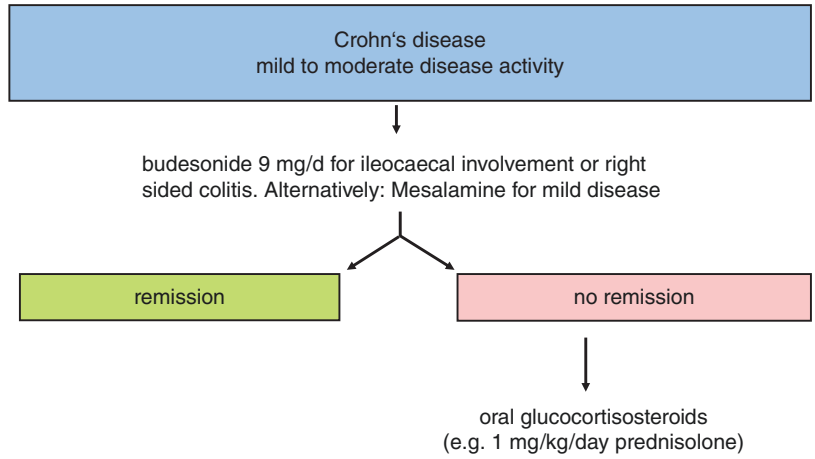

Fig. 11.2 Algorithm on conventional therapy in Crohn's disease with mild to moderate disease activity

comparison of efficacy, even though their mechanism of action is different depending on the disease location. A study that compared mesalamine with budesonide showed numerical but no statistical significant differences between both drugs suggesting that there must be some positive anti-inflammatory effect for mesalamine for induction therapy in CD (Tromm et al. 2011). Another study could document mesalamine dependency in patients with CD. These data suggest that those patients who had been mesalamine dependent must have had a response to treatment during induction therapy (Duricova et al. 2010). Mesalamine may therefore still be used during mild forms of ileocecal Crohn's disease.

Another potential indication for mesalamine in Crohn's disease may be the postoperative prevention of recurrence. It has been shown that mesalamine has a mild effect in preventing postoperative recurrence (Doherty et al. 2009).

In patients with rectal disease, topical treatment with mesalamine suppositories may sometimes be helpful as addition to systemic treatment with other drugs even though this strategy has not been proved in trials so far.

Any other manifestation of Crohn's disease including extensive small bowel disease or colonic Crohn's disease should be treated systemically with glucocorticosteroids. In addition, in patients with severely active CD, systemically acting glucocorticosteroids are suggested independent of disease localization at a concentration of 1 mg/kg body weight (Gomollon et al. 2017) (Fig. 11.3).

The risk of recurrence after induction of remission in CD is high and is quantified with 30–60% within the first year after induction of remission. As early recurrences appear to be associated with high risk of complicated disease course, it is suggested to keep those patients on maintenance therapy.

As already discussed in the previous chapter, there is currently no role for maintenance therapy with corticosteroids or budesonide in patients with CD or UC (Harbord et al. 2017; Gomollon et al. 2017). If the natural course of disease in a population-based cohort is determined, meta-analyses show that most of the CD patients reveal a disabling disease course and only 10% suffer from long-term clinical remission. Other trials describe a mild disease course in 29% of patients with CD treated with mesalamine. All these data have to be taken into account when maintenance therapy in CD individual patients has to be considered. However, mesalamine appears to be ineffective in prevention of recurrence in CD after induction of remission. Corticosteroids including budesonide should not be used because of less efficacy and because of potential side effects. Therefore, there is currently no role for these drugs for maintenance therapy in CD. If maintenance therapy appears to be useful, immunosuppressive drugs or biologicals should be used that are discussed in a different chapter.

Any course of disease that is steroid-dependent or steroid-refractory also requires more intensive immunosuppression that is discussed elsewhere.

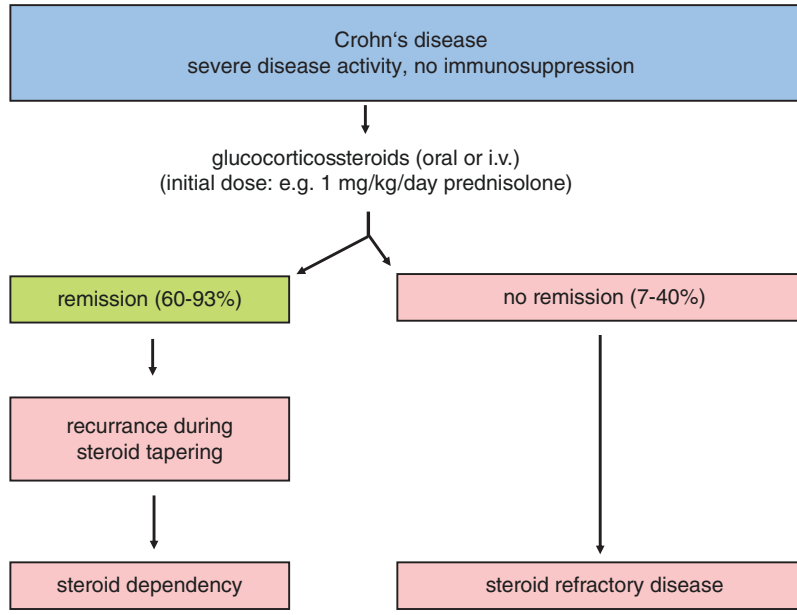

Fig. 11.3 Algorithm on conventional therapy in Crohn's disease with severe disease activity

11.7 Summary

Conventional therapy strategies in IBD include mesalamine and corticosteroids in different application forms. Gold standard for primary therapy in ulcerative colitis is the use of mesalamine. Mesalamine can be applied by use of suppositories, enema, foam or orally depending on the disease manifestation. Combined therapy of locally applied and oral mesalamine has been shown to be superior to oral or topical treatment alone. If mesalamine alone is not sufficient for induction of remission, local corticosteroids should be added. Systemic application of corticosteroids is required if these treatments fail. Systemic use of steroids may also be required initially in severe disease. After induction of remission with mesalamine or corticosteroids, long-term maintenance therapy for ulcerative colitis with mesalamine for at least 2 years is suggested.

Mesalamine plays only a minor role in mild Crohn's disease or for prevention of postoperative recurrence of CD. Budesonide is used as standard treatment for mild to moderate Crohn's disease with ileocecal involvement or manifestation in the right colon. Patients with other manifestations including patients with severely active disease are treated with systemic glucocorticosteroids. There is no role for maintenance therapy of Crohn's disease with mesalamine. There is also no role for glucocorticosteroids or budesonide as maintenance therapy neither for patients with Crohn's disease nor ulcerative colitis.

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12 Medical Management 3: Biologicals

Sofie Coenen, Ellen Weyts, Patricia Geens, and Marc Ferrante

Abstract

Anti-tumour necrosis factor (anti-TNF) agents have led to major progress for IBD patients refractory to conventional treatment (corticosteroids and immunosuppressive therapy). Infliximab and adalimumab have proven their efficacy for inducing and maintaining remission in CD and UC, and infliximab is also effective for acute severe colitis and perianal fistulising Crohn's disease. For both diseases a third anti-TNF agent has demonstrated its efficacy in a randomized controlled trial. Golimumab is available for UC patients and certolizumab pegol for CD patients, but the latter only in Switzerland and Northern America.

However, managing IBD remains challenging as prognosis and outcome vary between patients. Moreover, one-third of IBD patients seem to be primary non-responders, and an additional 40% loses effect over time (secondary nonresponders).

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Antitumour necrosis factor (anti-TNF) treatment in IBD is carried out using monoclonal antibodies (mAb) including infliximab (IFX; Inflectra®, Flixabi®, Remicade®, Remsima®), adalimumab (ADM; Humira®), golimumab (GOL; Simponi®) and certolizumab pegol (CZP; Cimzia®). Anti-TNFs are mostly used after failure of corticosteroids and/or immunosuppressive drugs such as thiopurines and methotrexate. The main limitation of anti-TNFs is that an important proportion of patients will be primary nonresponders, possibly due to a different pathophysiological mechanism driving the disease. A meta-analysis assessing efficacy of anti-TNF therapy in IBD demonstrated that induction of remission rates for IFX (at weeks 10–12) and ADM (at week 4) in CD are 45.3% and 24.2%, respectively (Ford et al. 2011). In UC, the remission rates have been reported as 57.1% for IFX (at weeks 6–12) and 17% for ADM (at week 6) (Ford et al. 2011; Sandborn 2013).

Moreover, around 40% of primary responders to anti-TNF therapy lose response to the drug over time (Ben-Horin and Chowers 2011). This loss of response (LOR) can be caused by accelerated clearance of the drug especially upon formation of antibodies against the drug (Ben-Horin and Chowers 2011). There are different ways to handle this LOR including switching to another agent or trying to optimize the dose of the current biological therapy. The latter can be performed by increasing the dose, decreasing the interval between doses or adding an immunosuppressive

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Table 12.1 Algorithm for therapeutic drug monitoring (Laboratory for Pharmaceutical Biology, Leuven)

Clinical scenario	Drug serum levels[a]	Antidrug antibodies[a]	Suggested intervention
Loss of response to biological therapy	High	Absent	Objectify loss of response If confirmed switch to a drug with another mode of action
	Adequate	Absent	Objectify loss of response If confirmed switch to a drug with another mode of action
	Low	Intermediate or absent	Check compliance Increase serum levels by decreasing the interval, increasing the dose or adding an immunomodulatory drug
	Absent	Intermediate or absent	Check compliance Increase serum levels by decreasing the interval, increasing the dose or adding an immunomodulatory drug
	Absent	High	Switch to another drug (with the same or another mode of action)

[a]Therapeutic range
For infliximab probably 3–7 μg/mL; for adalimumab probably 4–10 μg/mL; for golimumab probably >1.5 μg/mL

agent (Peyrin-Biroulet and Lémann 2011). Sandborn et al. demonstrated that in CD patients intolerant or with LOR to IFX, 21% achieved remission with ADA after 4 weeks, compared with 7% for placebo ($p < 0.001$) (Sandborn et al. 2007a). Decisions on the best treatment in case of primary nonresponse or loss of response can be based on results of therapeutic drug monitoring, taking into account the serum level of the biological therapy and the presence of antidrug antibodies (Table 12.1).

Anti-TNF therapy can also be associated with adverse events such as acute infusion reactions, delayed hypersensitivity and increased risk of infections (Singh et al. 2011; Bongartz et al. 2006; Lichtenstein et al. 2012). The most common side effects are allergic reactions, arthralgia, dry skin (sometimes psoriasiform or eczematous lesions), increased infection risk (cold, bronchitis, sinusitis) and potential slightly increased risk of melanoma skin cancer (Long et al. 2010).

The increased risk of infections can partly be reduced by administering the appropriate vaccinations as published in the second European consensus guidelines, ideally before the start of immunosuppressive therapy (Rahier et al. 2014). (See Section 6, Chap. 34).

Additionally, screening for tuberculosis is considered mandatory before using anti-TNF. This is done by performing a chest radiograph and tuberculin skin test and/or interferon-gamma release assay (according to country-specific guidelines). When these results are normal, the patient can start anti-TNF treatment. When the skin test is positive, the patient will be referred to a lung specialist to initiate appropriate tuberculostatic therapy, and anti-TNF treatment will be postponed.

The speed of response of all anti-TNF therapy varies from patient to patient and can be between days and several weeks.

Patients can become pregnant during anti-TNF therapy. The drug will usually be interrupted from week 22–24 of pregnancy until the delivery due to accumulation of antibodies in the unborn. In some cases, the treating physician may decide to continue the therapy throughout pregnancy. (See Section 5, Chap. 24).

12.1 Infliximab (Inflectra®, Flixabi®, Remicade®, Remsima®)

Infliximab (IFX) is an intravenous chimeric monoclonal antibody against TNF and was the first anti-TNF used in IBD. It's efficacy in CD and UC has been confirmed through different randomised clinical trials for inducing and maintaining remission (Hanauer et al. 2002; Rutgeerts et al. 2005; Peyrin-Biroulet et al. 2014). These clinical trials demonstrated the beneficial effect of infliximab on clinical symptoms, mucosal healing, quality of life and biochemistry and the need for surgery. Moreover, so far, infliximab is the only biological therapy with proven effect on perianal CD and acute severe UC (Sands et al. 2004; Laharie et al. 2015; Jarnerot et al. 2005).

12.1.1 Mode of Administration

Before every IFX administration, it is important to check whether the patient has signs and/or symptoms of an infection. Therefore, it is good to make an agreement with your patients to contact the infusion unit or IBD nurse before coming to the hospital in case of illness due to a potential infection. If necessary, the administration can be delayed for 1 week. In case of a suspected infection, the patient will first be seen by the appropriate clinician (attending physician or advanced nurse practitioner depending on experience and competence) for clinical examination, blood sampling and further diagnostics if necessary.

The administration schedule of IFX consists of an induction and maintenance phase (Fig. 12.1). During the *induction* phase, IFX is classically administered at a dose of 5 mg/kg body weight at weeks 0, 2 and 6. The first infusion (week 0) will be given over 2 h, the second infusion (week 2) will be started very slowly and the infusion rate can be accelerated every 20 min. Most of the infusion reactions appear after 30–60 min (Breynaert et al. 2011). Slowing down the infusion rate will allow a faster intervention during acute infusion reactions. At week 6, the infusion rate of week 2 will be repeated. When those infusions went smoothly, the fourth infusion (week 14) can be given over 2 h and the fifth (week 22) over 1 h (Fig. 12.2). When the patient did not experience any side effects during the first year of IFX therapy, further infusions can be administered over 30 min (Van Assche et al. 2010). To decrease the risk of antibody formation and allergic reactions, it is recommended to administer an immunosuppressive drug such as thiopurine or methotrexate. According to disease

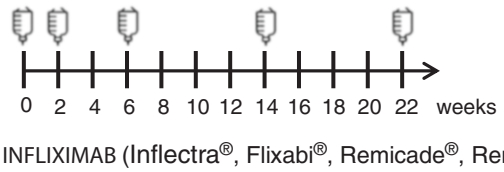

Fig. 12.1 Schematic overview of IFX administration

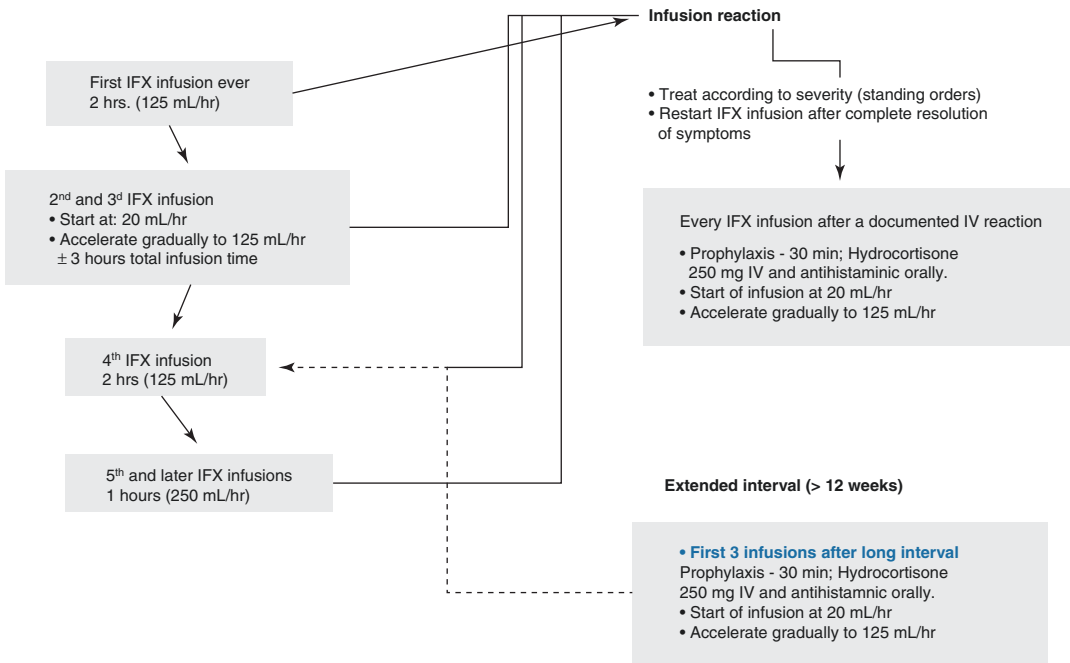

Fig. 12.2 Algorithms for infusion rates (example from the Department of Gastroenterology, University of Leuven)

severity, infliximab serum levels and local guidelines, the immunomodulator will be discontinued after 6–12 months of combination therapy (Pariente and Laharie 2014). The need for such combination therapy beyond 6 months is debated (Van Assche et al. 2008).

During the *maintenance* phase, IFX will be administered every 8 weeks. This interval can decrease (to every 4 or 6 weeks) or increase (to every 10 or 12 weeks), depending on the drug trough level, previous dose administered (5 mg/kg or 10 mg/kg) and the general wellbeing of the patient (Table 12.1) (Vande Casteele et al. 2015).

After a drug holiday of more than 12 weeks, reintroduction of IFX should be done at a slow infusion rate due to the possible antibody formation and increased risk of infusion reactions. Prophylaxis can be provided with 250 mg hydrocortisone IV (and in exceptional cases with promethazine 1 amp IM.) The first infusion can be given at a start rate of 20 mL/h, and the rate will be gradually increased every 20 min until a maximum infusion rate of 125 mL/h. This might be the standard procedure for infusions 1, 2 and 3. The next three infusions can be given over 2 h. From infusion 7 on, IFX can be administered over 1 h. Reasons for a drug holiday of more than 12 weeks could be pregnancy, surgery, therapy interruption for live vaccination (Varicella zoster virus, measles, mumps and rubella, yellow fever, typhoid fever), patient wish or financial issues.

12.1.2 Management of Infusion Reactions

An infusion reaction is defined as any adverse event occurring during or after infusion. A difference is made between acute and delayed reactions and in degree of severity. *Acute* infusion reactions occur within 24 h after start of infusion with the highest risk 30 min after the start of the second infusion. Possible symptoms are tightness in the chest, erythema and tingling (limbs and throat), facial flushing, nausea, sweating, headache or dizziness, hypo- or hypertension or shortness of breath.

In case of an acute infusion reaction, the symptoms appear very quickly. A trained nurse can manage the first minutes of the reaction independently. Standard operating procedures (SOPs) to manage such an acute reaction are:

- Stop the IFX infusion immediately and call the attending physician.
- Stay with the patient, observe severity and provide support.
- Treat the reaction according to severity and physician's orders.
- Check vital signs: blood pressure/pulse/respiratory rate.

In case of a *mild* infusion reaction, possible symptoms are facial redness, mild chest tightness, paresthesia, headache, nausea and a systolic blood pressure >110 mg Hg. Appropriate treatment according to the SOPs is the oral administration of paracetamol 500 mg and cetirizine 10 mg. Vital signs will be checked every 10 min for a period of 30 min. When symptoms are resolved and after physician's approval, infusion will be restarted at a very slow speed and can be accelerated every 20 min.

In case of a *moderate* infusion reaction, possible symptoms are significant chest tightness, bronchospasms or a drop in blood pressure of >20 mmHg. According to SOPs, appropriate treatment is the administration of hydrocortisone 250 mg IV and promethazine 1 amp IM. Thereafter, vital signs will be checked every 10 min for a 30 min time. After resolution of the symptoms and approval of the treating physician, IFX infusion will be restarted at a very slow speed. The infusion rate will be accelerated every 20 min. When symptoms reappear, the administration of IFX will be stopped definitively.

Symptoms of a *severe* infusion reaction are decreased consciousness, a systolic blood pressure <90 mmHg, severe bronchospasms or apnoea. According to SOPs, the emergency intervention team will be called, and hydrocortisone 250 mg IV and fluid expansion 500 mL will be administered until assistance arrives. If necessary, cardiopulmonary resuscitation will be initiated.

Patients experiencing an infusion reaction will always start the next infusion with prophylactic therapy of 250 mg of hydrocortisone IV and an oral antihistaminicum. This prophylaxis will be

given 30 min before start of the infusion. The IFX administration will start at a slow infusion rate of 20 mL/h. If the patient is stable after 20 min of infusion, infusion rate will be increased every 20 min with 20 mL/h to a max of 125 mL/h (Fig. 12.2). Infliximab can be continued after an infusion reaction, but prophylaxis will always be necessary.

Delayed infusion reactions (after 24 h) can occur until 2 weeks after the IFX administration. Possible symptoms are jaw claudication, myalgia and/or arthralgia with fever and/or rash, general malaise, pruritus, facial oedema, hand oedema, dysphagia, urticaria, throat pain and headache.

12.1.3 Additional Remarks

According to SOPs, vital signs (blood pressure, heart rate, respiratory rate and temperature) will be checked pre- and post-infusion. Thereafter, patients feeling well and having no complaints can leave the hospital. After the first infusion, patients will be kept for surveillance for 30 more minutes.

The dose of infliximab is always weight based, classically 5 mg/kg, but dose optimization up to 10 mg/kg can be necessary after thorough evaluation (Vande Casteele et al. 2015). In children or adults with a low body weight, higher doses may be necessary. Also, in patients with acute severe colitis and a high faecal clearance of infliximab, higher doses may be required (Brandse et al. 2015; Gibson et al. 2015).

Since 2015, biosimilars were introduced on the EU market. A large Norwegian randomised controlled trial (NOR-SWITCH) on patients with immune-mediated diseases found no differences in terms of clinical relapse and adverse events in patients switching from the originator to the biosimilar or continuing the originator infliximab (Jørgensen et al. 2017). Furthermore, Kim et al. demonstrated that the efficacy of the biosimilar was similar to the originator infliximab in terms of clinical remission and safety profile after 6 weeks in CD patients (Kim et al. 2017). These findings have contributed to a change in the perception of IBD experts, who now prescribe biosimilars with significantly more confidence.

12.2 Adalimumab (Humira®)

Adalimumab (ADM) is a fully human IgG1 monoclonal antibody to TNF and has also demonstrated to induce and maintain clinical remission in patients with active inflammatory CD and UC (Colombel et al. 2007, 2014; Sandborn et al. 2012; Hanauer et al. 2006; Reinisch et al. 2011).

Data on its efficacy in case of perianal CD are limited to sub-analyses, and data in acute severe colitis are lacking.

12.2.1 Mode of Administration

Based on trial data, classical *induction* currently consists of 160 mg (4 injections) of subcutaneous ADM at week 0 and 80 mg (2 injections) at week 2. Start-up of ADM therapy, which is available in a pen or syringe, is done ideally by the IBD nurse. The nurse educates the patient (or a relative) on (self-)administration of ADM at the week 0 visit. Four injections are administered, two by the nurse (one pen and one syringe) and two by the patient (one pen and one syringe). In this patient education process, the IBD nurse will hopefully meet best the patient needs. A pen will be advised in case the patient is afraid of needles. The nurse will educate the patient on possible injection sites, provide him with tips and tricks like rotation of injection site and inform him to keep an administration diary. Patients are advised not to inject immediately before scheduled appointments because often a blood test (serum level) will be collected for dose optimization.

From week 4 onwards, induction is followed by *maintenance* therapy with 40 mg (1 injection) ADM every other week (Fig. 12.3). In case of loss of response, the dose can be optimized with an increase to weekly administration of

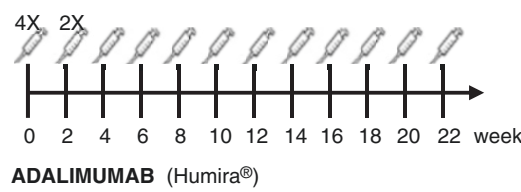

Fig. 12.3 Schematic overview of ADM administration

ADM. Retrospective surveys reported varying rates of need for ADM weekly dosing, ranging from 16% to 54% at approximately 1 year (Swoger et al. 2010; Russo et al. 2010; Ho et al. 2009). ADM maintenance therapy can be optimized to weekly therapy from week 4 onwards at the discretion of the investigator. The investigator should indicate the reason for dose optimization following daily clinical practice (symptoms, CRP, faecal calprotectin, adalimumab serum levels and/or imaging).

12.2.2 Management of Side Effects

If a patient is experiencing possible side effects of ADM therapy, the IBD nurse or treating physician will be informed. Possible side effects are similar to those occurring during IFX therapy: skin problems, increased infection risk, etc. In case the patient is feeling ill and/or has fever, he/she will be advised to give a phone call to the IBD nurse to discuss whether or not the injection should be postponed.

12.2.3 Additional Remarks

Adalimumab injections should be kept refrigerated at 2–8 °C. For patients' comfort, syringes are best kept out of the fridge for some time before injection. Patients planning a holiday need to take this into account. It is still debated if concomitant immunosuppressive therapy with adalimumab is beneficial. Due to a recent switch in formulation (from 40 mg/0.8 mL with citrate to 40 mg/0.4 mL without citrate), adalimumab injections are less painful, and injection site reaction is likely to occur less frequent. However, this option is not possible in all countries.

12.3 Golimumab (Simponi®) (Only for UC)

Golimumab (GOL) is the most recently marketed anti-TNF biological available to treat patients with moderate-to-severe UC. This subcutaneous administered fully human anti-TNF antibody presents another treatment option for patients with UC whose disease is responsive to anti-TNF.

The PURSUIT induction study demonstrated that 51.0% of the patients in the golimumab 200/100 mg group responded clinically at week 6 (Sandborn et al. 2014a). The PURSUIT maintenance study provided evidence that in 47.0% and 49.7% of the golimumab-induction responders, clinical response to, respectively, 50 and 100 mg golimumab every 4 weeks was maintained through week 54 (Sandborn et al. 2014b). So, today, a third anti-TNF biological is available for treatment of moderate-to-severe UC. Golimumab is not reimbursed for Crohn's disease and has no place in the treatment of acute severe colitis.

12.3.1 Mode of Administration

Golimumab is available in a pen of 50 or 100 mg and can be self-administered as well. During the *induction* phase, 200 mg (2 pens of 100 mg) will be administered at week 0 and 100 mg at week 2 (1 pen of 100 mg). The *maintenance* phase consists of four weekly injections of 50 mg (1 pen of 50 mg) or 100 mg (1 pen of 100 mg) from week 6 onwards (Fig. 12.4). In most European countries, the latter dose depends on the patient's body weight. If a patient weighs less than 80 kg, he will be dosed with 50 mg every 4 weeks. If the patient weighs more, 100 mg will be administered at every 4 weeks.

12.3.2 Additional Remarks

Additional remarks are comparable to those of adalimumab. Medication should be kept refrigerated (2–8°), and not in a freezer.

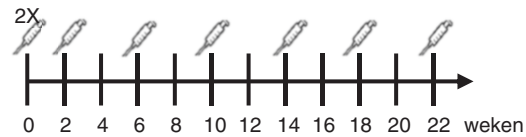

Fig. 12.4 Schematic overview of GOL administration

12.4 Certolizumab Pegol (Cimzia®)

Certolizumab (CZP) is a PEGylated Fab' fragment of a humanized TNF inhibitor mAb which is efficient for induction and maintenance treatment of CD (Sandborn et al. 2007b; Schreiber et al. 2007). In the PRECISE-1 study, 24% of patients treated with CZP (previously treated with IFX) presented clinical response at week 6 and only 15% at both week 6 and week 26 (Sandborn et al. 2007b). These rates were not different for placebo groups. Induction of remission rates in Crohn's disease is 24.7% at week 6–12 (Ford et al. 2011).

This humanized anti-TNF therapy is currently (2018) approved for the treatment of Crohn's disease only in Switzerland and Northern America. CZP is available in syringes and is classically administered at 400 mg on weeks 0, 2 and 4 and every 4 weeks thereafter.

Due to the PEG fragment, certolizumab pegol has no placental transfer and therefore has a better safety profile during pregnancy in jurisdictions where it is available (Ferrante et al. 2014).

12.5 Conclusions

- Currently, three anti-TNF agents (adalimumab, golimumab and infliximab) are available for UC patients, while two anti-TNF agents (adalimumab and infliximab) are available for patients with Crohn's disease. In some jurisdictions (Switzerland and Northern America), certolizumab pegol is also available for patients with Crohn's disease.
- Anti-TNF agents could be chosen based on a specific clinical scenario and patients wish.
- Patients with acute severe ulcerative colitis and perianal penetrating Crohn's disease will benefit most from infliximab.
- Infliximab should be initiated in combination with immunomodulatory therapy. For the other anti-TNF agents, the benefit of such combination strategy has not been demonstrated and is therefore debated.

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New Therapeutic Strategies

13

Klaartje Kok, Ana Ibarra, and James Lindsay

List of Abbreviations

CCR9	Chemokine receptor 9
CD	Crohn's disease
DAI	Disease activity index
EMA	European Medicines Agency
FMT	Faecal microbiota transplantation
FDA	Food and Drug Administration
HSCT	Haematopoietic stem cell transplantation
IBD	Inflammatory bowel disease
IFN-γ	Interferon γ
IL	Interleukin
ICAM1	Intracellular adhesion molecule-1
JAK	Janus kinase
MSCs	Mesenchymal stem cells
Treg cells	Regulatory T cells
STAT	Signal transducer and activator of transcription
S1P	Sphingosine 1-phosphate
Th cells	T-helper cells
TDM	Therapeutic drug monitoring
TNF-α	Tumour necrosis factor-α
UC	Ulcerative colitis

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13.1 Introduction

Despite major advances in the management of inflammatory bowel diseases (IBD) a considerable proportion of patients remain refractory to conventional and currently licenced biologic therapies. This chapter summarises the immunological pathways that drive intestinal inflammation in Crohn's disease (CD) and ulcerative colitis (UC) and then reviews emerging drugs targeting different components of these pathways. These include biological agents against integrins and cytokines, small molecules; anti-sense oligonucleotides and cell based therapies.

In each section first the immunological pathway that is targeted is briefly described. Then the drugs targeting this pathway are summarised, explaining their mechanisms of action, mode of administration, likely indication, efficacy and safety using the latest available trial data. Where possible practical information about drug preparation and administration is included.

A. Sturm, L. White (eds.), *Inflammatory Bowel Disease Nursing Manual*,
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The aim of this chapter is to provide those looking after IBD patients with

- A succinct overview of the immunology of IBD
- A summary of emerging treatments in IBD
- An understanding of the differences between various new treatments
- Knowledge that allows individualised treatment plans to be created and may help patients make informed decisions about their care.

13.2 Immunology of IBD

The mucosal immune system interacts with the diverse range of antigens within the intestinal tract which include food antigens, the commensal enteric flora and potential pathogens. It is designed to promote tolerance to food antigens and the commensal enteric flora whilst being able to mount a response to clear pathogens. The fundamental mechanism underpinning IBD is a dysregulated immune response to commensal microbiota in a genetically susceptible host. This leads to chronic intestinal inflammation. Important steps in the pathophysiological cascade of IBD are:

- Interaction between the mucosal immune system and microbiota whose composition is altered in IBD (a dysbiosis)
- Aggravated, pathological mucosal immune response
- Migration of white blood cells from bloodstream into the gut mucosa
- Production of excess inflammatory cytokines by immune cells
- Cytokine inflammatory pathways causing mucosal damage.
- Failure to control inflammation with normal homeostatic processes

Advances in the understanding of the roles of each of these components have resulted in the development of multiple new agents for the treatment of Crohn's disease and ulcerative colitis (Danese 2012), as illustrated in Fig. 13.1. Emerging therapies that target the different steps and components of this cascade will be discussed in turn and are summarised in Table 13.1.

13.3 Microbiota

Chronic mucosal inflammation in IBD is the result of abnormal immune reactivity towards microbiota that are normally found in the gut. In IBD there is a dysbiosis, an altered composition and function of gut microbiota as well as a reduction in the diversity of species present. This contributes to the immune response in IBD (Swidsinski et al. 2002).

13.3.1 Faecal Microbiota Transplantation

An innovative treatment targeting microbiota is faecal microbiota transplantation (FMT). Using stool from a healthy donor, the aim of FMT is to restore gut bacteria to normal composition and diversity. This was recently shown to be beneficial in the treatment of active ulcerative colitis (Paramsothy et al. 2017). Possible routes of delivery include retention enemas and administration per colonoscope but the optimum treatment regimen and mode of administration of FMT remain unknown.

A comprehensive discussion of the role of microbiota in IBD and treatments targeting microbiota, including antibiotics and FMT, can be found in Chap. 15.

13.4 Leukocyte Trafficking

IBD is characterized by infiltration of leukocytes (white blood cells) into the intestinal mucosa. Circulating leukocytes form a set of interactions with intestinal vascular endothelial cells to allow

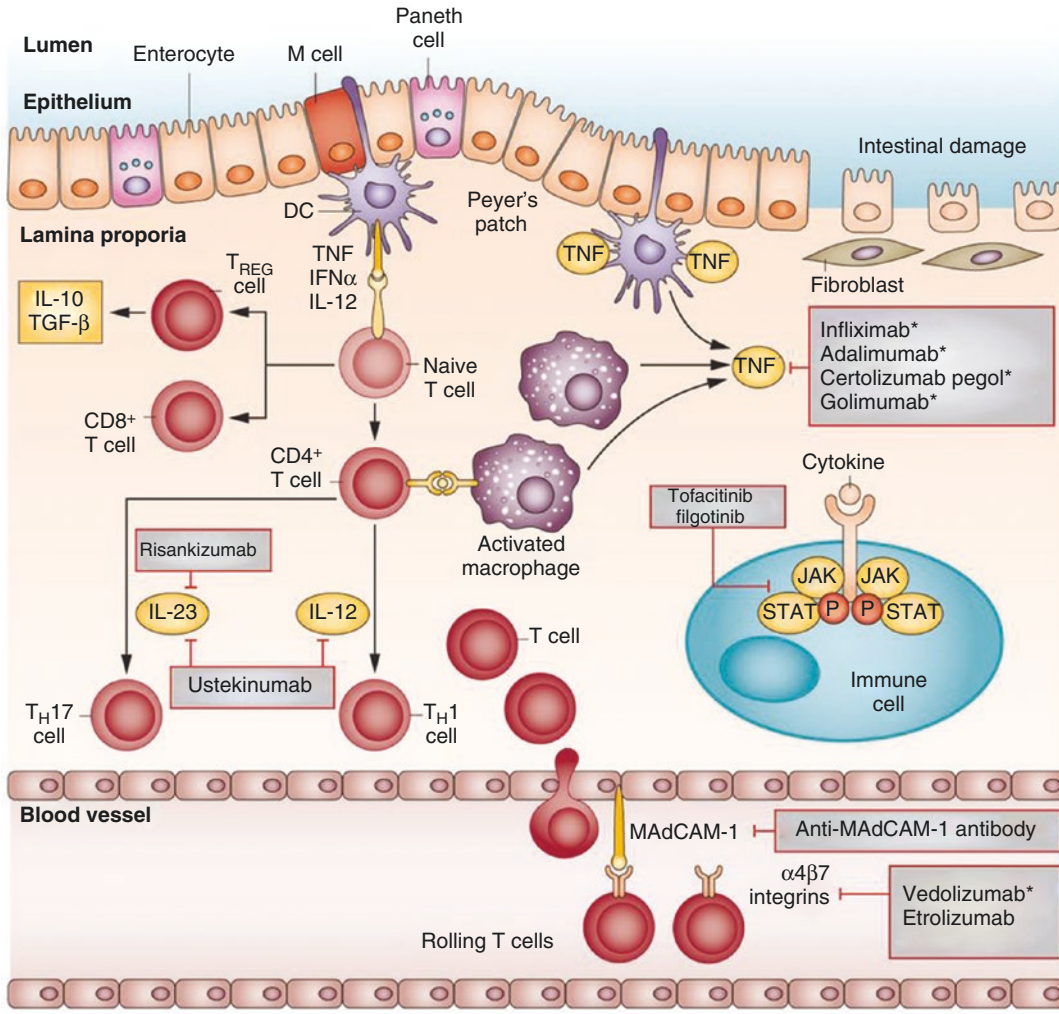

Fig. 13.1 Immunology of IBD—brief overview of the immunological pathways that drive intestinal inflammation in IBD and emerging therapies targeting different components of these pathways

adherence and migration of the leukocyte from blood vessels, across the endothelium, into the mucosal tissue. Pivotal molecules for these interactions are

- Integrin receptor molecules on circulating leukocytes and
- Cellular adhesion molecules on intestinal endothelial cells

Several new treatments target these molecules, thereby preventing leukocytes trafficking into the mucosa.

13.4.1 Integrins

- Molecules expressed on the surface of circulating leukocytes
- Composed of one α and one β subunit. Several forms of α and β subunits exist.
- The combination of subunits determines the target destination of the leukocyte.
- Integrins containing the β7 subunit are gut-specific and interact with the MADCAM adhesion molecule expressed on the enteric vascular endothelium (Ley et al. 2016).

Table 13.1 Overview of emerging drugs

Drug	Target	MOA	Class	Administration	Patients
Vedolizumab	Leukocyte migration	Binds α4β7 integrins	Monoclonal antibody	IV infusion	Approved for use in UC and CD
Etrolizumab	Leukocyte migration	Binds β7 integrins	Monoclonal antibody	SC injection	Trials show benefit in UC Trials in CD ongoing
Alicaforsen	Leukocyte migration	Binds ICAM-1 mRNA	Antisense oligonucleotide	Rectal retention enema	Trials show benefit in limited UC and chronic refractory pouchitis. No benefit in CD when given IV
Ozanimod	Lymphocyte egress from MLN	Sphongsine-1-Phosphate 1 and 5 agonist	Small molecule	Orally	Trials show benefit in UC Trials in CD ongoing
Ustekinumab	T-helper cell responses	Binds shared p40 subunit of IL-12 and IL-23	Monoclonal antibody	IV induction, SC maintenance	Approved for CD Trial in UC ongoing
Risankizumab	T-helper cell responses	Binds p-19 subunit of IL-23	Monoclonal antibody	IV induction SC maintenance	Trials show benefit in CD No trials in UC performed yet
Tofacitinib	JAK/STAT signalling	Inhibits JAK1, JAK2 and JAK3	Small molecule	Orally	Trials show benefit in UC Trials do not show benefit in CD
Filgotinib	JAK/STAT signalling	Inhibits JAK1	Small molecule	Orally	Trials show benefit in CD Trials in UC ongoing
Mongersen	SMAD7/ TGF-β pathway	Binds SMAD7 mRNA	Antisense oligonucleotide	Orally	Trials show benefit in ileocolonic CD. Trials in UC ongoing Trials in CD ongoing

See body text for dosing and a comprehensive description. *CD* Crohn's disease, *IL* interleukin, *IV* intravenous, *MLN* mesenteric lymph nodes, *MOA* mechanism of action, *SC* subcutaneous, *UC* ulcerative colitis

13.4.2 Therapies that Target Integrins

13.4.2.1 Vedolizumab

- Fully humanized monoclonal antibody against α4β7 integrins (Feagan et al. 2013; Sandborn et al. 2013).
- Binds α4β7 integrins thereby preventing leukocyte migration from bloodstream to the gut.
- Approved for clinical use in Europe (EMA, 2014) and USA (FDA, 2014)
- Evidence of benefit patients with moderately to severely active UC and CD.

Administration

- Given per intravenous infusion.
- Induction regimen of 300 mg on week 0, 2 and 6. Then maintenance infusion 8 weekly in patients who respond.
- Dose escalation in patients with partial response is permitted
- Reconstitute vedolizumab powder with 4.8 mL of sterile water for injection, using a syringe with a 21–25 gauge needle. Add the 5 mL (300 mg) of reconstituted vedolizumab to 250 mL of sterile 0.9% NaCl solution. Gently mix the infusion bag. Administer the infusion solution over 30 min.

Efficacy: Results from the Phase III GEMINI Studies

- Induction in CD: At week 6—Clinical remission in 14.5% (6.8% placebo) and clinical response in 31.4% (24.7% placebo).
- Induction in UC: At week 6—Clinical response in 47.1% (25.5% placebo).

- Maintenance in CD: At week 52—Clinical remission in 39% (21.6% placebo) of patients who responded to induction
- Maintenance in UC: At week 52—Clinical remission in 41.8% (15.9% placebo) of patients who responded to induction

Safety
- Common (>1 in 10) side effects are nasopharyngitis, headache and arthralgia.
- Infusion reactions in <5% of cases.
- No clinically important safety signals for adverse event, serious adverse events or malignancy have been identified. Considered a safe drug as mechanism of action is restricted to the gut.
- Not to be used in people with active serious enteric infections. Also should not be used in patients with active systemic infections such as tuberculosis, sepsis, listeriosis and opportunistic infections or in progressive multifocal leukoencephalopathy.

Dose Escalation and Therapeutic Drug Monitoring
- In UC escalation to 4 weekly
- In CD one extra dose at 10 week can be administered
- There is currently no commercially available drug level or antibody assay

13.4.2.2 Etrolizumab
- Fully humanized monoclonal antibody against β7 integrins (Vermeire et al. 2014)
- Binds β7 subunit of αεβ7 integrin (expressed on mucosal intraepithelial T-lymphocytes, binds E-cadherin on epithelial cells) and α4β7 integrin (expressed on leucocytes, binds MAdCAM-1 on endothelial cells) thereby preventing migration of leukocytes into bowel mucosa.
- Not approved for clinical use. Trial so far indicate possible use in moderately to severely active UC patients who do not respond to conventional therapy
- Phase II clinical trial completed. Phase III trials will be completed in December 2018

Administration
- Given per subcutaneous injection.
- Dosing in Phase II study: Dosing A: 100 mg at week 0, 4 and 8. Dosing B: Loading dose of 450 mg at week 0 then 300 mg at week 2, 4 and 8

Efficacy: Results from Phase II Trial
- Induction in UC: At week 10—Dosing A: Clinical remission 21% versus 0% placebo. Dosing B: Clinical remission 10% versus 0% placebo

Safety
- Common side effects are nasopharyngitis, headache and arthralgia
- Safety profile not expected to be different from vedolizumab

13.4.3 Cellular Adhesion Molecules

- Expressed on the surface of vascular endothelial cells
- Ligands to integrins
- Known to play a role in IBD are ICAM1, MAdCAM and VCAM1 (Ghosh and Panaccione 2010)
- Intracellular Adhesion Molecule-1 (ICAM1) is expressed at low levels on the surface of intestinal endothelial cells and is induced upon exposure to pro-inflammatory cytokines during inflammation. It binds leucocyte integrins during inflammation and in immune responses thereby facilitating leukocyte migration into mucosa (Ala et al. 2003).

Box 13.1 Antisense Therapy
Antisense therapy is a form of treatment targeting gene products. It uses a synthesized strand of nucleic acid (DNA or RNA) that will bind to the messenger RNA (mRNA) produced by that gene and inactivate it, effectively turning that gene "off". This synthesized nucleic acid is termed an "anti-sense" oligonucleotide because its base sequence is complementary to the gene's mRNA, which is called the "sense" sequence (Chirila et al. 2002).

13.4.4 Targeting Cellular Adhesion Molecules

13.4.4.1 Alicaforsen

- Antisense oligonucleotide to ICAM-1.
- Oligonucleotide strand consisting of the antisense sequence to ICAM-1 mRNA. This binds and neutralises ICAM-1 mRNA preventing ICAM-1 production and migration of leukocytes into bowel mucosa.
- Granted orphan drug status in the treatment of chronic refractory pouchitis by the FDA in 2008 and EMA in 2009.
- Trials also indicate possible use in limited UC. Not effective as intravenous drug in Crohn's disease (Yacyshyn et al. 2002, 2007).
- Phase II trials in UC completed, phase III trial in pouchitis ongoing.

Administration

- Given per rectal retention enema.
- Several doses trialled with best results in trials from 240 mg once daily for 4–6 weeks.

Efficacy: Results from Phase II Trials in UC

- Data from four phase II trials in UC show conflicting results with two positive and two negative studies (van Deventer et al. 2004, 2006; Miner et al. 2006a, b).
- Meta-analysis including 200 patients from these four phase II studies showed that alicaforsen 240 mg enema, once daily for 6 weeks is better than placebo for distal ulcerative colitis up to 40 cm, especially in patients with more severe disease. In the short term it is as good as rectal mesalazine, in the long-term it appears to be superior to mesalazine (Feagan et al. 2016).

Efficacy: Results from Early Trials in Pouchitis

- In small open label studies, once daily enema, 240 mg, for 6 weeks, showed improvement in DAI in in chronic, unremitting pouchitis (Miner et al. 2004).
- Efficaciousness also reported in pouchitis in case series (Greuter et al. 2016).
- A phase III Study of Alicaforsen enema in antibiotic refractory pouchitis is ongoing.

Safety

- None of the placebo-controlled studies reported an increased rate of adverse events or intolerance of alicaforsen. In all studies, alicaforsen enema was safe and well tolerated (Vegter et al. 2013).

13.4.5 Sphingosine-1-Phosphate

Sphingosine 1-phosphate (S1P) is a signalling molecule that regulates multiple biological, including immunological, functions through five different receptors (S1P1 through S1P5). Cell surface–associated S1P1 receptor plays a crucial role in the trafficking of lymphocytes from lymphoid organs. Lymphocytes use S1P1 to migrate from lymphoid organs to the blood and mucosal tissues. Treatment targeting S1P has already been approved for the treatment of relapsing multiple sclerosis (Sandborn et al. 2016; Baeyens et al. 2015).

13.4.6 Targeting Sphingosine-1-Phosphate

13.4.6.1 Ozanimod

- Specific S1P1 and S1P5 agonist (Sandborn et al. 2016).
- Small molecule that binds S1P1 and S1P5 and reduces circulating lymphocytes by trapping them in mesenteric lymph nodes.
- Not approved for clinical use. Trials so far indicate possible use in patient with moderately to severely active UC.
- Phase II trials in UC completed. Open label extension and phase III trial in UC and phase II study in CD are ongoing.

Administration

- Given orally.
- 0.5 mg and 1 mg once daily for 8 weeks tested in UC phase II trial with only 1 mg dose superiority compared to placebo.

Efficacy: Results from Phase II Trial in UC

- Clinical remission at 8 weeks. Dose 1 mg. 16% remission versus 6% placebo.

Safety

- The most common adverse events overall are anaemia and headache.
- No differences in this trial between ozanimod and placebo groups.
- This study was not large enough to comment on safety profile. For fingolimod, a less selective S1P modulators, that targets S1P1, 3, 4 and 5, disseminated varicella zoster and herpes simplex infections have been reported, as well as arrhythmias and increased liver enzymes (Francis et al. 2014).

13.4.7 Other Treatments Targeting Leukocyte Migration

Chemokine receptor 9 (CCR9) binds the lymphocyte chemoattractant CCL25 promoting adherence and migration of T lymphocytes. An orally bio-available small molecule that selectively blocks the CCR9 receptor (Vercinon) was tested in Crohn's disease but after one phase III trial failed to meet its endpoints other phase III trials were terminated early and the drug is longer being developed for this indication.

Box 13.2 Small Molecules

A small molecule is a low molecular weight organic compound that regulates a biological process. Most drugs are small molecules. Due to their small size they rapidly diffuse across cell membranes so that they can reach intracellular sites of action (Veber et al. 2002). Major advantages of small molecules are that they can be administered orally and do not cause immunogenicity in the form of anti-drug antibody formation or hypersensitivity.

13.5 Cytokines

Cytokines are a broad category of small proteins that are important in responses to infection, immune responses and inflammation. In IBD there is an increase in intestinal tissues of activated immune cells that secrete inflammatory cytokines in the mucosa, such as tumour necrosis factor-α (TNF-α), interferon γ (IFN-γ), interleukin 1β (IL-1β), IL-6, and IL-23, as well as T-helper (Th)17 cell pathway cytokines. This cytokine secretion leads to recruitment of more immune cells that produce further inflammatory cytokines thus contributing to the uncontrolled imbalance between pro-inflammatory and anti-inflammatory response that leads to the intestinal damage observed in patients with IBD. An example of a drug targeting cytokines is Infliximab, a monoclonal antibody against TNF-α, which has been used and has transformed the treatment of IBD since 1999. Various new treatments targeting cytokines to dampen inflammation are emerging (Abraham et al. 2017).

13.5.1 Interleukin 12 (IL-12) and Interleukin 23 (IL-23)

Levels of interleukin 23 (IL-23) are increased in inflamed intestinal tissues of patients with IBD. IL-12 and IL-23 are produced by inflammatory cells and influence the development of T-helper cell responses. IL-12 and IL-23 share the IL-12p40 subunit. Several therapeutic agents targeting IL-12 and/or IL-23 are being tested for use in the treatment of IBD (Abraham et al. 2017; Teng et al. 2015).

Box 13.3 Phases of Clinical Trials

- Pre-clinical—drug discovery or design and animal testing
- Phase 0—very small studies to test pharmacokinetics of drug
- Phase I—testing drug in small group of healthy volunteers for the first time to evaluate its safety, determine a safe dosage range and identify side effects.
- Phase II—testing drug on patients to see if it is effective, explore different doses and to further evaluate safety.

- Phase III—testing drug on large number of patients to confirm its effectiveness, monitor side effects, compare it to commonly used treatments, and collect information that will allow the drug or treatment to be used safely.
- Phase IV—post-marketing surveillance. Watching the drug and its effects in real life to gather information on the drug's effect in various populations and any side effects associated with long-term use.

Individual trials may cover more than one phase such as combined phase I/II or phase II/III trials. Therefore, trials or often referred to as early phase studies and late phase studies

13.5.2 Targeting IL-12 and IL-23

13.5.2.1 Ustekinumab

- Monoclonal antibody targeting the shared p40 subunit of IL-12 and IL-23 (Feagan et al. 2016).
- Binds IL-12 and IL-13 thereby preventing T-helper cell mediated inflammation.
- Approved for use in Crohn's disease in Europe (EMA, 2016) and USA (FDA, 2016). For patients with moderately to severely active CD, when conventional therapy is ineffective, no longer effective, or cannot be tolerated by the patient.
- The UNIFI phase III trial is in progress, testing the use of ustekinumab in UC.
- Already approved for use in psoriasis since 2008 and psoriatic arthritis since 2013.

Administration in Crohn's disease

- One induction dose is given per intravenous infusion. In trials doses of 130 mg and approximate 6 mg/kg were tested (for patients ≤55 kg: 260 mg, for patients >55 kg to ≤85 kg: 390 mg and for patients >85 kg: 520 mg).
- For induction infusion: Calculate ustekinumab volume needed (26 mL per 130 mg). Withdraw and discard this volume from 250 mL bag of 0.9% NaCl solution. Withdraw 2, 3 or 4 times 130 mg/26 mL ustekinumab as needed and add to 0.9% NaCl solution. Gently mix the infusion bag. Use an infusion set with filter (pore size 0.2 μm). Administer the infusion solution over 60 min.
- Followed by maintenance dosing of 90 mg subcutaneous after 8 weeks, then every 12 weeks or every 8 weeks depending on response at week 16.

Efficacy: Results from the Phase III UNITI and IM-UNITI Studies

- UNITI-1. Induction study in CD patient with primary or secondary non-responsiveness or intolerance to TNFalpha agonists. Clinical response at week 6. Dose 130 mg: 34.3% and dose ~6 mg/kg: 33.7% (21.5% placebo).
- UNITI-2. Induction study in CD patient who failed conventional treatment. Clinical response at week 6. Dose 130 mg: 51.7% and dose ~6 mg/kg 55.5% (21.5% placebo).
- IM-UNITI. Maintenance study in patients who responded to induction. Clinical remission at week 44. Dose 90 mg 8 weekly: 53.1%, dose 90 mg 12 weekly: 48.8% (35.9% placebo).
  - In a sub-study ustekinumab also induced significantly greater reduction in endoscopic disease activity versus placebo in both the induction and maintenance phases of these studies (William et al. 2017).

Safety

- Most common (>5%) side effects are headache and nasopharyngitis. Also injection site erythema, vulvovaginal candidiasis, bronchitis, pruritus, urinary tract infection and sinusitis.
- Not to be used in people with significant active infection.
- Favourable safety profile from studies following long-term use in psoriasis with no increased rates of adverse events, including serious adverse events and infections.
- No cases of anaphylaxis or serum sickness-like reactions reported.
- Neither the dose of drug nor the cumulative exposure impacts long-term safety outcomes (Chiu et al. 2013).

Dose Escalation and Therapeutic Drug Monitoring

- No algorithms for dose escalation in CD yet available but increase from 12 weekly to 8 weekly maintenance injections is within the current licence.
- There is currently no commercially available drug level or antibody assay.

13.5.2.2 Risankizumab

- Monoclonal antibody targeting the p-19 subunit of IL-23.
- Not approved for clinical use.
- Trials so far indicate possible use in patients with moderately to severely active Crohn's disease.
- Phase II induction phase completed and maintenance phase ongoing.

Administration

- Induction regimen intravenously. Doses of 200 mg and 600 mg tested at week 0, 4 and 8.
- Followed by maintenance dosing per subcutaneous injection.

Efficacy: Results from Phase II Trial

- After induction. At week 12. Clinical remission in 36.6% of patients given 600 mg risankizumab and 24.4% of patients given 200 mg risankizumab (15% placebo) (Feagan et al. 2017).
- 26 week maintenance phase is ongoing.

Safety

In the induction study, adverse events were similar between risankizumab and placebo with no dose-related increase in adverse events.

13.5.2.3 Other Cytokines

Monoclonal antibodies targeting several other inflammatory cytokines are being developed and trialled:

- Several monoclonal antibodies targeting IL-13 are in clinical trial. IL-13 is a cytokine of the Th2 cytokine family that activates the JAK/STAT pathway.
- Tocilizumab, a monoclonal antibody targeting IL-6 showed efficacy in Crohn's disease in a phase 2 trial but a troubling number of adverse events were reported, including 1 death, 2 perforations, and 4 gastrointestinal abscesses in the group given the anti-IL6 antibody (Danese et al. 2016).

13.5.3 JAK/STAT Pathway

When cytokines bind to their cell receptors, Janus kinases (JAK) associate with the cytokine receptor and activate Signal Transducer and Activator of Transcription (STAT). This JAK/STAT pathway transmits information from the extracellular cytokines to the cell nucleus resulting in DNA transcription and expression of genes. By blocking the JAK/STAT pathway the aim is to prevent the production of further inflammatory mediators. This approach targets pathways used by multiple cytokines at once. The JAK family of proteins are receptor tyrosine kinases comprising four members: JAK1, JAK2, JAK3, and TYK2 (Abraham et al. 2017; Dudakov et al. 2015; de Vries et al. 2017).

13.5.4 Targeting the JAK/STAT Pathway

13.5.4.1 Tofacitinib

- Oral JAK inhibitor that inhibits JAK1, JAK2 and JAK3 with varying degree of specificity (Sandborn et al. 2012, 2014).
- Blocks signalling of cytokines including interleukins 2, 4, 7, 9, 15, and 21. These cytokines are integral to lymphocyte activation, function, and proliferation.
- Not yet approved for clinical use. Trials so far indicate possible use in patients with moderately to severely active UC.
- Phase III trials in UC have been completed.
- Trials of tofacitinib in CD have produced disappointing results and the drug is no longer being developed for this indication (Sandborn et al. 2014).

Administration

- Given orally.
- In phase III induction trials 10 mg was given twice daily for 8 weeks (Sandborn 2016). In phase III maintenance study 5 mg and 10 mg were given twice daily for 52 weeks (Sandborn and Panés 2017).

Efficacy: Results from Phase III Octave Trials in UC

- At week 8. Remission 18.5 and 16.6% (8.2 and 3.6% placebo) in two identical induction trials.
- At week 52. Remission dose 5 mg BD 34.3%. Dose 10 mg BD 40.6% (placebo 11.1%) of patients with clinical response after induction.

Safety

- A dose-dependent increase in both low-density and high-density lipoprotein cholesterol, creatine kinase and herpes zoster infections was observed.
- Tofacitinib targets all JAK family members. This has raised concerns regarding side effects and safety profile, including malignancy risk.

13.5.4.2 Filgotinib

- Oral JAK inhibitor that inhibits JAK1 selectively (Vermeire et al. 2017).
- Not approved for clinical use.
- Trials so far indicate possible use in moderately to severely active CD and further trials in CD and UC are ongoing.

Administration

- Given orally.
- 200 mg once daily for 10 weeks in the phase II trial.

Efficacy: Results from the Phase II FITZROY Study in CD

- At week 10. Clinical remission in 47% (23% placebo).

Safety

- Serious treatment-emergent adverse effects reported in 9% of patients treated with filgotinib and 4% of patients treated with placebo.
- Safety profile possibly superior to tofacitinib due to selectivity.

13.5.5 Other Small Molecules

- Laquinimod is a small molecule immunomodulators. A phase II study using laquinimod in moderately to-severely active CD suggests treatment benefit. In this study it was safe and well tolerated (D'Haens et al. 2015) and phase IIb/III trials are awaited.

13.5.6 SMAD7/TGF-β Pathway

In this cytokine pathway the protein SMAD7 binds and inactivates the cytokine TGF-β. TGF-β inhibits inflammatory signalling. Increased levels of SMAD7 are observed in patients with UC and Crohn's disease (Monteleone et al. 2001; Boirivant et al. 2006).

13.5.7 Targeting the SMAD7/TGF-β Pathway

13.5.7.1 Mongersen

- SMAD7 antisense oligonucleotide (Monteleone et al. 2015).
- Antisense sequence that binds to SMAD7 mRNA to reduce levels of SMAD7 protein. Reducing SMAD7 leads to increased anti-inflammatory signalling by TGF-β.
- Not approved for clinical use. Results from phase II clinical trials indicate possible benefit in moderately to severely active ileal or ileocolonic Crohn's disease.
- Further studies in both CD and UC are ongoing.

Administration

- Given orally.
- pH-dependent release tablet, allows the drug to become active in terminal ileum and right colon.
- In phase II trial once daily doses of 40 mg and 160 mg for 2 weeks were tested.

Efficacy: Results from Phase II Trial in CD

- On day 15. Clinical remission. Dose 40 mg: 55%. Dose 160 mg: 65% (10% placebo)

Safety

- Most adverse events were related to complications and symptoms of Crohn's disease.
- There is potential concern about this drug as TGFβ is also an activator of cells that contribute

to stricture formation (Li and Kuemmerle 2014) and increasing TGFβ signalling carries a theoretical increased colon cancer risk (Okamoto and Watanabe 2016).

13.6 Cell Based Therapies

Cell-based therapies are treatments that aim to regenerate and restore intestinal mucosal functions with use of cells such as stem cells. Trials of these highly experimental treatments have so far have focused on a minority of patients with very refractory, chronic active disease (Okamoto and Watanabe 2016).

13.6.1 Haematopoietic Stem Cell Transplantation (HSCT)

Stem cells are undifferentiated immune cells that have the ability to differentiate into specialized mature cells. Haematopoietic stem cells are found in bone marrow and make all of the body's blood cells, including the immune cells that overreact in IBD. Bone Marrow Transplantation for the treatment of leukaemia is an example of treatment using haematopoietic stem cells. Case reports of patients with Crohn's disease who underwent bone marrow transplantation for haematological malignancies and were also relieved of their IBD symptoms led to trials of transplantation of haematopoietic stem cells as treatment of IBD. The objective of HSCT is to shut down the immune response and allow the transplanted stem cells to develop into self-tolerant lymphocytes (Hawkey and Hommes 2017).

13.6.1.1 The Autologous Stem Cell Transplantation for Crohn's Disease (ASTIC) Trial

- Using the patient's own stem cells.
- Failed a very stringent primary endpoint in a group of patients with severe refractory disease (clinical remission off all medication with no evidence of active disease on endoscopy or small bowel imaging) (Hawkey et al. 2015).
- Subsequent analysis using endpoints that are more traditional in trials of Crohn's disease (steroid free clinical remission or mucosal healing) showed patients in this trial did benefit (Lindsay et al. 2017).
- A follow-up trial using a different protocol is in progress.

Autologous hematopoietic stem cell transplantation will likely remain a last resort rescue therapy in specialized centres for patients for whom most available drugs have failed.

13.6.2 Mesenchymal Stem Cells

Mesenchymal stem cells (MSCs) are adult stem cells with immunomodulatory properties that can differentiate into a variety of cell types. They can be obtained from bone marrow, fat tissue or placenta. When transplanted they do not alarm the host immune system and donor to recipient matching is not required. MSCs are thought to facilitate tissue repair and maintain immune homeostasis which is of particular interest in fistulising Crohn's disease (Otero-Vinas and Falanga 2016).

13.6.3 Using Mesenchymal Stem Cells

13.6.3.1 Cx601 Cells

- Fat-derived, expanded, mesenchymal stem cells (Panes et al. 2016).
- Not approved for clinical use.
- Data from phase III study show benefit in complex perianal fistulas in Crohn's disease and may get approval for clinical use in 2017 (EMA) in treatment-refractory complex perianal fistulas.

Administration for Complex Refractory Perianal Disease

- Administered by local injection by surgeon after drainage of sepsis and curettage of the fistula track.
- Single intra-lesional injection of 120 million Cx601 cells.

Efficacy

- 50% of treated patients versus 34% in placebo group were in combined remission at week 24 (clinical assessment of closure of all treated external openings that were draining at baseline, and absence of collections >2 cm of the treated perianal fistulas confirmed by MRI).

Safety

- Most common side effects were anal abscess and proctalgia.

Trials using MSCs for luminal IBD have thus far not been effective (Duijvestein et al. 2010).

13.6.4 Regulatory Immune Cells

Not all immune cells cause inflammation. A subset of immune cells protect against inflammation and certain regulatory T cells (Treg cells) can block other inflammation-producing T cells.

13.6.4.1 The Crohn's and Treg Cells Study (CATS1) Tested Treg Cells in Crohn's Disease

- Evaluated the safety and efficacy of antigen-specific Treg cells.
- For treatment of patients with refractory CD.
- Phase I/IIa study.
- Treg cells were made from patients' peripheral blood, exposed to ovalbumin (the main protein found in egg white).
- The Treg cells were then administrated intravenously back into the patient and activated by letting the patients eat egg white (merengue).
- This treatment was well tolerated and had dose-related efficacy (Desreumaux et al. 2012).
- Results from a follow-up trial are expected in 2018.

13.7 Summary

Recent increased insight into the pathogenesis of IBD has led to several new therapeutic strategies.

The recruitment of inflammatory leukocytes to the gut plays an important role in IBD. Understanding the molecular basis that directs migration of leukocytes from blood stream to the gut has led to development of treatments targeting integrins and cellular adhesion molecules. The best known example is vedolizumab, which is already widely used and several other therapies targeting leukocyte trafficking are in the pipeline. An important advantage of vedolizumab and other treatments targeting β7 integrins is that due to their gut specificity they are likely to have a good safety profile.

Of other new biologics Ustekinumab will be next to become available in clinical practice. This monoclonal antibody against IL-12/23 has recently (2016) been approved for the use in Crohn's disease following favourable phase III trial data. It has a good safety profile from long-term use in psoriasis.

Not only are there new targets for treatment in IBD but also medication with novel modes of action are being developed. Antisense therapies target expression of inflammatory mediators at mRNA levels and show promising results when targeting ICAM1 in ulcerative colitis and chronic pouchitis (alicaforsen).

Small molecules targeting cytokines pathways by blocking the JAK/STAT pathway or lymphocyte egress by targeting Sphingosine-1-phospate are orally administered and offer an attractive alternative mode of drug administration. However, their lack of specificity raises some concern regarding their side effect profile. Small molecules with more selective targets are being developed, they are expected to have a better safety profile.

Finally, despite all advances in the treatment of IBD, there will likely remain a subset of patients that is refractory to all treatment. Cell based therapies using stem cells or regulatory T cells could be a final resort for these patients.

Together, these emerging treatment provide an alternative to the currently available IBD treatments.

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Microbiota, Prebiotics, Antibiotics and Fecal Microbiota Transfer

14

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Abstract

Microbiota is the collectivity of microorganisms settling in the gut of humans and animals. The symbiotic interactions between microbiota and his hosts are of essential physiological and pathophysiological importance. Compositional and metabolic changes in the gastrointestinal microbiota ("dysbiosis") are associated with the development and maintenance of several inflammatory disorders including chronic inflammatory bowel disease (IBD).

IBD-associated dysbiosis can be treated by the administration of antibiotics and of prebiotics/probiotics and by fecal microbiota transfer (FMT). It was found that treatment with *antibiotics* can harm beneficial microorganisms leading to a changed composition of microbiota and therefore is no longer the first choice. *Prebiotics* are food ingredients that induce growth or activity of beneficial microorganisms. *Probiotics* include nonpathogenic living microorganisms that overpopulate the gut. They have positive impacts on the balance of microbes and improve the absorption of micronutrients. Therefore they may have positive impacts on the course of IBD.

Recently, the effectiveness and safety of a novel therapeutic application such as *FMT* have been demonstrated. It is about a transplantation of fecal microorganisms from a healthy donor in the form of stool suspensions applicated by endoscopy or gastronasal tubes into the patient's small or large intestine. Although further research is still needed to understand the relationship between dysbiosis of gut microbiota and extra- and intraintestinal inflammation, FMT is a promising approach to treat IBD.

14.1 Introduction

All humans live in a symbiotic relationship with a multiplicity of microorganisms that are summarized under the term "microbiota." The extensive interactions between microbiota and his host are of essential physiological and pathophysiological importance. Compositional and metabolic changes in the gastrointestinal microbiota ("dysbiosis") are associated with the development and maintenance of several inflammatory disorders including chronic inflammatory bowel disease (IBD) such as Crohn's disease (CD), ulcerative colitis (UC), or

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pouchitis. Experimental models and clinical studies suggest that gastrointestinal microbiota drives immune activation and perpetuate IBD. However chronic inflammation itself shapes the gut microbiota and can contribute to dysbiosis. Nevertheless, several controlled clinical studies demonstrated that modification of dysbiosis could improve diseases. Recently, effectiveness and safety of novel therapeutic application such as fecal microbiota transfer (FMT) as a radical modification of patients' microbiota in treatment of IBD, especially UC, have been demonstrated. The purpose of this book chapter is to discuss the potential role of microbiota-focused interventions in the treatment of human IBD.

14.2 Gastrointestinal (GI) Microbiota

The human body is colonized by a vast number of microorganisms representing the so-called microbiota. These microorganisms colonize the surface of the human body exposed to the external environment, including the skin, oral cavity, and respiratory, urogenital, and GI tract. Of these, the latter is the most densely colonized organ. It has been known for many decades that the GI microbiota is composed of trillions of bacteria, viruses, bacteriophages, fungi, and parasites. This biomass is about 1.5 kg of the body weight of an adult. The number of microorganisms in the GI microbiota with an estimated 40 trillion microorganisms corresponds approximately to the total number of all human cells in the body (Sender et al. 2016). When we look at the genes of the microbiota, the GI microbiome, there is a numerical dominance with a ratio between man and microbiome of approximately 1:150 (Qin et al. 2010).

The number and composition of microbiota vary in different regions of the GI tract with a relatively low number as well as few species residing in the stomach and upper small intestine. However, there is a diverse and dense population of microbiota in the distal part of the small intestine and colorectum ranging up to 10^{11}/g to 10^{13}/g of stool. In addition to numerical differences in the GI tract, composition of luminal and mucosa-adherent microbiota differs (Zoetendal et al. 2002). Therefore it is important to investigate and compare the microbiota of both of these niches.

The extensive interactions between host and microbiota are of essential importance for humans. The GI microbiota plays a role in digestive processes much more than an "auxiliary function": it modulates central physiological reactions. Disorders of the microbiota and its metabolite (the totality of the metabolic properties of the microbiota) are therefore also linked to a variety of GI and extraintestinal diseases. The changes underlying the diseases are well understood, but we are still far away from a sufficient clarification. Further, the composition of the intestinal microbiota is strongly influenced by both environmental (nutrition, pharmaceuticals) and genetic factors. Against this background, there are numerous attempts to modify the GI microbiota, to "normalize" it or "heal" it.

14.3 Pathogenesis of IBD and Modulation of GI Microbiota

IBD are chronic inflammatory disorders of an unknown etiology; however, an increased understanding of the molecular mechanisms in IBD during the last two decades causes changes of our pathogenetic concept of IBD. Nowadays we understand the pathogenesis as a complex interplay of genetic, environmental, and immunological factors. These diseases are results of an overwhelming immune response of the acquired (adaptive) immune system in deficiencies in the GI barrier with disorders at the level of the congenital (innate) immune system. The entrance of microbiota activation with the activation of the mucosa-associated immune system resulting from the barrier plays a central role. In this context microbiota is subject to a shift to genes in chronic inflammatory diseases that:

- Play a role in inflammatory pathways
- Cause increased oxidative stress
- Reduce the production of short-chain fatty acids

Thus the microbiota and its changes with an IBD-typical dysbiosis is a new therapeutic goal.

14.4 GI Microbiota in IBD

Once it was thought that the infectious pathogens cause IBD, nowadays it is known that the continuous stimulation of the intestinal immune system by microbiota or microbiota-derived antigens causes chronic intestinal inflammation. Several studies from various disciplines have shown that abnormal host-microbial interactions play a role in the pathogenesis of IBD including pouchitis and their complications (for review see Sartor 2008). Dysbiosis with a breakdown of physiological host-microbial interactions is probably the defining event in the development of IBD. It is well accepted that IBD is characterized by a shift in the composition of the GI microbiota with a loss of diversity. Patients with CD, UC, and pouchitis show a reduced variety of microbiota compared to healthy volunteers (Gong et al. 2016; Nagalingam and Lynch 2012). The IBD metagenome contains 25% fewer genes than the healthy intestine with metaproteomic studies showing a correlative decrease in proteins and functional pathways (Hold 2014). However, no uniform microbial signature has been detected for all patients with IBD so far. Several clinical studies described variations in microbiota composition, which were summarized in Table 14.1.

14.5 Modulation of GI Microbiota in IBD

In principle, the IBD-associated dysbiosis could be treated by:

1. The administration of antibiotics
2. The administration of prebiotics or probiotics
3. A fecal microbiota transfer (see also Fig. 14.1)

However, with none of these possibilities, a targeted intervention in the composition of the individual microbiome of the affected patients is possible so far. It is also problematic that the exact "defect" to be treated is not known. It remains unclear how a "good microbiome" is composed for the IBD patient and whether this is to be achieved in long term in view of the above-described genetic changes and their consequences on microbiota composition. Clinical studies are not conclusively indicative of the modulation of the microbiota in patients with IBD, but a distinction has always to be made between uses for remission induction and relapse prophylaxis.

14.6 Role of Antibiotics in the Treatment of IBD: A Double-Edged Sword

The dramatic increase in our knowledge of GI microbiota and their consequences has changed our view on antibiotics. Antibiotics are, indeed, no

Table 14.1 Alterations of the microbiota during IBD

	UC	CD	Pouchitis
Lower abundance	Phylum *Firmicutes* (Chen et al. 2017)	Bacteroidales and clostridia (Gevers et al. 2014)	*Faecalibacterium* (Reshef et al. 2015)
	Akkermansia muciniphila, *Butyricicoccus pullicaecorum*, and *Clostridium colinum* (Bajer et al. 2017)		
Higher abundance		Phylum *Proteobacteria*	*Fusobacteriaceae* (Reshef et al. 2015)
		Enterobacteriaceae, *Pasteurellaceae*, Veillonellaceae, and Fusobacteriaceae (Gevers et al. 2014)	

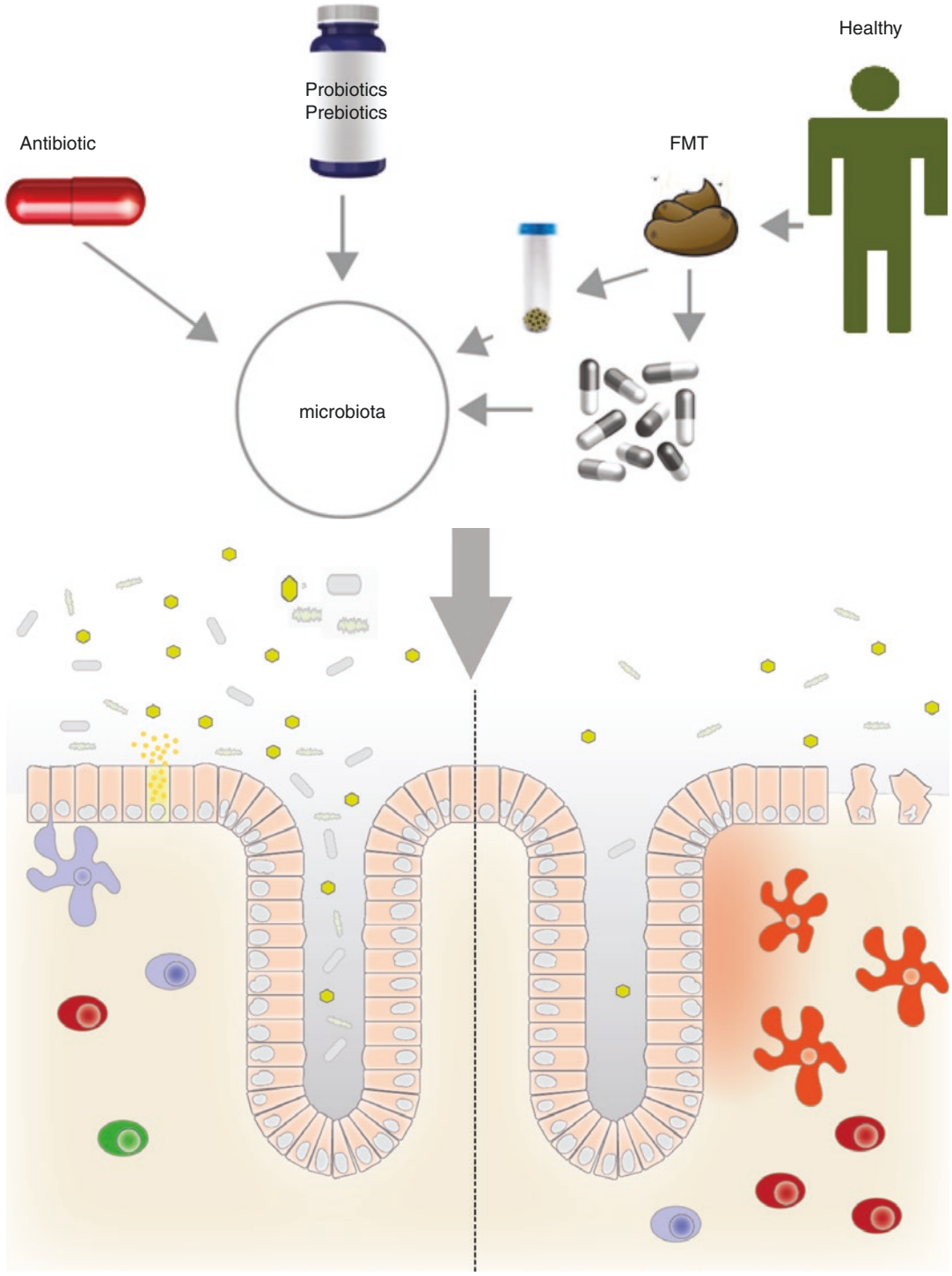

Fig. 14.1 Importance of microbiota in the pathogenesis of IBD and modulation possibilities by antibiotics, prebiotics/probiotics and FMT. The left side (physiological situation) shows a highly diverse microbiota. The mucosa-associated immune system is in balance between pro- and contra-inflammatory control circuits. Through the innate immune system, for example, the defensins maintain its barrier function. On the right side it is shown an inflammatory mucosa with barrier disorder, loss of defense, and an increase in proinflammatory responses by activated macrophages and T cells. The microbiota is much less diverse; its components lead to the activation of the immune system. In the upper part of the illustration there are shown possibilities for interventions, represented by antibiotics, prebiotics/probiotics and FMT on the microbiome

longer considered only beneficial but also potentially harmful drugs, as their uncritical application appears to play a role in the pathogenesis of several disorders associated with microbiota impairment (e.g., *Clostridium difficile* infection). At first sight, dysbiosis in the pathogenesis of IBD could provide a strong rationale for antibiotic use. However, therapeutic value of antibiotic treatment in IBD remains controversial.

By taking antibiotics, the bacterial concentration would be reduced in the intestinal lumen, and the composition of the microbiota could be changed with the potential to favor the establishment of beneficial bacteria and therefore a decrease in bacterial tissue invasion. This can affect clinical severity of the IBD. There are some clinical observations supporting a close association of a modified intestinal microbiota with the development and course of IBD. For example:

- An ideal stoma for the derivation of feces improves the clinical presentation in patients with CD (Harper et al. 1983).
- Enteric bacterial infections can lead to a deterioration of IBD (Stallmach and Carstens 2002).

Antibiotics have been used to treat complications in IBD for long time. Antibiotics were applied primarily as an adjunctive treatment in specific clinical scenarios, such as perianal and intra-abdominal abscesses, fistula, and toxic megacolon (Hartong et al. 1977; West et al. 2004; Feagins et al. 2011). In addition, certain antibiotics such as ciprofloxacin, metronidazole, rifaximin, and other with broad-spectrum antimicrobial coverage have been explored as a primary therapy. In clinical terms, treatment with these antibiotics has been shown to reduce intestinal inflammation and has been efficacious during mucosal inflammation in IBD. In a randomized, placebo-controlled, blinded study of 213 adult patients with active CD, a combination of clarithromycin, rifabutin, and clofazimine resulted in short-term improvement with higher remission rates after 16 weeks compared to placebo (66% vs. 50%; $P = 0.02$). However, this concept offered no benefit for prevention of long-term relapse (Selby et al. 2007). Two meta-analyses evaluated randomized controlled trials in which antibiotic therapy was compared with placebo for the treatment of IBD. In active CD the first one demonstrated a statistically significant effect of antibiotics (antituberculosis therapy, macrolides, fluoroquinolones, 5-nitroimidazoles, and rifaximin) compared to placebo, based on 10 randomized controlled trials (RCT) with 1160 patients (relative risk (RR) of active CD not in remission = 0.85; 95% confidence interval (CI) = 0.73–0.99, $P = 0.03$) (Khan et al. 2011). The second meta-analysis demonstrated that clinical improvement occurred in 56.1% (214/429) of patients in the antibiotic group and 37.9% (153/403) of patients in the placebo group (Wang et al. 2012). In summary, the benefit for patients with active CD after antibiotic treatment could be about 15–20%; this indicates only moderate efficacy. The therapeutic effects of antibiotics might be stronger for patients with UC: a total of nine studies included in the analysis demonstrated remission in 64.2% of the patients treated with antibiotics, compared with 47.5% of the placebo group (Wang et al. 2012) or RR of UC patients to do not enter in remission with a RR 0.64 (95% CI = 0.43–0.96).

Moreover, antibiotics can induce dysbiosis which can promote the development and maintenance of IBD. Several studies have shown that antibiotic exposure prior to the development of IBD is associated with development of IBD. Two Scandinavian retrospective cohorts of Danish or Finnish children and a large retrospective cohort study from the UK demonstrated a greater relative risk of developing IBD among children exposed to antibiotics (Hviid et al. 2011; Virta et al. 2012; Kronman et al. 2012). In a recent meta-analysis, exposure to antibiotics during childhood was shown to be associated with increased risk of CD but not UC (Ungaro et al. 2014). Moreover the need for antibiotic treatment in IBD is associated with a more severe disease pattern (Hashash et al. 2015). Together, these findings suggest that early life and repeated exposures of antibiotics may result in sustained, potentially detrimental effects on the intestinal microbiome and could contribute to the pathogenesis of IBD. However, a causal link between the antibiotic-induced dysbiosis and the development of IBD is not proven. In fact, reducing the presumably protective bacteria *Faecalibacterium prausnitzii* by exclusive

enteral nutrition was not associated with a more severe course of CD in children but led to a clinical improvement in a recent study (Gerasimidis et al. 2014).

14.7 Pre- and Probiotics in IBD

Since gut dysbiosis has a pathogenetic role in IBD, several therapies targeting the microbiota with aim of controlling the disease were performed in the last years. Prebiotics are food ingredients that induce the growth or activity of beneficial microorganisms (e.g., bacteria and fungi). Probiotics include nonpathogenic live microorganisms that overpopulate the gut with potentially beneficial microbes. They have positive impact on the balance of microbes and improve the absorption of micronutrients such as calcium and iron from the ingested food. Therefore, they may have in turn positive impact on the course of IBD.

The therapeutic effects, however, are limited and focus on the remission rate and less on the acute situation. There are three randomized controlled trials (RCT) with the mixed probiotic preparation VSL#3® (four strains of Lactobacilli (*L. paracasei*, *L. plantarum*, *L. acidophilus*, and *L. delbrueckii* subsp. *bulgaricus*), three strains of Bifidobacteria (*B. longum*, *B. infantis*, *B. breve*), one strain of *Streptococcus thermophilus*) for remission induction at CU. The pooled analysis of these three studies shows a significant advantage for achieving a remission at CU with a RR 1.69 (95% CI: 1.17–2.43) (Sood et al. 2009; Tursi et al. 2004, 2010). In contrast, two studies with *B. breve* and *bifidum* and *L. acidophiles* showed no improved remission induction at CU (Jonkers et al. 2012). There is only one positive pilot study in children showing positive effects with *Lactobacillus GG* (Gupta et al. 2000) and few in adults with remission-inducing or preserving effects (Schultz et al. 2004; Malchow 1997) for remission induction in CD. Studies on the uptake of oligosaccharides and inulin in patients with active CD showed that they recorded less of the prebiotics than patients in remission and controls (Anderson et al. 2015). However, the only controlled study on the use of prebiotics as an adjunctive therapy (fructo-oligosaccharides) in CD led to a negative result (Benjamin et al. 2011). In summary, the results are heterogeneous meaning that prebiotics and probiotics for inducing a remission have not received a positive recommendation in national and international guidelines.

Most of the data on the remission rate due to the use of probiotics are available for UC. In three large RCTs, *Escherichia coli* strain Nissle 1917 was tested with 5-aminosalicylic acid (5-ASA, 1200–1500 mg) for remission in UC. Similar recurrence rates were observed after 12 weeks to 12 months. Relative risk (RR) is 1.08 (95% CI: 0.86–1.37); the results show that the *E. coli* strain Nissle 1917 is not inferior to standard therapy with 5-ASA in recurrent prophylaxis (Jonkers et al. 2012). The approval of this probiotic as a medicinal product led to the possibility of the prescription to be paid by the health insurance companies to patients with proven 5-ASA intolerance.

A very good evidence for a probiotic therapy is the acute and chronic pouchitis, a complication after proctocolectomy with ileoanal pouch system occurring in approximately 40% of patients in the course of time. In a meta-analysis, three RCTs with VSL#3 show remission induction and maintenance (RR, 0.17; CI 0.09–0.33) (20, 33–35). This probiotic is also effective in primary prophylaxis. Patients who begin therapy with VSL#3 after ileostomy dislocation are significantly less likely to develop pouchitis than patients without probiotics (Singh et al. 2015). But in contrast to the *E. coli* strain Nissle 1917, this is a dietary supplement; therefore, no costs are assumed by statutory health insurance funds, and patients have to pay the treatment costs themselves.

A clinical study on the effect of prebiotics has also been carried out in pouchitis. Thus, in a placebo-controlled study, after 3 weeks of supplementation with 24 g of inulin, an increased concentration of butyrates, a lowered pH value, a reduced concentration of secondary bile acids, and a reduced number of *Bacteroides fragilis* could be detected (37). In addition, there was an improvement in endoscopic and histological parameters. However, a clear clinical improvement that could be detected for the patient was not described. In addition, patients who are

already receiving 10 g of inulin per day sometimes report very disturbing side effects (e.g., flatulence), so that this may be a theoretical approach, but it also highlights the difficulties of this therapeutic concept. Own data of taxonomic composition of the intestinal microbiota in a 41-year-old female patient with chronic, antibiotic-refractory pouchitis before (week 0) and during a 2-week ingestion of 10 g of inulin per day showed changes in the frequency of single species with the increase of *Streptococcaceae* and decrease of *Bacteroidaceae.* In the course of the "inulin therapy," there are partly clear changes in the composition of the intestinal microbiota on family level. The extent to which these changes have occurred after discontinuation of the inulin intake must be analyzed by further studies.

14.8 FMT in IBD

As mentioned above dysbiosis plays an important pathogenetic role in IBD. The FMT is a radical therapeutic concept for this, transplant fecal microorganisms from a healthy donor in the form of stool suspensions applicated by endoscopy or gastronasal tubes, with capsule or enemas, into the patient's small or large intestine. Theoretically, this usually results in the restoration to a normalized microbiome. Primarily, this has been done on treatment-resistant patients with *Clostridium difficile* infections, and there are now several studies about irritable bowel syndrome (IBS) and IBD. However, the exact explanation of this method has not yet been completely explained. We know that the bacterial diversity increases according to FMT and almost grows up to donor level. An increase of *Firmicutes* and *Bacteroides* with an accompanying decrease of *Proteobacteria* was observed after FMT in IBD.

14.8.1 Donor Selection

A careful selection of the stool donor is of central importance for the FMT. Patients usually prefer family members as a stool donor but can also be an unknown person. For safety reasons the screening of FMT donors is taken very serious, so the donor has to answer many personal questions, including medication and drug use, and has a laboratory screening with HIV ELISA tests, syphilis, and hepatitis serology. From the stool cultures, testing for *Clostridium* and undertaking an examination for ova and parasite (*O&P exam*) are necessary. If these points are passed, the donor is able to donate for FMT (see Table 14.2).

14.8.2 How to Perform FMT

There is no clear evidence favoring one of the potential routes of administration of donor fecal microbiota, and decisions should be based on the proximal/distal location of the disease in the intestine, the physician's expertise, and patient's preferences. However, upper GI tract application of FMT has been associated with more severe side effects than lower GI tract application.

Potential routes of administration are:

1. Application into the upper GI tract via nasogastric, nasoduodenal tubes or by endoscopic procedures
2. Instillation into the proximal colon by endoscopic procedure
3. Rectal or distal colonic administration via enema
4. Combined approaches as well as oral application of capsules

Enema	Sigmoidoscopy	Colonoscopy
Needs an active patient to rotate during procedure, so that stool suspension is able to move through entire colon	Preparation in a more proximal segment of colon, beneficial for patients with difficulties to retain material	Infusion with suspension through entire colon, so endoscopic examination and transplantation can be done in one go, high inflamed areas can be treated more

Endoscopic and tube application may cause a discomfort or pain, so a sedation is often required. The transplantation via capsule does not require

Table 14.2 Screening procedure for microbiota donors

Diseases and circumstances that should lead to (transient or permanent) exclusion of a potential donor for FMT
IBD or other chronic gastrointestinal diseases including IBS
Chronic diarrhea and chronic constipation
Psychiatric diseases (depression, schizophrenia, autism, Asperger syndrome)
Autoimmune diseases and/or patients receiving immunosuppressive medications
Chronic pain syndromes (e.g., fibromyalgia)
Major relevant allergies (e.g., food allergy, multiple allergies)
Chronic neurological/ neurodegenerative diseases (e.g., Parkinson's disease; multiple sclerosis)
HIV, hepatitis A, B, C, or E, or known exposure within the recent 12 months
Obesity (BMI >30), metabolic syndrome
Recent (GI) infection (within last 6 months)
Travelling in countries with low hygiene or high infection risk for endemic diarrhea or acquisition of multiresistant bacteria within the last 6 months
Tattoo or body piercing placement within the last 6 months
Colonization with vancomycin-resistant enterococci; MRSA, methicillin-resistant *Staphylococcus aureus*
Promiscuity antibiotic therapy within the last 3 months
Drug abuse
Other chronic use of drugs that may affect the microbiome, e.g., proton pump inhibitor
Serological parameters for infection that should be tested and lead to exclusion if positive
HIV-1 and HIV-2
Hepatitis A, B, C
Human T-lymphotropic virus (HTLV)
Syphilis (TPHA)
Cytomegalovirus (CMV) (Epstein-Barr virus (EBV) (especially if the patient is negative)
Stool parameters (anal swab) for infection that should be tested and lead to exclusion if positive
Microscopic examination for ovae and parasites (e.g., amoeba)
Infectious bacteria (including enterohaemorrhagic *E. coli*, *salmonella*, *shigella*, *yersinia*, *campylobacter*)
Clostridium difficile (PCR)
Multiresistant bacteria (e.g., ESBL-producing organisms, MRGN 3 und 4, VRE, MRSA)
Helicobacter pylori (if nasogastric or oral capsules are used for FMT)
Calprotectin >50 mg/kg

any sedation but also has a psychological discomfort in some patients. For this procedure it is not necessary to use fresh stool—successful transplantations were also published with frozen capsules. In this procedure the patient digests a capsule that usually deliver transferred microbiota in small intestine. So the stool suspension goes its natural way through the digestive system.

As a first step of the FMT, the stool (50–100 g) of the donor will be worked up. For this purpose, the stool is mixed with a sterile conical solution (200 ml) under a lamina airflow and homogenized in a conventional household mixer. The suspension is sieved through a standard commercial sieve, filtered twice, and the resulting suspension (about 250 ml) is suitable for the transfer. Either this is carried out as a transfer with fresh stool suspension, or after the preparation, the suspension is admixed with 10% glycerol and is frozen at −80 °C. For the preparation of capsules, the suspension is concentrated by centrifugation and 650 µl is pipetted in size 0 capsules. These are sealed with size 00 capsules and stored at −80 °C. One to two hours before use, it can be restored in a −20 °C freezer and then transported on dry ice. Commercially available acid-resistant hypromellose capsules (DRcaps, Capsugel) can be used. These capsules are stable at 37 °C and at a pH of 3 or less for 115 min (Youngster et al. 2014).

14.8.3 Results of FMT in IBD

The feasibility and tremendous success of FMT to treat relapsing CD have been established FMT

as a new potential treatment for IBD. Several trials of FMT in IBD showed attractive results, especially for patients with UC. The majority of trials about FMT for IBD are one-armed uncontrolled cohort studies or case series. In general, FMT treatment successes were even published with long-term clinical remissions and in individual cases also with total discontinuation of the immunosuppressant. Patients with UC treated with FMT have an outcome from 0% to 100%. Although 22 studies (4 RCT, 18 cohort studies) with 518 patients with UC were published, only 5 were controlled trials. Two of five RCTs were negative (Rossen et al. 2015; Mizuno et al. 2017), whereas three placebo-controlled RCTs (Moayyedi et al. 2015; Paramsothy et al. 2017a; Costello et al. 2017) were positive. Post hoc analyses demonstrated that endoscopic severity and the need for corticosteroid therapy were factors associated with clinical outcome suggesting that patients with milder disease activity are more likely to respond to FMT. However, studies are needed to define the best indications, optimal timing, frequency, mode of delivery, and the optimal donor for each patient. In CD and pouchitis, there are limited published FMT results. The current data of CD patients FMT treatment have shown some good transplantations and also worsenings, so the efficacy is currently heterogenous. The biggest study from China has shown a 70% remission rate when fecal microbiome was transplanted in the duodenum. To show the efficacy in CD, higher patient numbers and especially controlled studies are needed. In pouchitis, Lang et al. assessed the effects of FMT on clinical outcome in eight patients with chronic pouchitis (LIT-Steele). They observed no significant FMT-induced metabolic or immunological changes or beneficial clinical response after single FMT via a single nasogastric administration. We studied in 14 patients with antibiotic refractory pouchitis the therapeutic effect of single donor FMT by endoscopic jejunal application. Clinical response occurred in 7 of 14 patients after 2 to 4 FMTs. Four patients showed clinical worsening and three patients showed no improvement. Fecal calprotectin levels as a marker for mucosal inflammation dropped in responders from 536 mg/kg stool (median) (minimum-maximum, 116–3000) to 150 mg/kg (median) (minimum-maximum, 191–1409), whereas in patients with flare FCP values increased from 1005 mg/kg (529–1579) to 1450 mg/kg (1221–1778). FMT in patients with chronic pouchitis is a promising therapeutic option, and donor microbiomes could successfully be transferred via capsules or via jejunoscopy delivering fresh stool filtrate. However, a simple increase in microbial diversity and successful establishment of members of the butyrate producing *Lachnospiraceae* and *Ruminococcaceae* families is not sufficient for a successful outcome of FMT. A recently published meta-analyses with 53 studies (41 in UC, 11 in CD, 4 in pouchitis) showed an overall success with 36% (201/555) of UC patients, 50.5% (42/83) of CD patients, and 21.5% patients (5/23) of pouchitis patients achieved clinical remission (Paramsothy et al. 2017b). Authors concluded that FMT appears effective in UC remission induction, but long-term durability and safety remain unclear. Additional well-designed controlled studies of FMT in IBD are needed, especially in CD and pouchitis.

14.8.4 Safety of FMT

Short-term adverse events after FMT appear to be uncommon, often mild and self-limiting; however, serious adverse events including bacteremia, perforations, and death have been reported. Preparation of microbiota for FMT bears major problems of standardization and is accompanied by potentially incalculable long-term risks, many of which are inherent to the transfer of living microorganisms (Cammarota et al. 2017; König et al. 2017). Moreover, even the most rigorous and costly donor screening procedures (Paramsothy et al. 2015) cannot exclude the risk of transferring unknown pathogens to the recipient, including bacterial or viral risk factors for metabolic diseases, cancer, atopy, or autoimmunity.

14.8.5 Legal Aspects of FMT

We are currently experiencing an increased demand from patients for FMT as a treatment method for various diseases. The legal regulations for treatment with FMT are country-specific and must, of course, be adhered to. In the USA FMT has been treated sporadically since the 1950s, without great regulations. In the USA FMT has gained in popularity over the past few years, but it is estimated that the current treatment rate is less than 500 patients. In 2013, the FDA announced that they classified the feces as an Investigational New Drug (IND) and a Biologic so that from now on, only doctors with approved IND application are allowed to conduct FMT, which is only a couple of physicians. Due to protests, the FDA revised this decree on June 17, 2013, and announced that qualified physicians could continue to perform FMT for recurring *Clostridium difficile* infections however with tested donors and the written consent of the patient. The European Medicines Agency has not announced its position. The UK National Institute for Heath and Care Excellence does not regard FMT as a transplant because no body tissue is "transplanted"; the French regulatory authority Agence nationale de sécurité du médicament et des produits de santé (ANSM) and the German Bundesinstitut für Arzneimittel und Medizinprodukte (BfArM) declared FMT as a drug in March 2014. However, fecal microbiota is a complex and very variable admixture for transplantation, its components cannot be fully characterized, and to date composition quality cannot be assessed.

14.9 Summary

Inflammatory bowel diseases (IBD) may result from dysregulated mucosal immune responses directed toward the resident intestinal microbiota. Clinical and experimental data suggest that dysbiosis may play a pivotal role in the pathogenesis of IBD. Treatment with pre- and probiotics addresses this dysbiosis and improves intestinal mucosa barrier function and immune system function and promotes secretion of anti-inflammatory factors, thereby inhibiting the growth of harmful bacteria in the intestine. However, therapeutic efficacy especially in acute flares is limited. Fecal microbiota transplantation (FMT) provides a novel strategy to restore the normal gut microbiota in patients with IBD. Most adverse events became mild and included transient gastrointestinal symptoms. Serious adverse events did not differ significantly between the FMT and control groups, and a marginal increased rate of IBD flares following FMT was observed. Further large and well-designed trials are necessary to resolve critical issues such as donor selection, ideal method of administration, duration and frequency of FMT, as well as long-term sustained efficacy and safety.

14.10 Conclusions

The concept of host-gut-microbiome interaction in the pathogenesis of various complex immune-mediated chronic diseases, including IBD, has recently generated immense interest. Although further research is still needed to establish a definite cause-effect relationship between dysbiosis of gut microbiota and extra- and intraintestinal inflammation, such studies may provide novel approaches for prevention and treatment of IBD. Numerous limitations and challenges, however, still exist within this newly emerging field, which requires further investigation.

14.11 Resource Section

- Fecal microbiota transplantation in *Clostridium difficile* on YouTube: https://www.youtube.com/watch?v=Awn3haOpfcI
- Homepage Fecal Transplant Foundation: http://thefecaltransplantfoundation.org/what-is-fecal-transplant/

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15 Risks and Side Effects of Medical Therapy

Tracey E. Peterson and Corey A. Siegel

Abstract

The risks of treatment for inflammatory bowel disease (IBD) are of concern for both patients and providers. Overall, IBD treatments are safe, but there are a range of important potential side effects that need to be discussed with patients. This chapter will review the risks associated with aminosalicylates, corticosteroids, immunomodulators, biologics, and the newer small molecules. In addition to discussing these possible adverse events, guidance is offered on the best methods for communicating these risks to patients.

15.1 Introduction

The risks of treatment for inflammatory bowel disease (IBD) are of concern for both patients and providers. It is a complex topic with a lot of data and uncertainty around how risks of treatment may be different to individual patients. Patients receive information from multiple sources: friends, family, the Internet, and their providers often leading to misconceptions about the effectiveness and risks associated with treatment options. Oftentimes they are making decisions about treatments without enough information.

IBD therapy options range from aminosalicylates that have been used for over 60 years to biologics that are more recent. These treatments are overall safe, but they do come with a risk of side effects, ranging from mild and quickly reversible adverse events to life-threatening processes such as cancer and sepsis. Because of the concern of these risks, both patients and providers may delay treatment or avoid therapy altogether. Not only do providers need to have a clear understanding of risks of the medications that they are recommending, they also need to have the tools and guidance on how to appropriately and confidently convey these risks to patients. There are tools now available to assist providers in presenting these risks to patients to facilitate the conversation around risk and improve the process of shared decision-making.

15.2 Aminosalicylates

Aminosalicylates are primarily used to treat mild to moderate ulcerative colitis (UC). They are occasionally used to treat Crohn's disease; however, data do not support their efficacy beyond possibly mild Crohn's colitis (Lim et al. 2016).

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This class of drugs includes sulfasalazine and the 5-aminosalicylic acid drugs (5-ASAs) mesalamine/mesalazine, olsalazine, and balsalazide, which are dispensed as multiple different brands. They are generally well tolerated although some serious side effects have been reported. Sulfasalazine, developed in the 1940s originally intended for the treatment of rheumatoid arthritis, is associated with more frequent side effects compared to mesalamine and balsalazide (Curkovic et al. 2013). In a dose-dependent fashion, patients taking sulfasalazine may experience headaches, nausea, and abdominal discomfort (Loftus et al. 2004). This can typically be managed with a slow increase in dose over a few weeks, and many people tolerate sulfasalazine very well with this strategy. Case reports of rare adverse events that have been reported included agranulocytosis, alveolitis, and pancreatitis (Curkovic et al. 2013), but due to the very few cases reported, it is not even possible to estimate a frequency of occurrence. Both sulfasalazine and other 5-ASAs have been associated with a paradoxical worsening of colitis (likely related to hypersensitivity), and worsening symptoms after initiating these medications should lead to a cessation of therapy and observation if symptoms improve. Nephrotoxicity, specifically interstitial nephritis, has been reported in association with 5-ASA use. The estimated frequency of occurrence is very low at approximately 11 people per million treated (Ransford and Langman 2002), and there is some controversy around if this association is even real (de Jong et al. 2005). General recommendations for monitoring patients using mesalamine include monitoring a total blood count and renal function every 6–12 months.

15.3 Corticosteroids

Corticosteroids are used often in IBD to treat flares and to induce remission while waiting for other treatments to take effects. It should be noted that corticosteroids have never been approved for the treatment of Crohn's disease or ulcerative colitis but have been part of the therapeutic armamentarium since the 1950s. Systemic corticosteroids, although inexpensive and quickly effective in improving symptoms, carry with them a long list of short-term and long-term side effects.

Systemic corticosteroids (most commonly used in IBD include prednisone, prednisolone, methylprednisolone, and hydrocortisone) lead to side effects in the vast majority of those taking these medications and require cessation of therapy in over 50% due to these adverse events. Table 15.1 shows the estimates of frequency of events associated with systemic corticosteroids. Although patients often express concerns related to immunomodulators and biologics (see below), the frequency of adverse events related to corticosteroids are far higher than any other medications used to treat IBD. Patients need to understand that short-term and reversible side effects include ankle and facial swelling, easy bruising, acne, psychosis in the form of confusion and agitation, and minor and serious infection. Side effects associated with longer-term use may be irreversible and include suppression of the adrenal axis, cataracts, increased intraocular pressure (glaucoma), hypertension, osteoporosis, avascular necrosis, change in body habitus ("buffalo hump"), and diabetes (Present 2000; Rutgeerts et al. 1994; Rutgeerts 2001).

Budesonide, a newer corticosteroid formulation, has a very low systemic exposure and although not completely free of steroid-related side effects, is very well tolerated with side effects occurring at the

Table 15.1 Frequency of adverse events associated with systemic corticosteroid use (Present 2000; Rutgeerts 2001)

Event	Estimated frequency
Stopping therapy due to an adverse event	55%
Ankle swelling	11%
Facial swelling	35%
Easy bruising	7%
Acne	50%
Psychosis—confusion/agitation	1%
Infections	13%
Cataracts	9%
Increased intraocular pressure	22%
High blood pressure	13%
Osteoporosis	33%
Diabetes	Chance increases 10×

same frequency as placebo in clinical trials (Danese et al. 2014). When using budesonide beyond a few weeks, it is prudent to recommend co-administration of calcium and vitamin D to prevent bone loss, as is always recommended with systemic corticosteroid use as well.

15.4 Immunomodulators

Immunomodulators that are commonly used for the treatment of IBD include azathioprine (AZA), 6-mercaptopurine (6MP), and methotrexate. They are used to treat IBD as either primary monotherapy to maintain remission and allow for steroid sparing or in combination with biologic drugs to enhance and prolong their efficacy.

AZA and 6MP are thiopurine drugs and have been used to treat IBD since the 1960s. Overall they are well tolerated, and approximately 90% of patients continue these medications without having adverse events requiring stopping. Most of the common adverse events are reversible, and although can be serious (e.g., pancreatitis, infections) when recognized and treated early, these are short-lived (Siegel and Sands 2005). Table 15.2 shows the estimated frequency of these common adverse events and also an estimate for the most concerning associated side effect of non-Hodgkin's lymphoma.

The risk of cancer associated with thiopurines is often emotionally the biggest issue in talking with patients and their families. Appropriately, patients want to understand more about this risk and if it is outweighed by the benefits of treatment. There are significant misperceptions of the real risks of cancer (Siegel et al. 2008), and oftentimes patients will know that there is some cancer risk associated with these drugs but are not clear of the specifics. It is important to clarify with patients that the only cancers associated with thiopurines include non-Hodgkin's lymphoma and non-melanoma skin cancer.

Table 15.2 Frequency of adverse events associated with immunomodulators

Event	Estimated frequency
Stop therapy due to an adverse event	11%
Allergic reactions	2%
Nausea	2%
Hepatitis	2%
Pancreatitis	3%
Serious infections	5%
Non-Hodgkin's lymphoma	0.04–0.09% 4–9 per 10,000 treated

Adapted from Siegel CA. Lost in translation: helping patients understand the risks of inflammatory bowel disease therapy. Inflamm Bowel Dis 2010;16:2168–72 (Siegel 2010)

Non-Hodgkin's lymphoma is thought to be related to Epstein-Barr virus and its influence on cellular proliferation and ultimately lymphoma (Dayharsh et al. 2002; Vos et al. 2011). Although enormous attention and energy are given to discuss lymphoma in the office, thankfully the absolute risk of this occurrence in relationship to thiopurines is very low, with an estimate between 4 and 9 people out of 10,000 treated with azathioprine over the course of 1 year (Siegel et al. 2009; Beaugerie et al. 2009). This is compared to the expected rate in the general population of 2 out of 10,000 people. Therefore, although there is a 2×–4.5× increased risk, the rate of occurrence is thankfully very low. Young male patients and people older than 65 appear to be at the highest risk across the age spectrum, but this can occur at any age and in females as well. The risk appears to go back to baseline after stopping thiopurines, which has led to a strategy by some of shorter term (<2 years) use of thiopurines, as the risk appears to increase after 2 or more years of exposure (Beaugerie et al. 2009).

Hepatosplenic T-cell lymphoma is a particular subtype of non-Hodgkin's lymphoma, which is far less treatable and nearly universally fatal. It has been associated with use of thiopurines, particularly when used in combination with antitumor necrosis factor (TNF) drugs. As also noted with standard non-Hodgkin's lymphoma, the association is directly related to time exposure of thiopurines, with almost every case reported in the literature occurring after 2 years of therapy. The estimated rate of occurrence in the "at risk" population of young male patients is estimated to be approximately 1–3 patients out of 10,000 treated (Kotlyar et al. 2011; Magro et al. 2014).

There has never been a clear association between thiopurines and solid tumors, other than with non-melanoma skin cancer (Mason and Siegel 2013). The increased rate of basal cell and squamous cell skin cancers has been reported consistently with thiopurine use, but the increase is fairly modest. The absolute rates reported are estimated to be approximately 3/1000 patient-years for the age group of 50–65 years and 4/1000 patient-years for patients older than 65 years (Peyrin-Biroulet et al. 2011). If patients do develop non-melanoma skin cancers while on thiopurine, it is tempting to consider stopping therapy. However, this does not lead to a significant decrease in future risk and may be risking disease exacerbation if AZA or 6MP was leading to a sustained long-term remission (Peyrin-Biroulet et al. 2011).

Methotrexate is overall a safe treatment in IBD. Nausea and fatigue are the most commonly complained about side effects in patients taking methotrexate. These side effects can usually be minimized by having the patient take the medication at night rather than in the morning and by increasing folic acid from 1 to 2 mg daily (Siegel and Sands 2005). More serious side effects of methotrexate use are hepatotoxicity and hypersensitivity pneumonitis, but these are very unusual in patients with IBD and seen more commonly in those with psoriasis and rheumatoid arthritis, respectfully (Siegel and Sands 2005). Although there are data to suggest that methotrexate is associated with lymphoma in patients with rheumatoid arthritis (Baecklund et al. 2004; Buchbinder et al. 2008), these findings have been inconsistent and not seen globally (Wolfe and Michaud 2007). There have been cases reported in IBD (Farrell et al. 2000), and the mechanism of methotrexate-associated lymphomas also appears to be EBV mediated (Ejima-Yamada et al. 2017). Therefore, it is possible that we have a false sense of security related to methotrexate and lymphoma, as we simply do not have enough safety data on its use in IBD. Methotrexate is both teratogenic and a known abortifacient. Woman of childbearing age needs to be sure to use adequate birth control. In addition methotrexate can be toxic to sperm, so men should stop taking it at least 3 months prior to trying to conceive (Siegel and Sands 2005).

15.5 Biologics

Biologics, although considered by many patients to be more potent than other therapies, have a similar side effect profile to immunomodulators and may in fact be safer over long periods of exposure. These drugs have a long list of potential side effects but overall are very well tolerated, and serious adverse events are very unusual. The currently available biologics are across three different classes including anti-TNFs, anti-adhesion molecules, and an anti-interleukin 12/23 molecule.

Anti-TNFs have been approved for the treatment of IBD since 1998, and we have gained significant insight into their short-term and long-term side effect profile. All anti-TNFs are not approved globally for IBD, but those approved include adalimumab, certolizumab pegol, golimumab, and infliximab. Infliximab is given intravenously, and the others are administered as a subcutaneous injection. Other than a difference in injection site and infusion reactions across these anti-TNFs, the nature and frequency of adverse events are considered roughly equivalent across the class. Table 15.3 reviews the most important associated adverse events

Table 15.3 Frequency of adverse events associated with anti-TNF drugs

Event	Estimated frequency
Stop therapy due to an adverse event	10%
Injection site or infusion reactions	3–20%
Drug related lupus-like reaction	1%
Tuberculosis	0.05% (5/10,000)
Serious infections	3%
Non-Hodgkin's lymphoma	0.06% (6 per 10,000 treated)

Adapted from Siegel CA. Lost in translation: helping patients understand the risks of inflammatory bowel disease therapy. Inflamm Bowel Dis 2010;16:2168–72 (Siegel 2010)

and the estimated frequency. Of note, although these drugs have been reported as a cause of multiple sclerosis (MS) and heart failure, these data originally come from clinical trials for MS and heart failure where they used anti-TNF to treat these conditions, but instead of helping they led to exacerbations of the preexisting problem (Arnason et al. 1999; Chung et al. 2003). Based on known risks of reactivation of tuberculosis and hepatitis B, baseline testing to make sure latent disease is not present is highly recommended prior to starting therapy.

It has been very difficult to determine if anti-TNFs on their own have an association with causing lymphoma. Early reports led to a black box warning from the Food and Drug Administration (FDA); however, most of these patients had also been exposed to immunomodulators as well, confounding the data. A meta-analysis published in 2009 showed the absolute rate of lymphoma for patients who had received anti-TNFs together with immunomodulators as 6 per 10,000 patients over the course of 1 year (Siegel et al. 2009). Although this is statistically higher than the expected rate of 2 per 10,000 in the general population, it was not statistically higher than the expected rate of immunomodulators alone. Therefore, one conclusion could be the using anti-TNFs together with immunomodulators are likely associated with a small numerically increased risk of lymphoma, but anti-TNFs on their own may not have this associated risk. As noted above, anti-TNFs together with thiopurines have a small increased risk of hepatosplenic T-cell lymphoma. As with immunomodulators, anti-TNFs do not have an increased risk for solid tumors, other than possibly skin cancers. Data show a small increased risk of melanoma related to anti-TNF use, but this absolute risk is still very low, at about 1 per 1000 patients treated (Long et al. 2012).

Combination therapy using an anti-TNF agent together with an immunomodulator has been shown to be more effective than using either drug class alone (Colombel et al. 2010). Intuitively, you would think that this would increase the overall rate of adverse events, but this really hasn't shown to be true in the literature. The Mayo Clinic performed a study showing that a combination of medications did increase the rate of opportunistic infections but the drug implicated in increasing this risk was corticosteroids, not combining anti-TNFs with immunomodulators (Toruner et al. 2008). Also, the large clinical trials for anti-TNFs had similar rates of infections and other serious events whether patients were treated with anti-TNFs alone or in combination with immunomodulators (Colombel et al. 2010; Feagan et al. 2013). One exception may be that adding an immunomodulator to an anti-TNF agent may slightly increase the cancer risk (Kotlyar et al. 2011; Osterman et al. 2014).

The newest biologic agents approved for IBD include natalizumab, vedolizumab, and ustekinumab. Natalizumab and vedolizumab are anti-adhesion molecules, and ustekinumab is an anti-IL 12/23 molecule. Natalizumab is getting very little use globally for IBD based on its clear association with progressive multifocal leukoencephalopathy (PML) related to proliferation of the JC virus in the brain (Van Assche et al. 2005). But its successor anti-adhesion molecule vedolizumab is specific for mucosa in the gastrointestinal tract and therefore has no known relationship to PML (Colombel et al. 2017; Sands 2017). In clinical trials and clinical practice, vedolizumab is proving to be a highly safe drug with a side effect profile that mirrors that of the placebo arm (Colombel et al. 2017; Dulai et al. 2016). Although it is possible that new adverse events associated with vedolizumab will emerge over time, it has become a first choice for patients who are felt to be at particularly increased risk for infections (e.g., elderly) or those simply risk averse and want to avoid biologics altogether. Ustekinumab is the most recently approved biologic drug, and although doesn't have the gastrointestinal specificity like vedolizumab, in the clinical trials and in years of use for psoriasis, very few significant adverse events have been seen (Feagan et al. 2016; Meng et al. 2014). More time and experience is needed in the IBD population, but thus far, ustekinumab is also emerging as a very safe alternative for patients with Crohn's disease.

15.6 Small Molecules

The small molecules are the next frontier in IBD treatment. The first to get approved for IBD is tofacitinib, a Janus Kinase (JAK) inhibitor. This immune suppressant drug appears to be associated with increased infections, the most notable being herpes zoster (shingles) that occurred approximately 5% in clinical trials (Sandborn et al. 2017). Now that there is killed zoster vaccine on the market, the expectation is that broad immunization of IBD patients will render this risk far less significant. In the rheumatoid arthritis population, who also uses tofacitinib, there is some concern over cardiac risk due to increasing LDL cholesterol in those treated with this agent. For patients with IBD in the tofacitinib clinical trials, this changing cholesterol profile has not been clinically significant, but it is probably wise to check baseline and follow-up cholesterol to make sure there is not a significant rise over time.

15.7 Communicating Risk to Patients

Clearly communicating risk of medical therapy to patients and families can be very challenging. Patients are trying to learn a lot of new information, and the Internet and family and friends often compound any baseline fear. The most difficult part is in trying to take the complex statistics used in academic publications and convert that to a patient friendly format (Siegel 2010).

Tips for clear communication include:

- Report data using absolute (e.g., 6 per 10,000) as opposed to relative risk (e.g., 3× the general population).
- Keep denominators common. Report risk as 4 per 10,000 vs 9 per 10,000 as opposed to 1/2500 versus 1/1111.
- Using decimals for small number on their own can be confusing. Present data as 9 per 10,000 if reporting an absolute chance of 0.09%.
- Avoid vague descriptive words such as "rare" and "common" as these are often misperceived and can have wildly varying interpretations.
- Using visual tools can always help. A number have been developed including risk palettes and decision aid videos (Siegel 2010).
- Give perspective to other life risks. The risk of getting into a car accident is far higher than adverse events associated with any IBD treatments.

Using these techniques, web-based programs have been developed and are available on the Crohn's and Colitis Foundation website free of charge that help patients understand the risk and benefit tradeoffs for the treatment of both Crohn's disease and ulcerative colitis. The link to these videos can be found here: http://www.crohnscolitisfoundation.org/resources/treatmentdecisions.html.

15.8 Summary

There have been significant advances for the treatment of Crohn's disease and ulcerative colitis with medications that are significantly more effective then what we have had available in the past. Many patients and providers are intimidated by the side effects that are reported with the immunomodulators and biologics; however, significant side effects are very unusual and now very well understood. Patients need to be reminded that although these newer medications are not risk free, compared to prednisone, chances of serious adverse events are significantly lower, and these medications are offering their best chance to avoid future complications of their disease, which is their biggest risk.

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Surgical Management

16

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Abstract

Crohn's disease (CD) is a chronic relapsing inflammatory disease, typically characterized by transmural inflammation of the intestine and could affect any part of the gastrointestinal tract, from mouth to perianal area. In terms of distribution of the disease 25% of the patients have colitis only, 25% ileitis only, and 50% ileocolitis. Approximately 70% of patients with CD require surgical intervention within 10 years of their initial diagnosis, with surgical recurrence in 25% of the patients by 5 years and 35% of the patients by 10 years after initial surgery. Ulcerative colitis (UC) is a chronic inflammatory bowel disease with mucosal inflammation that involves only the colon and the rectum, characterized by a proximal extension from rectum to cecum, without small bowel involvement. Surgery is still required in 15–35% of patients affected by UC, also in emergency setting. In this chapter we have analyzed clinical presentations of both diseases with surgical indications, type of surgery, and management of complications. In conclusion, we underline the importance of the role of IBD nurse in the management of all the complex situations that IBD patients live, solving problems and improving quality of life.

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16.1 Introduction

Crohn's disease (CD) is a chronic relapsing inflammatory disease, originally described in 1932 by Crohn, Ginzburg and Oppenheimer. CD is typically characterized by transmural inflammation of the intestine and could affect any part of the gastrointestinal tract, from the mouth to perianal area. In terms of distribution of the disease, 25% of the patients have colitis only, 25% ileitis only and 50% ileocolitis. Presenting symptoms are often variable and may include diarrhoea, abdominal pain, weight loss, nausea, vomiting, fevers or chills. There are three main disease phenotypes: nonstricturing/nonpenetrating, stricturing and penetrating.

Stricturing phenotype is most common in small bowel disease and is often associated with penetrating phenotype. Strictures can also develop post-surgery for CD. Penetrating phenotype is associated with intra-abdominal abscess and fistulae. Stenoses, fistulae and abscesses are the main reasons for bowel resection in patients with CD.

Stricture is defined as persistent narrowing through which an endoscope could not be passed or a narrowing with radiographic pre-stenotic dilatation.

Abscess is a purulent collection in a non-preexisting cavity and cause fever and intense pain. Spontaneous or surgical drainage of abscess

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hesitates in purulent discharge and often in fistula.

Fistula is a tract that connects two organs or an organ with skin surface. In CD the most common type of fistula is enteroenteric, followed by enterocutaneous, enterosigmoid and enterovesical. Anal fistula (a tract that connects the anal canal to the perianal skin) is the most common manifestation of perianal CD.

Perianal CD affects almost 25% of patients and includes both fistulizing (anal and rectovaginal fistulas, abscesses) and non-fistulizing (skin tags, haemorrhoids, anal fissures) lesions. Perianal disease has a great impact on patients' quality of life due to pain, discharge and recurrent abscess formation. The presence of proctitis and the disease duration increase the cumulative incidence of perianal involvement in CD.

16.2 Summary

In this chapter will be discussed surgical indications in CD, type of surgery for each localization of the disease and management of complications.

16.3 Surgical Indications in CD

Approximately 70% of patients with CD require surgical intervention within 10 years of their initial diagnosis, despite advanced medical treatment such as biologics, immunosuppressive drugs and steroids. Unfortunately, surgery is not curative, and surgical recurrence occurs in 25% of the patients by 5 years and 35% of the patients by 10 years after initial surgery. The risk of intestinal failure rises significantly after multiple surgeries and when intestinal length is shorter than 150 cm.

Indications for surgery in CD include:

- Medically refractory disease
- Recurrent obstruction from stricture
- Abdominal abscess not amenable to percutaneous drainage
- Fistula
- Dysplasia or cancer
- Growth retardation
- Bowel perforation
- Toxic megacolon
- Major gastrointestinal bleeding.

Prolonged medical management in order to delay surgery may increase complication rates, the technical difficulties during surgery and the rates of emergency surgery. Emergency surgery is associated with increased stoma rates and increase in mortality compared to elective surgery. The risk of postoperative infectious complications is high after prolonged corticosteroid therapy.

Preoperative assessment must be provided:

- *Endoscopy:* upper or lower GI endoscopy confirms diagnosis and disease location.
- *US:* ultrasound is useful for small bowel in order to assess the wall diameter and thickness and mural and extraintestinal vascularity.
- *CT scan:* abdominal CT enterography is the most preferred first-line radiologic study to assess small bowel disease.
- *MRI:* MRI of small bowel and colon can reveal wall thickening, oedema, ulcers and hyper-enhancement with intravenous contrast. Pelvic MRI is useful in the evaluation of perianal fistulas and adjacent abscess.
- *Wireless video capsule endoscopy (VCE):* VCE can detect occult bleeding in the small bowel.

Malnutrition affects up to 85% of patients with CD awaiting surgery as a consequence of active disease, and nutritional support strategies are crucial to decrease postoperative morbidity. BMI is a follow-up tool of nutritional status during nutritional support.

A dedicated IBD unit with a multidisciplinary team (MDT) is the best way to manage these complex diseases and their impact on a patients' quality of life. Specialities involved in MDT are gastroenterology, surgery, nutrition specialists, psychology, rheumatology, dermatology, ophthalmology, gynaecology/urology and IBD nurses. IBD nurses help the patient to accept and

understand illness and to understand the risks and benefits of the proposed therapies. IBD specialist nurses provide patients with complication management, education, advocacy and physical and emotional support. Their role may also include performing patient reviews and encouraging treatment adherence, laboratory follow-ups and prescription repeats. Some IBD nurses also provide to stoma care, but in many countries there is also a stoma specialist that is involved in IBD unit.

16.4 Type of Surgery

In CD patients, laparoscopic surgery is safe and feasible, with better outcomes compared to open surgery. Mortality is almost none and morbidity rates are lower than open surgery in recurrent CD. The spread of laparoscopic techniques has reduced the duration of postoperative ileus, length of hospital stay and complication rates when compared to open surgery.

16.4.1 Surgical Treatment of Small Bowel CD

Ileocaecal or distal ileal disease is the most common presentation of CD and usually determines stricture that require resection in approximately 87% of patients. Surgical treatment in these cases consists of ileocaecal resection that removes terminal ileum and caecum with ileocolic anastomosis. The resection can be extended proximally or distally, depending on the extension of disease. If a CD patient is dependent on steroids, has an abscess or requires emergency surgery, the risk of anastomotic leak is 40%, and anastomosis should be protected with a stoma. Anastomotic stricture appears in almost 30% of patients and requires surgery with resection of primary anastomosis or strictureplasty.

Strictureplasty is a safe alternative to resection in stricture in order to preserve bowel length. This procedure provides dilatation of the intestinal stricture without resection. There are different techniques to perform strictureplasty: the most important are Heineke-Mikulicz, Finney and Michelassi, and the choice depends on length of stricture.

Small bowel fistulas without intra-abdominal abscess have a reasonable outcome when treated with medical therapy. Intraabdominal abscesses or enterocutaneous fistulas usually require intestinal resection and often temporary stoma.

16.4.2 Surgical Treatment of Colonic CD

The surgical treatment of colonic CD is still matter of debate. Stricturing colonic CD can be conservatively treated with endoscopic balloon dilatation in order to delay the need for surgery. Surgical treatment is nearly always necessary in fistulizing colonic CD. The proposed surgical techniques are subtotal colectomy, segmental colectomy and total proctocolectomy.

Segmental resection and subtotal colectomy with or without stoma are reasonable treatments in colitis with relative rectal sparing and minimal or no perianal disease.

Total colectomy is reserved for patients with multiple strictures, severe pancolitis, fulminant colitis, toxic megacolon or cancer. Subtotal colectomy with ileorectal anastomosis (IRA) avoids proctectomy, but it exposes the patient to anastomotic and rectal recurrence. Total proctocolectomy seems to be the best surgical option with low risk of recurrence, but permanent stoma formation has high impact on patients' quality of life and risk of perianal wound complications.

Total proctocolectomy with ileal pouch reconstruction has been proposed in a few centres in selected patients without small bowel and perianal involvement, but there is a high risk of pouch failure, so this approach is uncommon.

Strictureplasties may be performed for CD large bowel strictures with good results but higher risk of recurrence when compared to resection.

Type of surgery	Definition	Indication
Segmental resection	Resection of a part of the colon	Segmental colitis with relative rectal sparing Minimal or no perianal disease
Total colectomy	Removal of the entire colon	Multiple strictures Severe pancolitis Fulminant colitis Toxic megacolon Cancer
Subtotal colectomy with ileorectal anastomosis	Removal of the colon and restoration of intestinal continuity with ileorectal anastomosis	Colitis with rectal sparing No perianal disease
Total proctocolectomy with end ileostomy	Removal of colon and rectum with permanent ileostomy	Pancolitis with involvement of rectum and perianal disease
Total proctocolectomy with ileal pouch reconstruction	Removal of the colon and rectum and restoration of intestinal continuity with ileo pouch anal anastomosis	No small bowel involvement No perianal disease Uncommon because of high risk of pouch failure
Strictureplasty	Suture of bowel loop in order to dilate lumen	Bowel strictures

16.4.3 Surgical Treatment of Perianal CD

Fistulizing perianal CD requires surgical intervention in up to 83% of patients. The goal for management for fistulizing CD is to control fistula and preserve sphincter function. Medical therapy with anti-TNF agents is an effective treatment in fistulas, while surgical approach is reserved for patients with abscesses or perianal sepsis. If patients are asymptomatic, there is no need for surgery.

The management of perianal abscess is incision and drainage. Low and simple CD perianal fistulas can be treated by fistulotomy. Fistulotomy lays the fistulous tract open and leaves a small wound that leads to early healing. High and complex CD fistulas should be treated with placement of long-term setons to limit recurrent abscess formation. Seton is a suture wire that is inserted in the fistula track in order to promote adequate drainage of infection. Loose seton is preferred to cutting seton in order to preserve sphincter integrity, and its placement is successfully associated to treatment with anti-TNF agents. Other surgical options are advancement flap closures, fibrin glue or plug, but more studies are necessary to confirm their long-term efficacy. These treatments will be discussed in detail in Chap. 22 (Cancer).

Refractory to medical and surgical therapies is an indication for temporary or permanent faecal diversion.

16.5 Management of Complications

CD is associated with high surgical recurrence, and patients will undergo multiple operations with need of parenteral nutrition in 5–18% of cases.

Patients often experience chronic diarrhoea after ileocolic resection due to the loss of ileocaecal valves and in 30% of cases develop an anastomotic stricture. Endoscopic balloon dilatation (EBD) is a valid therapeutic option in order to delay surgery, but the failure of endoscopic treatment requires anastomotic resection.

Anastomotic leak is defined as the leak of luminal contents from a surgical join of two hollow viscera and can lead to abscess formation, peritonitis and sepsis if untreated. The incidence of anastomotic leak in CD varies from 3% to 20% and increases in patients with low albumin, intra-abdominal abscess and prolonged corticosteroid therapy. In ileocolic anastomosis, a recent study showed that a side-to-side stapled anastomosis is associated with decreased rates of anastomotic leak and surgical recurrence. The rate of anastomotic leak is higher in colo-colonic anas-

tomosis than entero-enteric or entero-colic. This kind of complication requires re-intervention, but image-guided percutaneous drainage is a valid therapeutic option when feasible.

Proctectomy in CD is associated with a high risk for perineal wound complications in 40% of patients. Delayed perineal wound is defined as a wound that has not healed within 4–6 months following proctectomy. Perineal wound complications include non-healing wound and persistent sinus drainage and their incidence increases in presence of perineal sepsis, complex fistulas, intraoperative faecal contamination and rectal stenosis. Conservative management consists of hygiene optimization and frequent debridement that can be continued for up to 12 months. Negative pressure wound therapy is another useful alternative to help healing. Primary re-approximation of local tissues is the standard surgical treatment to attempt closure of a perineal wound. Large perineal defect or failure of primary approximation is an indication to perineal reconstruction with flap.

16.6 Introduction

Ulcerative colitis (UC) is a chronic inflammatory bowel disease with mucosal inflammation that involves only the colon and the rectum. The disease course is characterized by a proximal extension from rectum to cecum, without small bowel involvement. Patients with UC typically present with rectal bleeding, bloody diarrhoea, abdominal pain and weight loss. Laboratory studies showed elevated calprotectin concentrations, accelerated erythrocyte sedimentation reaction, elevated concentration of C-reactive protein and anaemia. The course of disease is chronic, with periods of relapse and remission.

16.7 Summary

In this chapter it will be discussed surgical indications in UC, type of surgery according to different clinical presentation of the disease and management of complications.

16.8 Surgical Indications in UC

Despite the wide range of available medical therapies, surgery is still required in 15–35% of patients affected by UC. Surgical indications in the elective setting are:

- Dysplasia or cancer
- Medical refractory disease
- Steroid dependence
- Side effects of medical therapy or lack of adherence

Surgical indications in the emergency setting are:

- Haemorrhage
- Perforation
- Toxic megacolon
- Acute severe colitis
- Worsening clinical condition during second-line therapy

16.8.1 Acute Severe Colitis

About 15–20% of the UC patients will require hospitalization and subsequent emergency surgical treatment because of acute severe or fulminant colitis.

Truelove and Witts criteria define severe UC as the passage of at least six daily bloody stools, along with any of the following signs of systemic disease:

- Erythrocyte sedimentation rate >30 mm/h
- Temperature >37.8 °C
- Heart rate >90 bpm
- Haemoglobin <10.5 g/dl

Lichtiger created a different scoring system for UC based on:

- Frequency of stools
- Presence of nocturnal diarrhoea
- Blood in stool
- Faecal incontinence
- Abdominal pain

The guidelines of the American College of Gastroenterology defined fulminating colitis as situations of diarrhoea (more than 10 evacuation per day), continuous rectal bleeding, systemic signs of toxicity (fever, tachycardia, hypotension), anaemia that requires blood transfusion and abdominal distension with pain.

The diagnosis is suspected from the history and physical examination and is confirmed through laboratory tests and abdominal radiography. Laboratory tests show elevated CRP, thrombocytosis and hypoalbuminemia (<3.5 g/dl): CRP is an important predicting index of therapeutic response to corticosteroid therapy and subsequently need for colectomy. Abdominal radiography is useful to monitor colon diameter and the possible evolution in toxic megacolon. Faeces examination for the presence of toxins A and B for *C. difficile* and rectosigmoidoscopy with biopsy to investigate cytomegalovirus is always indicated.

Patients with acute severe colitis have to be admitted to an intensive care unit. Hydration and correction of hydroelectrolyte disorders and anaemia need to be started as soon as possible, and a wide-spectrum antibiotic regimen would always be used. Thromboembolic prophylaxis has to be started because thromboembolic phenomena are important causes of morbidity and mortality in IBD patients. Combinations of clinical data (frequency of evacuations, diarrhoea, rectal bleeding, abdominal pain), laboratory results (Hb, Ht, CRP, albumin, ESR) and radiological findings (progressive colon dilatation) are predictors of colectomy.

The absence of response after 48–72 h of intravenous corticosteroid therapy is an indication to start rescue therapy with cyclosporine, infliximab or tacrolimus. Surgical treatment is required in case of clinical worsening or absence of improvement 5–7 days after medical therapy. Profuse bleeding, perforation or toxic megacolon requires emergency surgery.

16.8.2 Toxic Megacolon

Toxic megacolon refers to states of acute abdominal pain and distension with radiological finding of dilated colon of >6 cm. This serious condition may occur in approximately 15% of UC patients, usually in the presence of acute severe or fulminating colitis and in cases of extensive colitis (macroscopic disease proximal to the splenic angle). The toxiemic state results from diminished motility, colon dilatation and faecal ectasia with bacterial translocation. Abdominal X-ray reveals colon dilatation, oedema of the intestinal wall and loss of haustration. Abdominal CT scan may reveal abdominal complications such as cancer, free fluid in the peritoneal cavity and pneumoperitoneum.

Support measures are the same as in acute severe colitis. A nasogastric probe needs to be positioned. If no improvement occurs after 24–48 h or a perforation occurs, surgery is required. The mortality rate is of the order of 1–8% without perforation but reaches 40–50% when perforation and subsequent peritonitis occurs.

16.8.3 Cancer in UC

Patients with UC have a higher risk of developing colorectal cancer (CRC) than the general population. The cumulative risk reaches 7.5–18.4% at 30 years from onset of the disease. Risk factors are early and late onset of UC, family history of CRC, pseudopolyps, primary sclerosing cholangitis, male sex and longer duration of extensive disease with pancolitis. The pathogenesis of CRC in UC follows the sequence dysplasia to carcinoma.

Colonoscopy allows for early detection of cancer or premalignant lesions. Current guidelines recommend a screening colonoscopy 6–8 years after beginning of symptoms in order to assess the individual risk profile. Endoscopic surveillance is not necessary when disease activity is limited to the rectum without previous or current endoscopic or microscopic inflammation proximal to the rectum. Surveillance colonoscopy intervals are: every 1–2 years (high-risk) or every 3–4 years (low-risk) from the eighth year after the first manifestation of the disease.

16.9 Type of Surgery

Despite remarkable advances made in the medical treatment of UC, the rates of colectomy have not significantly changed. The spread of laparoscopic surgery both in elective and emergency settings allows a reduction in postoperative pain, time to stoma function and overall hospital stay. Laparoscopic approach is equally safe and feasible in comparison to the open approach.

Surgical management of UC involves the performance of a total colectomy with an optional ileo-anal pouch anastomosis (IPAA) in two or three stages. In a three-stage approach:

- The initial operation is a total colectomy with creation of an end ileostomy.
- The second stage of the procedure involves pouch construction with diverting ileostomy.
- The third stage involves takedown of the diverting ileostomy and re-establishment of intestinal continuity.

16.9.1 Colectomy

Patients are referred for colectomy after multiple attempts at medical salvage or in emergency for acute severe colitis or toxic megacolon. These patients are often malnourished and anaemic after prolonged steroid therapy and have an increased rate of postoperative complications. During this operation the surgeon removes the colon leaving in the rectum. Faecal stream is diverted with the creation of an end ileostomy.

Total colectomy with end ileostomy as the first stage allows for immediate faecal diversion and avoids the danger of a pelvic dissection or anastomosis in critically ill patients.

16.9.2 Restorative Proctectomy

Restorative proctectomy (RP) with ileal pouch-anal anastomosis is the standard procedure for most UC patients. It removes the diseased bowel and provides definitive surgical care while preserving adequate functional outcomes. The procedure involves identification of the rectal stump and its full mobilization with subsequent proctectomy. Then the pouch can be constructed. Pouch is a reservoir of terminal ileum that acts as a neorectum to optimize function. After pouch construction, an anastomosis is performed between the terminal ileum and the anal stump. There are several pouch designs, but the J-pouch is the most popular type because of its relatively simple construction and better functional outcomes than others. The IPAA may be stapled or handsewn, but stapled anastomoses have reported better long-term results and less complications. In 5% of patients, the rectum is not diseased, so total colectomy with end ileostomy remains the first step, and an ileorectal anastomosis may be a surgical alternative in selected cases.

RP with IPAA is an elective operation that has to be reserved for UC patients in good clinical conditions, well-nourished, off steroids and not in acute flare. For this reason, time interval between total colectomy and restorative proctectomy is about 6 months. Diverting ileostomy reduces the risk of anastomotic leakage and pelvic sepsis. Stoma closure may be performed about 3 months after pouch construction after check of anastomotic patency and integrity with water-soluble contrast enema of the pouch.

Pouch construction is not mandatory for all patients, and many choose to forgo the pouch with equivalent improvement in quality of life related to the control of disease symptoms.

16.10 Management of Complications

Postoperative complications include leak of rectal stump, anastomotic leak, stricture, fistulae, bowel obstruction, pelvic sepsis and pouchitis. The rate of postoperative complications is higher in patients who undergo surgery after receiving high-dose steroids or infliximab or who are malnourished. Also, longer duration of medical therapy with delay of surgery is a risk factor for major complication: mortality rates 3 years after

elective colectomy (3.7%) are significantly lower than after admission without surgery (13.6%) or with emergency surgery (13.2%) in patients with acute severe UC. Major complications, especially in septic conditions, adversely affect functional outcomes and quality of life.

Pelvic sepsis includes ileo-anal anastomotic leakage, pouch leakage, peri-pouch abscess formation and pouch perianal fistula, and clinical manifestations are fever and abdominal and pelvic pain. Pelvic sepsis occurs in up to 10% of patients undergo IPAA and is diagnosed by contrast enema examination, CT scan and endoscopy. The aim of treatment is to control the sepsis with antibiotic therapy, US- or TC-guided percutaneous drainage or surgical drainage. In patients who required surgery, the treatment is usually combined with the creation of a diverting ileostomy. If management of the pelvic sepsis fails, there is a high rate of pouch failure.

Pouch-specific complications include pouchitis, stricture, fistula, obstruction and change of diagnosis to Crohn's disease. Long-term consequences include frequent stooling requiring antidiarrheal medication (44%) and difficulty conceiving (25% in female patients).

Pouchitis is characterized by inflammation confined to the ileal pouch, and its symptoms are increased bowel movements, abdominal cramps, mucous and bloody discharge and fever. The diagnosis requires endoscopy of the pouch that shows inflammation with similar features to UC. Antibiotic therapy is the first line of treatment for acute pouchitis. Unfortunately, some patients do not respond to medical therapy, requiring a diverting ileostomy or a pouch resection with permanent ileostomy.

16.11 Conclusion: IBD Nursing Perspective

The long-term course of IBD is characterized by symptomatic flare-ups and intermittent periods of remission, with many patients that develop a chronic perpetual activity and debilitating complications.

IBD nurse is the first point of contact for patients. IBD nurses play a wide range of roles to support patients and healthcare providers: they give advice, support and education for patients and their families, discuss living problems related to disease and help the patients to understand medical and surgical therapy. Furthermore, several studies have reported better patient outcomes when a dedicated IBD nurse is involved in patient care, including fewer hospital admissions, reduced length of hospital stay and improvement in health-related quality of life (Kemp et al. 2013; Nightingale et al. 2000; Leach et al. 2014). IBD nurses should receive appropriate training according IBD guidelines. Well-trained IBD nurses can manage all the complex situations that IBD patients live and help them to resolve problems, improving quality of life; for these reasons IBD nurse should be a part of the standard of care for patients with IBD.

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Short Bowel Syndrome

17

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Abstract

Short bowel syndrome (SBS) is a rare clinical condition which often results in chronic intestinal failure (CIF) due to surgical resection of parts of the gastrointestinal tract. The surgery may be necessitated by severe complicated inflammatory bowel disease, mesenteric infarction, mesenteric thrombosis, or abdominal trauma. In general, SBS patients present with heterogeneous postsurgical small and/or large bowel anatomy resulting in decreased absorptive surface area and compromised absorptive function. Oral autonomy may be ultimately acquired in some but not in all patients. In particular, irreversible CIF is associated with deficient calorie, nutrient, and fluid absorption and often requires permanent or intermittent parenteral nutrition for maintaining homeostasis of metabolism and hydration status. Handling parenteral nutrition requires individual metabolic consideration and eventually adjustment, vivid monitoring of fluid and electrolyte as well nutritional status and accurate care and hygiene of the central venous catheter access. Long-term complications of CIF and SBS may comprise macro- or micronutrient and/or fluid deficiency, renal impairment, endocarditis, and/or intestinal failure-associated liver disease (IFALD). Intestinal transplantation and a glucagon-like peptide-2 analogue (teduglutide) have emerged as additional successful therapeutic options for patients with complicated CIF.

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Abbreviations

BW Bodyweight
CD Crohn's disease
CIF Chronic intestinal failure
CT Computed tomography
EN Enteral nutrition
ESPEN European Society for Clinical Nutrition and Metabolism
GLP-2 Glucagon-like peptide-2
HPN Home parenteral nutrition

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i.m. Intramuscularly
i.v. Intravenously
IF Intestinal failure
IVF Intravenous fluid support
MRI Magnetic resonance imaging
PN Parenteral nutrition
PPN Partial parenteral nutrition
PS Parenteral support
s.c. Subcutaneously
SBS Short bowel syndrome
TPN Total parenteral nutrition

17.1 Introduction

Short bowel syndrome (SBS) is a complex and rare clinical condition which is the result of a reduced anatomical or functional intestinal surface area caused by different underlying diseases, such as mesenteric ischemia, inflammatory bowel diseases, malignancies, or postsurgical complications (Pironi et al. 2016). SBS is clinically characterized predominantly by diarrhea and malabsorption, which may lead to malnutrition, dehydration, and weight loss. In patients with inflammatory bowel disease, SBS is usually the result of multiple resections due to recurrent Crohn's disease (CD) or of a single extensive surgical resection due to failure to respond to medical therapy in some very rare cases of ulcerative colitis. Furthermore, intestinal fistula, a common complication of CD, may result in functional SBS with malabsorption of food and fluids in patients with intact bowel length but reduced functional small bowel surface area for absorption. Both, the anatomic and functional SBS are (besides mechanical obstruction, extensive mucosal disease, or intestinal dysmotility) major conditions of the superordinate condition of chronic intestinal failure (CIF). CIF is present, if gut function is below the minimum necessary for the absorption of macronutrients and/or water and electrolytes via oral intake. As a result intravenous parenteral support (PS) is required to maintain health and/or growth. Compared to the course of CD, ulcerative colitis is much less commonly associated with intestinal failure because the small intestine is uninvolved. If the impaired gut function does not require PS, the clinical situation is called intestinal insufficiency (Pironi et al. 2016; Harrison et al. 2014).

17.2 Pathophysiology

The severity of symptoms and onset of CIF are dependent on remaining bowel length, condition of present bowel parts, and resected bowel regions, all of which are in fact surrogates of small and large intestinal surface area.

The postoperative anatomy of the gastrointestinal tract is the main characteristic of SBS pathophysiology and determines the absorptive capacity. While functional SBS (due to fistulae, diseased mucosa as in extensive CD, celiac disease, or severe dysmotility) is very different in each individual case and frequently temporary, SBS resulting from resection is a terminal anatomical state and can be classified into three categories depending on the bowel remnants (for illustration see Fig. 17.1):

- End enterostomy with no colon in continuity (type 1)
- Jejunocolic anastomosis with part of the colon in continuity (type 2)
- Jejunoileocolic anastomosis with or without ileo-cecal valve and the entire colon or part of it in continuity (type 3) (Messing et al. 1999)

After substantial resection of the small intestine, the remaining gut undergoes three functional phases of intestinal rehabilitation (see Fig. 17.2):

- Phase 1 is an acute and short-term condition of *hypersecretion* occurring in the postoperative setting with limited absorption of nutrients and more pronouncedly fluids, encompassed by high stool volumes and even nocturnal (secretory-type) diarrhea. Cave: during this phase oral/enteral feeding should be initiated, but if transit time in the remaining intestine is too fast, it is associated with aggravated osmotic diarrhea.
- Phase 2 is a prolonged subacute condition of progressive intestinal *adaptation* following the hypersecretory phase 1 (usually 48 h to 2 years after surgery, clinically visible at the

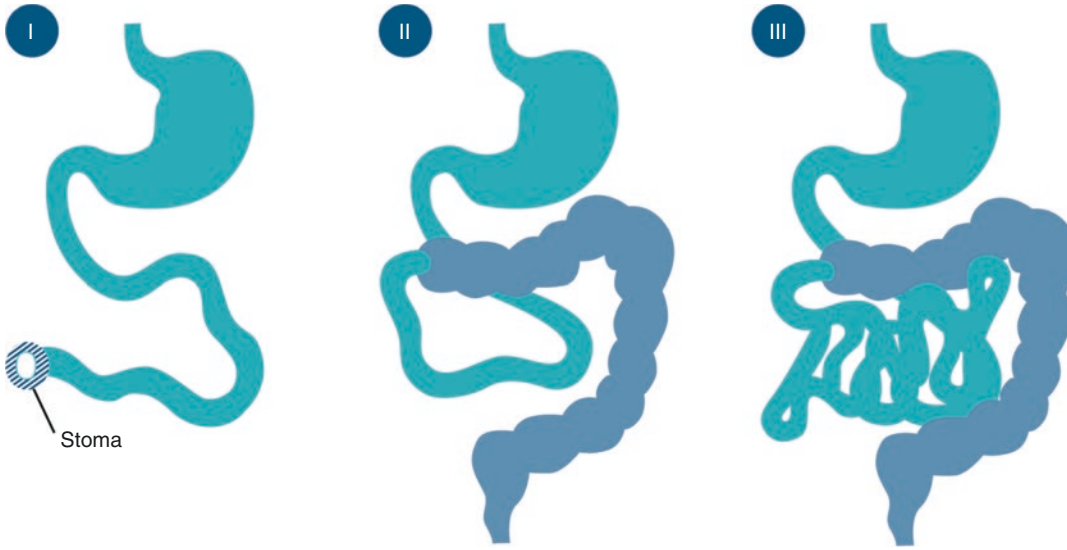

Fig. 17.1 Anatomical short bowel syndrome types, according to Messing et al. (1999)

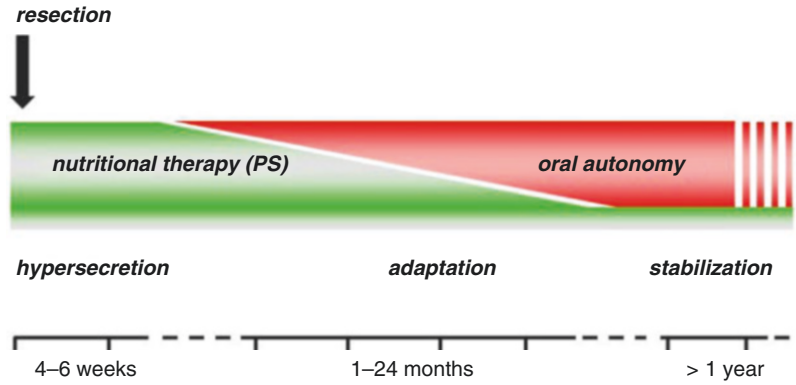

Fig. 17.2 Phases of intestinal rehabilitation in postoperative SBS patients

earliest after 4–8 weeks), which is characterized by reduction of intestinal fluid losses (characterized by reduced stool frequency and increased consistency) due to increasing absorption of nutrients and fluids. During this adaption phase, diarrhea is still present, but as the secretory component of diarrhea diminishes continuously, the osmotic component is more apparent (during the course of a day and with continuous oral intake, the stool frequency is rising, and consistency liquefies).

– Phase 3 is characterized by the maximal possible adaptation of the residual intestine and called *stabilization* phase. The onset of intestinal stabilization is different in each individual case. It follows the adaption phase and can even occur in some rare cases beyond the 2 years post surgery (Tappenden 2014). Clinically, stool characteristics clearly have improved by then. Often, due to the structural (hypertrophy of the intestinal villi with increase of the diameter and villus height) and functional intestinal adaption, the intestine becomes more efficient in nutrient and fluid absorption resulting in complete weaning or at least partial reduction of parenteral support (Pape et al. 2013; Sundaram et al. 2002).

17.3 Diagnostics

For successful management of SBS, it is important (1) to characterize the extent of malassimilation, (2) to identify specific nutrient deficiencies

and characterize the nutritional status and predominant complications, and (3) to quantify residual bowel length. More precisely, the following characteristics can help to manage and monitor SBS patients (Pape et al. 2013; Parrish 2005).

(a) Nutritional status: Body weight, body mass index BMI, body composition measurements such as bioelectrical impedance analysis
(b) Urine and stool analysis: Urine volume per 24 h, urinary sodium and potassium excretion, stool weight, or volume per 24 h
(c) Blood analysis (see Table 17.1)
(d) Anatomical information: Surgical reports, small bowel follow through or enteroclysis (SBFT), endoscopy
(e) Functional information: intestinal transit time
(f) Additional intakes: current medications (including dosing, timing, and route of delivery), detailed enteral, i.v. and/or PN regimens (including infusion time and volume)

17.4 Management

17.4.1 Medical Treatment

Several drugs can be useful in the treatment of SBS depending on the amount and on the anatomy of small bowel remnant, the severity of symptoms, and the intestinal adaptation of the remaining bowel over time (Bechtold et al. 2014; Pape et al. 2013; Matarese and Steiger 2006).

17.4.1.1 Anti-diarrheal and Anti-motility Treatment

Loperamide and Narcotic Agents (Tincture of Opium and Codeine)

Anti-diarrheal agents such a *loperamide*, *tincture of opium (1%)*, *or codein* slow down the intestinal transit via their actions on opiate receptors. This medication can be used both in the early and in the stabilization phase after intestinal resection.

Octreotide

Subcutaneously applied somatostatin analogue *octreotide* increases the absorption of water and salts as well as may reduce diarrhea by prolonging intestinal transit time. Because of the risk of unfavorable effects on nutrient absorption, *octreotide* should only be considered during the hypersecretory phase in patients with pronounced secretory diarrhea.

Clonidine

Clonidine is a medication used for treatment of difficult-to-treat hypertension. The transdermal and subcutaneous administration of clonidine in patients with SBS is associated with a decrease in both gastric secretion and intestinal motility; however, surveillance for cardiac side effects (e.g., hypotension, substantial bradycardia) is essential.

Table 17.1 Blood parameters to be monitored regularly (modified from Hartl et al. 2009)

	Short-term control						Long-term control			
Parameter	week 0	week 1	week 2	week 4	week 6	week 8	month 3	month 6	month 9	annually
Glucose, sodium, potassium, calcium, magnesium, phosphate, CRP, creatinine, urea	+	+	+	+	+	+	+	+	+	+
Venous blood gas analysis, AST, ALT, GGT, AP, triglyceride	+		+		+		+	+	+	+
Protein, albumin, blood count	+				+		+	+	+	+
Bilirubin, amylase	+							+	+	+
Uric acid, INR, vitamin K, folate, vitamin B12, vitamin D	+							+		+
Ferritin, zinc, copper, selenium, manganese				+				+		+
Vitamin A, vitamin E, vitamin B6, parathyroid hormone										+

17.4.1.2 Inhibitors of Gastric Acid Secretion

Treatment of Gastric Hypersecretion and Hyperacidity

After the resection of ileum and proximal colon, the gastrointestinal-hormone mediated inhibitory feedback regulation of gastrin is diminished leading to unphysiologically high gastric acid secretion. Proton pump inhibitors (PPI) such as *omeprazole or histamine receptor antagonists such as ranitidine* can be used to regulate the excessive production of gastric acid and volume and thereby alleviate discomfort in the esophagus, stomach, and intestines as well as reduce fluid losses caused by hypersecretion of gastric acid.

17.4.1.3 Bile Acid-Binding Agents

Treatment of Cholerheic/Bile Salt Diarrhea

Bile salt-binding agents such a *colestyramine* work by binding excess bile salts. In patients with extensive ileal resections and colon in continuity, cholerheic diarrhea can be treated with *colestyramine* or *colesevelam.* Because of their binding properties, *colestyramine* or *colesevelam* can interfere with absorption of other drugs; therefore it is recommended to take other medicines at least 1 h prior to or 2 h after taking *colestyramine/colesevelam*.

17.4.1.4 Treatment of Short Bowel Syndrome Associated Malabsorption

Pancreatic enzyme replacement therapy optimizes the timely availability of digestive enzymes in the proximal gastrointestinal tract and thereby increases protein and fat absorption after small intestinal resection. The (exogenous) supplementation of pancreatic enzymes can alleviate digestion of complex nutrients.

17.4.1.5 Treatment with Glucagon-Like Peptide-2 Analogues

Glucagon-like peptide-2 (GLP-2) is an endogenous meal-stimulated hormone, released from endocrine L-cells of lower parts of the small intestine and proximal colon, which has protrophic effects to the intestinal mucosa. Subcutaneously applied teduglutide, a glucagon-like peptide-2 analogue, was shown to increase for instance villus height and crypt depth in SBS patients (Jeppesen et al. 2005). Clinical trials showed that treatment with teduglutide was effective to reduce volume and number of days of parenteral support (Jeppesen et al. 2012; Schwartz et al. 2016; Carter et al. 2017; Iyer et al. 2016). These results lead to approval of teduglutide for enhancing intestinal adaption in PS-dependent SBS patients with the aim to gain infusion-free days. For practice purposes, it is useful to consider that during the initial phase of teduglutide treatment, gastrointestinal side effects like cramps, flatulence, and enlargement of stomal nipple (if present) can occur and represent teduglutide's specific effects on mucosal hypertrophy as well as gastrointestinal motility (Pape et al. 2016). Regular monitoring is crucial to detect and manage side effects such as the aforementioned gastrointestinal symptoms, volume overload (peripheral edema, increased blood pressure, transient headaches), or enhanced drug absorption.

17.4.2 Nutritional Support in Short Bowel Syndrome

Thorough nutritional management is an important factor in achieving the best possible outcome in SBS patients. The goals of nutrition support are to provide sufficient calories and nutrients and to minimize symptoms to meet a patient's needs. If oral nutrition does not supply enough nutrients, parenteral and/or enteral nutrition should be initiated.

17.4.2.1 Parenteral Nutrition

The extent of parenteral support (PS) is dependent on the progress of intestinal rehabilitation (see Fig. 17.2). If nutrition is delivered exclusively i.v., it is called *total parenteral nutrition* (TPN). TPN usually will be initiated within 24 or 48 h after resection, after the patient's pulmonary and cardiovascular functions have stabilized, while i.v. fluids are continuously administered as required. If PN is additive to oral nutrition, it is called *partial parenteral nutrition* (PPN). The

oral contribution should always be optimized in order to minimize PN requirements. Both, TPN and PPN, need to cover resting energy expenditure and physical activity. PN overfeeding should be avoided to prevent hyperalimentation and consecutive intestinal failure-associated liver disease (IFALD).

Cave: as much as necessary and as little as possible.

Furthermore, the anatomical SBS type also determines the nutritional requirements. To give a short overview, the nutritional support can be planned as follows (see Table 17.2):

In *standard parenteral nutrition solutions*, the amount of electrolytes is based on normal requirements and needs to be supplemented depending on the clinical situation; adjustment according to serum electrolyte values is frequently mandatory on initiation of PN until laboratory and clinical stabilization. Patients with complex electrolyte or other metabolic imbalances such as anabolic conditions may not be sufficiently supplemented with standard parenteral nutrition solutions and thus need *individualized parenteral nutrition solutions* (i.e., so-called compounding). In SBS patients low blood levels of sodium, potassium, and magnesium are common, and PS should be adjusted based on the clinical situation, stoma losses, and renal function (Staun et al. 2009).

Standard prescribing ranges for patients, who are exclusively on TPN, are as follows (comorbidities require additional considerations) (see Table 17.3).

Accurate fluid and electrolyte replacement therapy (30–40 ml/kg/d plus intestinal and renal losses) are indispensable to reduce life-threatening dehydration and electrolyte derailment (see Table 17.4) (Messing and Joly 2006).

Intestinal adaption phase-specific considerations:

- Phase 1 (acute/hypersecretion phase): Clinical manifestation of this phase includes poor absorption of electrolytes, proteins, fats, carbohydrates, trace elements, vitamins, and water (ostomy outputs may exceed 5 L/d). In such situations feeding is accomplished through i.v. nutrient supplementation via a central venous catheter. This is surgically inserted into a large vein—typically in the chest, the arms, or the neck.
- Phase 2 (adaptation phase): During this period most of the adaptive potential of the remaining

Table 17.2 Nutritional management of short bowel syndrome

	Categories depending on the anatomy of the bowel remnant		
	Type I	Type II	Type III
Phase I acute phase	Early modest oral nutrition TPN IVF	Moderate oral nutrition PPN or TPN IVF	Complete oral nutrition PPN or TPN IVF
Phase II adaptation phase	↑[a] Oral nutrition ↔ TPN ↔ IVF	↑[a] Oral nutrition ↔ PPN ↓ TPN ↓↓ IVF	↑↑[a] Oral nutrition ↓ PPN ↓↓ TPN ↓↓ IVF
Phase III stabilization phase	↑ Oral nutrition ↔ (↓) TPN ↔ (↓) IVF	↑↑ Oral nutrition ↓ PPN ↓↓ TPN ↓↓↓ IVF	↑↑↑ Oral nutrition ↓↓ PPN ↓↓↓ TPN ↓↓↓ IVF

[a]Arrows referring to phase I: ↑–↑↑↑ slightly to intensely increased; ↔ unchanged, ↓–↓↓↓ slightly to intensely decreased; *PPN* partial parenteral nutrition, *TPN* total parenteral nutrition, *IVF* intravenous fluid support

Table 17.3 The composition of total parenteral nutrition for short bowel syndrome patients (reference values)

	Recommendations	Literature
Caloric requirement	20–35 kcal/kg BW	Staun et al. (2009)
Protein	1.0–1.5 g/kg BW	Staun et al. (2009)
Carbohydrates	40–60% of the nonprotein kcals	Pironi et al. (2016), Olveira et al. (2012)
Fat	60–40% of the nonprotein kcals	Pironi et al. (2016), Olveira et al. (2012)
Vitamins, minerals, and trace elements	Should be added to the parenteral nutrition to restore and maintain their normal blood concentrations	Staun et al. (2009), Olveira et al. (2012)

BW body weight, *SBS* short bowel syndrome

Table 17.4 Nutrition-related complication of short bowel syndrome

Cause (global)	Complication	Cause (specific)	Prevention/treatment	Literature
Macronutrient deficiency (undernourishment)/ hyperalimentation	Cachexia	Protein, carbohydrate, and/or lipid deficiency	Parenteral nutrition (PN), oral supplementation with drinking formulas	Pironi et al. (2016)
	Refeeding syndrome results in electrolyte derailment of phosphate (and magnesium) may result in cardiac failure	If severely undernourished: too fast and too many nutrients (shift from fat to glucose metabolism)	Slow introduction of nutrients, phosphate monitoring, and supplementation	Terlevich et al. (2003), Zeki et al. (2011)
	Edema	Protein/albumin deficiency	Protein supplementation	Whicher and Spence (1987)
	Intestinal failure-associated liver disease (IFALD)	Multifactorial condition: sepsis, intestinal anatomy, oral/enteral nutrition, PN infusion modality, nutrient deficiency or excess. May also be caused by inappropriate hyperalimentation	Not well understood. Optimization of PN regarding glucose and lipid content (use of 4th-generation lipids), wean of PN if possible	Pironi et al. (2016)

(continued)

Table 17.4 (continued)

Cause (global)	Complication	Cause (specific)	Prevention/treatment	Literature
Micronutrient deficiency/ electrolyte derailment (malnutrition)	Macrocytic anemia	Vitamin B12 or folate deficiency	Vitamin B12 has to be supplemented s.c. especially, if terminal ileum is resected	Duerksen et al. (2006)
	Mucocutaneous bleeding and/or osteopenia	Vitamin K deficiency	Vitamin K has to be supplemented especially, if upper jejunum is resected Cave: some combined vitamin preparations do not contain vitamin K	Duggan et al. (2004)
	Warfarin resistance	Exogenous vitamin K	Reduction of vitamin K supplementation	Ward (2010)
	Osteoporosis	Vitamin D + calcium deficiency	i.v. supplementation if PS is required, otherwise oral might be sufficient	Ellegard et al. (2013), Thomson and Duerksen (2011), Pironi et al. (2016)
	Iron deficiency anemia	Iron deficiency	i.v. supplementation	Khaodhiar et al. (2002), Pironi et al. (2016)
	Zinc deficiency: diverse; zinc is needed for wound healing, skin/nails, immune system, growth, and others	Zinc deficiency	Zinc has to be supplemented additionally to trace element supplementation, if diarrhea and stoma output is high	Jeejeebhoy (2009), Pironi et al. 2016
	Secondary hyperaldosteronism	Volume depletion	i.v. supplementation	Ladefoged and Olgaard (1985)
	Tetany, tremor, and muscle fasciculation, among others	Magnesium deficiency due to high stoma/enteral output	Supplementation especially if distal ileum and colon are resected	Hardwick et al. (1991)
	Cardiac dysrhythmias, fatigue, muscle weakness, and tingling	Hypokalemia	Oral or i.v. potassium	Pironi et al. (2016)
	Cardiac dysrhythmias	Hyperkalemia	Hyperkalemia treatment depends on the degree of elevation and the rapidity of the elevation. This may include i.v. insulin, i.v. fluids, a cation exchange resin, and hemodialysis, as well as discontinuation of the cause for the elevation	Pironi et al. (2016)
	Oxalate kidney stones	Oxalate rich foods	Reduced amounts or avoidance of oxalate rich foods + simultaneously eating of calcium-rich foods	Pironi et al. (2016)
	Metabolic acidosis	Hydrogen ion delivery to the body fluids, excess bicarbonate loss, or diminished hydrogen ion excretion	Bicarbonate substitution Acetate buffering of PN	Kushner (1986)
Fluid deficiency	Kidney failure	Enteral fluid malabsorption and thus loss and electrolyte imbalance	(Increase of) parenteral volume and physiological electrolyte balance	Pironi et al. (2016)

intestine will be realized. Adaptive changes also occur in the stomach and colon. This phase is characterized by stabilization of fluid and electrolyte levels, weight change, and in some cases partial reduction of PS.
– Phase 3 (stabilization phase): At this point of maximal absorptive capacity, the patient is either dependent on supplementation or complete nutritional support for life (mostly if the total amount of small intestine remaining less than 100 cm), or the bowel has adapted to such an extent that sufficient nutritional supply can be achieved entirely by oral food intake. Cave: Monitoring and if necessary substitution of micronutrients are essential to prevent long-term complications.

A functional retrospective classification has been suggested for categorizing CIF by guidelines (Pironi et al. 2016); however, since this system reflects on the functional outcome (retrospective analysis), it is not well suitable for (prospective) management decisions during early phases of intestinal adaption.

17.4.2.2 Enteral Nutrition

Because luminal nutrition is essential for adaptation of intestinal mucosal epithelia, it should be initiated as early as possible. Early tube feedings with high viscosity enteral diets may help to reduce duration of TPN therapy if the patient is not able to eat independently (Klein 2002) but should be the exemption from the rule. *Enteral nutrition* (EN) can be administered through different types of tubes. In most cases, this special diet must be given through a nasogastric tube leading down to the stomach or bowel. Other kinds of tubes (gastrostomy or jejunostomy tubes) should generally not be used because of side effects of EN including increased gastrointestinal fluid losses due to osmotic diarrhea (Pironi et al. 2016). Therefore, in almost all cases, EN will not suffice for adequate nutrition of SBS patients.

17.4.2.3 Oral Nutrition

Certain factors affect the absorption of nutrients in patients with SBS and are closely related to the causes for CIF (extent and site of resection, the presence or absence of terminal ileum, the resection of ileocecal valve, the capacity of the remaining bowel to adapt, and the disease in the remaining gastrointestinal tract). Working with registered nutritional support specialists (registered dietitian, nutritionists, and physicians) can help to create an effective dietary plan according to individualized patient's needs and nutritional requirements and should be tailored according to current dietary guidelines for this specific patient group (Lochs et al. 2006).

17.4.2.4 Dietary Consultation of Short Bowel Syndrome Patients

There is no single specific diet for patients with SBS. However, it is possible to reduce symptoms with the following recommendations:

– Small, solid, and frequent meals
– Five to six small meals per day should be offered to patients to meet their caloric and nutrient requirement.
– Limited intake of fluid during the meals
– Patients should drink either half an hour before or 1 h after a meal. Large amounts of fluid intake can decrease transit time leading to diarrhea. Intake of very low osmolality drinks such a water, coffee, and tea (particularly with little or no sodium and sugar content) can also result in diarrhea.
– Patients with SBS should eat meals that are:
– High in protein: eggs, tofu, fish, meat, poultry
– High in low-fiber, complex carbohydrates: pasta, white bread, rice, cereals
– Low in concentrated sweets, thus avoid, e.g., honey, sugar, fruit juices, soft drinks, because oral diets with simple sugars contribute to fluid loss into the intestine.
– Low intake of fat
– Dietary fat is largely absorbed in the small intestine. The absence of terminal ileum affects the absorption of fats and bile acids. Especially for SBS patients experiencing steatorrhea a low fat diet with moderate intake of foods such margarine, butter, oils, mayonnaise, high-fat meat and full-fat cheese are recommended.

- Middle chain triglycerides (MCT) supplementation
- MCT can be absorbed from the gastrointestinal tract without further cleavage by enzymes and thus are easily gained energy supply.
- Intake of "constipating food"
- Foods that can help to normalize evacuation time are also recommended: bananas, rice, oatmeal, blueberries, smashed apples, etc.
- Low-oxalate diet
- A diet low in oxalates is considered to reduce susceptibility to form oxalate kidney stones for patients who have had a terminal ileum resection with their colon in continuity. Foods high in oxalate such a tea, cola, chocolate, spinach, strawberries, rhubarb, and nuts should be avoided.
- Vitamins and minerals
- It is important to maintain an adequate intake of fat-soluble vitamins, vitamin A, D, E, K if fat malabsorption is occurring in water-soluble vitamins, multivitamins, vitamin B12 if terminal ileum is removed mineral supplements, and trace elements, calcium, magnesium, and iron supplements (Lochs et al. 2006) (see also Table 17.4).

17.4.3 Surgical Management

17.4.3.1 Intestinal Rehabilitation with Surgery

The improvement of intestinal function via non-transplant intestinal surgery comprises the following (Buchman et al. 2003; Geltzeiler et al. 2014):

- The surgical reconnection of disconnected bowel parts, which were excluded from digestion and absorption (e.g., restoration of intestinal continuity of small intestine with colon, also called reanastomosis)
- Fistula surgery (the rate of recurrence of fistula is very high especially in perianal CD without medical treatment)
- Intestinal lengthening surgery (only performed in children)

However, gut-sparing surgery particularly in CD patients with strictures including surgical stricturoplasty instead of respective strategies may help in avoiding SBS in a given patient, thus preventing intestinal failure.

17.4.3.2 Intestinal Transplantation in SBS

SBS is the leading indication for intestinal transplantation and has shown remarkable progress during the last decades. CD is the second most frequent cause of SBS patients who are listed for intestinal transplantation, but still (total) parenteral support is fist-line therapy. Intestinal transplantation has 5-year survival rates of 56% and is mainly indicated if long-term complications like intestinal failure-associated liver disease (IFALD), limited intravenous access, or frequent catheter-related sepsis make it a life-saving procedure (Grant et al. 2015).

17.5 Complications of Short Bowel Syndrome and Their Prevention

As mentioned above, CIF in general has its own set of complications mainly caused by diarrhea, high stoma output, or malabsorption, especially if bowel parts are resected which account for absorption of specific nutrients. One also has to be aware that absorption of oral medications may be limited and inconsistent; therefore dosages may have to be adapted or the medication has to be given i.v., i.m., or s.c.

17.5.1 Nutrition-Related Complications

Common nutrition-related complications are summarized in Table 17.4. Specific amounts to be supplemented in deficiency status cannot generally be recommended because severity has to be taken into account in each individual case. If PN is necessary SBS patients often need compounded PN instead of standardized formulas to especially maintain physiological electrolyte levels. Cave: Depending on resected bowel part, different complications are common or rather have to be prevented.

17.5.2 Catheter-Related Complications

17.5.2.1 Catheter-Related Bloodstream Infections

A specific nutrition-related complication in SBS patients who are dependent on parenteral support is the infection of the intravenous catheter or port system, also called catheter-related bloodstream infections (CRBI).

During non-aseptic insertion or maintenance of the catheter exit site or during hub manipulation, the intravascular devices become contaminated on the outer surface or endoluminally. Symptoms of catheter-related bloodstream infections may be spiking fever, especially shortly after hub manipulation, sweating, hypotension, and malaise. Severe complications of catheter-related bloodstream infections comprise endocarditis, septic shock, metastatic lung infection, and septic thrombophlebitis and are potentially lethal (Sitges-Serra and Girvent 1999). Thus, in patients receiving PN, specialized nursing teams should care for intravascular devices who are adequately educated and trained in aseptic care. To give a short overview, the risk of catheter-related bloodstream infections can be reduced by:

- An adequate policy of hand washing/disinfection
- Use of skin antiseptics
- Appropriate dressing of the exit site
- Disinfection of hubs, stopcocks, and needle-free connectors
- Regular change of administration sets

The treatment of catheter-related bloodstream infections depends on signs and location of the infection. It may comprise the attempt to save the device with an antibiotic lock technique or also removal of the intravascular device with concomitant antibiotic therapy (Pittiruti et al. 2009).

The use of lock solutions like, for example, ethanol, antibiotics or taurolidine, has been under discussion (Vassallo et al. 2015). Especially taurolidine seems to be effective in the prevention of CRBI, and further studies are important to establish its use in standard HPN care (Pittiruti et al. 2016; Olthof et al. 2014; Hulshof et al. 2017).

17.5.2.2 Catheter-Related Vascular Thrombosis

Another noninfectious catheter-related complication in long-term PN-dependent SBS patients is catheter-related thrombosis which may lead to pulmonary embolism, loss of venous access, delay in treatment, or post-thrombotic syndrome. Risk factors for development of catheter-related thrombosis comprise patient factors (hypercoagulable states like sepsis, malignancy, inflammation, thrombophillia), the type of catheter, and the location of insertion. The majority (two-thirds) of catheter-related thrombosis cases occur asymptomatically. Clinical symptoms may present self-evidently as arm or neck swelling or discomfort of venous distension, but clinical course can also be atypical in some cases with head discomfort, jaw or shoulder pain, or erythema of limb. Nevertheless, nursing personnel may be confronted most likely with difficulties in infusion or aspiration. Not always catheter-related thrombosis is the cause—mechanical obstruction including malposition, fibrin sheath formation, an intraluminal clot, and mural thrombosis may also cause obstruction. Inspecting the catheter with regard to mechanical obstruction, repositioning of the patient, injecting solutions to clear the occlusion, or thrombolytic treatment may help to restore lumen patency. If procedures are not successful, diagnostic approaches (e.g., with venous duplex scanning) and further treatment (e.g., systemic anticoagulation, line removal) have to be performed (Baskin et al. 2009; Wall et al. 2016).

17.6 Transition Management for Home Parenteral Nutrition

It is essential for CIF patients requiring home parenteral nutrition (HPN) to manage the transition from hospital to home without a gap to ensure constant energy intake. Especially in the early phase of adaption, PN-free days are not

well tolerated. Country-specific regulations have to be taken into consideration.

Transition of former pediatric patients into adult management programs is a hitherto poorly structured process in most countries; however, it will become more relevant in the near future due to more and more patients in the pediatric group surviving CIF through adolescence.

17.7 Final Summary

After extensive intestinal resection, the anatomy of the small bowel remnant determines the extent of malabsorption and consequently the symptoms and profile of future complications.

Especially the initial phase after surgery requires intense nutritional management and often goes along with parenteral support because of limited absorption of nutrients and fluids. Oral autonomy may be ultimately acquired in some but not in all patients.

Decreased absorption of oral drugs may be compensated by other application modes (i.v., s.c., i.m.).

Treatment of common SBS-related symptoms like diarrhea should—besides medical treatment—comprise appropriate counseling for oral nutrition (e.g., limited intake of fluid during the meals) given from a nutritional support specialist. An additional medical option for SBS patients on PS is GLP-2 analogue treatment with the intention to gain infusion-free days or even weaning from PS.

Handling parenteral nutrition requires individual metabolic consideration and eventually adjustment, vivid monitoring of fluid, electrolytes and nutritional status, and accurate care and hygiene of the central venous catheter access.

17.8 Resource Section

ESPEN guidelines on chronic intestinal failure in adults (Pironi et al. 2016)

Pharmacological strategies to enhance adaptation in intestinal failure (Pape et al. 2016)

ESPEN guidelines on Parenteral Nutrition: Home Parenteral Nutrition (HPN) in adult patients (Staun et al. 2009)

The Clinician's Guide to Short Bowel Syndrome (Parrish 2005)

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Complementary Therapies

18

Jost Langhorst

18.1 Introduction

"Complementary and alternative medicine (CAM) is used to described a wide variety of methods, procedures, substances, and medical systems. Complementary medicine is practiced in addition to conventional medicine, whereas alternative medicine is intended to replace standard methods. For this reason, alternative methods are generally rejected by the scientific community."

The Cochrane Collaboration has developed its own definition with the following classification:

1. Natural product-based therapies
2. Whole medical systems
3. Mind-body interventions
4. Energy therapies
5. Manipulative and body-based methods

18.2 Use of Complementary Methods in IBD

Patients may believe that conventional medicine consists of the exclusive use of synthetic drugs. Particularly in the field of immunosuppressants, there is the impression that the steps to therapy will be crude without the possibility of fine-tuning. Complementary therapy offers a variety of therapeutic tools to fill this perceived gap.

In international representative studies, the proportion of IBD patients who report having had personal experience with complementary medicine is between 21 and 60% (Langhorst 2006). The main motives for using naturopathic or complementary medicine treatment methods were:

- Search for the optimal therapy
- A holistic therapeutic approach
- Increased personal involvement and responsibility
- Side effects of conventional therapies
- Lack of success of conventional therapies

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The methods, procedures, and substances of complementary medicine vary strongly from country to country based on experience, availability, cultural circumstances, and medical systems. As the author is practicing in Germany, heading the chair of Naturopathic and Integrative Medicine at the University of Duisburg-Essen, his experience and recommendations are primarily based on the German health systems and its patients. However, most of the recommendations can be extrapolated for the use worldwide.

18.3 Natural Product-Based Therapies

18.3.1 Phytotherapy

The most important form of therapy for IBD from the field of natural product-based therapies is phytotherapy. In Germany, roughly every fourth patient with chronic inflammatory bowel disease reports having had personal experience of the complementary *use of herbal medicines* (Langhorst et al. 2005).

Few or no studies have been done on the use of most phytotherapeutic agents in the complementary treatment of chronic inflammatory bowel diseases. Plants from the field of Chinese medicine are not considered in this chapter.

The use of herbal teas with various herb components plays an important role as a self-help strategy.

At least one clinical study is available for the indication of the following medications in CD or UC.

18.3.2 Phytotherapeutics with First Clinical Data for Ulcerative Colitis

18.3.2.1 Psyllium Seed (Psyllii Semen) (Plantago Ovata)

Psyllium husk powder—fiber—*stabilizing and gelling agent via water retention*.

Contraindicated in cases of known gastrointestinal stenosis; can bind and therewith reduce the effect of prescription medication taken at the same time and therefore should be taken at least 1 h after prescription medication.

Possible *side effects* are flatulence, bloating, and, in rare cases, hypersensitive reactions.

Dosage for maintaining remission in ulcerative colitis: (e.g., Flosa®; Mucofalk®) 1–3 times per day 5 g sachet.

According to the German AWMF (*Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften e.V.* or Association of the Scientific Medical Societies in Germany) guidelines on ulcerative colitis, psyllium seed can also be used in the treatment of ulcerative colitis as a complementary therapy.

18.3.2.2 Myrrh, Chamomile Flower, and Coffee Charcoal (Myrrhinil Intest®)

Myrrh—dried resin extracted from the bark: commiphoric acid; *anti-inflammatory, anti-diarrheal, and antimicrobial effect*; allergic reactions are very rare.

Chamomile flower: dried extract; anti-inflammatory, antimicrobial, and antispasmodic effect.

Coffee charcoal is derived from the green, dried fruit of *Coffea arabica* which are roasted until the outer seed parts are blackened and charred and then ground.

Used in combination: myrrh resin (100 mg), dried chamomile flower extract (70 mg), and coffee charcoal (50 mg); *dosage*: three times per day, four tablets—myrrh tincture for the treatment of oral aphthae or stomatitis, well tolerated.

According to the AWMF guidelines on ulcerative colitis, the combination of myrrh, chamomile flower, and coffee charcoal can be used in the treatment of ulcerative colitis as a complementary therapy.

Authorized for use in Germany as a traditional pharmaceutical drug.

18.3.2.3 European Blueberry (Vaccinium Myrtillus)

Active ingredients: inter alia, rich in anthocyanins; administered, e.g., in the form of cold-pressed juice or dried fruit.

Dosage: 100 ml per day.

No relevant side effects have been observed.

Theoretically, interactions that increase the effect of anticoagulants cannot be ruled out.

To date no recommendation in guidelines; available in Germany as a food/food supplement.

18.3.2.4 Tormentilla (Potentilla Erecta)

Active ingredients: rich in tannins; administered in the form of a tea, tincture, or finished product.

Dosage: average daily dose: 1.5–3 g of finished product: 3 × 2 capsules per day (200 mg standard extract).

Well tolerated (mild dysphagia; heartburn).

No recommendation in guidelines to date.

Available in Germany as a food supplement.

18.3.2.5 Curcuma/Turmeric (Curcumae Longae Rhizoma)

Curcuma root extract.

Dosage: average daily dose: 1.5–3 g drug powder; tincture; 2 × 1 capsule per day (81 mg standard extract) as a finished product.

According to a statement in the AWMF guidelines on ulcerative colitis, there are two studies reporting positive effects of curcuma—one as complementary therapy to aminosalicylate as part of maintenance treatment and one in the treatment of mild to moderate active ulcerative colitis. In Germany, however, curcuma is only available as a food supplement and not as a medicinal product.

18.3.2.6 Indian Echinacea (*Andrographis Paniculata*)

A bitter-tasting annual plant commonly found in large parts of Asia.

Side effects: rarely reported headache, fatigue, allergic reactions, lymph node swelling, painful lymph nodes, nausea, diarrhea, and alterations in taste. Any cases of skin rash or anaphylactic reactions were reported.

In Germany, *Andrographis paniculata* currently does not play a clinical role in IBD indications.

No recommendation in guidelines to date.

18.3.2.7 Wheatgrass Juice (Tritium Aestivum)

Active ingredients: Vitamins and minerals.

No relevant side effects were observed.

No recommendation in guidelines to date.

Not clinically relevant at present.

In the clinical context, psyllium seed, myrrh, chamomile flower, coffee charcoal, and more recently curcuma receive more attention. They can be used for the complementary treatment of diarrhea in an acute flare or for maintenance therapy in patients with side effects from conventional treatment.

High-quality organic blueberry juice can be used complementary for the treatment of diarrhea in an acute flare as self-help strategy.

18.3.3 Phytotherapeutics with First Clinical Data for Crohn's Disease

18.3.3.1 Frankincense (Boswellia Serrata)

Main active ingredient: dried resin extracted from the bark, boswellic acid.

Side effects: good tolerability profile; rare gastrointestinal symptoms, allergic reactions.

Dosage: 3 times per day, 1–2 tablets (400 mg/tablet).

No recommendation in guidelines.

In Germany, preparations are only available as food supplements.

18.3.3.2 Absinthe (Artemisia Absinthium)

Active ingredient: bitter substances including, among others, artemisinin.

Side effects are rare. Gastrointestinal symptoms or lowering of the seizure threshold are known to have occurred when used as a finished product.

No recommendation in guidelines to date.

Administered as a tea (very bitter!).

18.3.3.3 Cannabis

Active ingredients: numerous cannabinoids, esp. 9-tetrahydrocannabinol and cannabidiol. Application via medical vaporizer.

Cannabis is subject to the law on narcotics. In Germany, it has not been authorized for the indication of Crohn's disease.

18.3.4 Fish Oil (n-3 Polyunsaturated Fatty Acids)

Fish oil (n-3 polyunsaturated fatty acids) is thought to have modulating effect on inflammatory mechanisms. N-3 is incorporated into the wall of inflammatory cells and decrease the concentration of arachidonic acid (C20:4, n-6). Arachidonic acid is the key substrate of cyclooxygenase and 5-lipoxygenase enzymes which produce proinflammatory cytokines.

Dosage is not finally clarified.

No recommendation in guidelines.

In the clinical context omega 3 fatty acids might be beneficial in maintaining remission of Crohn's disease.

18.4 Whole Medical Systems

The area "alternative medical systems" includes, among others, anthroposophic medicine, Kampo medicine, and homeopathy, for which no clinical studies for IBD are available to date.

18.4.1 Acupuncture and TCM

Acupuncture has been in use for thousands of years in the treatment of many different diseases. It has proved effective in the treatment of various pain syndromes and gastrointestinal disorders, especially perioperative nausea, chemotherapy, pregnancy, and travel sickness.

According to the AWMF guidelines on ulcerative colitis, acupuncture can be used as a complementary therapy for maintenance of remission in ulcerative colitis.

In the clinical context, acupuncture might be beneficial as complementary therapy to improve the quality of life during an acute flare of IBD in patients open to this therapy.

18.5 Mind-Body Interventions

18.5.1 Mind-Body Medicine/ Regulative Therapy/MBSR

Mind-body medicine is a multimodal therapy combining classical naturopathy with a focus on lifestyle modification and the permanent integration of health-promoting elements from the fields of nutrition, exercise, hydrotherapy, relaxation, and stress management into everyday life promoting self-efficacy.

For the content represented in the individual modules—nutrition, exercise, relaxation methods, and stress reduction—various publications are available. Natural self-help strategies such as herbal teas or poultices using essential oils are of importance.

One goal is to increase patients' ability to cope with stress. An important precondition for this is the promotion of self-competence and the so-called internalized control behavior and self-efficacy, i.e., patients' awareness that they have the ability to actively influence their quality of life, the disease process, and the course of disease.

Recommended stress management therapies include:

- Diaphragmatic breathing
- Meditation
- Autogenic training

- Progressive muscle relaxation
- Yoga
- Qigong
- Mindfulness (mind-body medicine, MBSR)

In the clinical context, meditation and relaxation are helpful to improve quality of life and inflammatory activity in IBD patients with high levels of perceived stress. More recently promising results especially in yoga in UC have been shown. A comprehensive lifestyle modification including mindfulness-based interventions represents a broader approach to impact on quality of life and disease activity.

18.6 Concluding Remarks and Outlook

The various naturopathic and phytotherapeutic approaches provide an important impetus in the area of self-help strategies. Mind-body medicine in particular broadens this spectrum and adds a resources-oriented salutogenic dimension to the multimodal integrative treatment approach.

There should be an open dialogue between IBD patients and physicians about the possibilities and limits of complementary therapies. It is plausible to integrate complementary therapies into a science-based system of medicine. As suggested by the WHO, therapies which are supportive and improve patients' quality of life should be used and valued as part of an integrative concept. In addition, self-help strategies are of high interest in the national self-help organizations. In Germany, the German Crohn's and Colitis Association (*Deutsche M. Crohn/Colitis ulcerosa-Vereinigung e.V.—DCCV*) plays a leading role.

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Suggested Readings

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Part IV

Complications and Comorbidities

Extra-intestinal Manifestations

19

N. Chapelier, I. Dury, and E. Louis

Abstract

Extra-intestinal manifestations (EIM) affect up to 50% of the patients with inflammatory bowel disease. The most classical EIM are spondyloarthritis, skin lesions like erythema nodosum and pyoderma gangrenosum, eye inflammation with episcleritis, scleritis and uveitis, and also primary sclerosing cholangitis. These manifestations will classically present as axial or peripheral arthralgias or arthritis, inflammatory lesions of the skin, a red inflammatory eye or abnormal liver function tests. EIMs may evolve in parallel or independently from the gastrointestinal inflammation. Some of them may require specific management and treatment. More seldom manifestation may also affect most organs of the body and can be the consequence of chronic systemic inflammation or due to shared genetic or environmental predisposing factors.

19.1 Introduction

Patients with inflammatory bowel diseases (IBD) are affected in up to 50% with extra-intestinal manifestations (EIM) (Bernstein et al. 2001). They are important to recognize and identify because they may significantly impact on quality of life, and some of them are associated with severe consequences including the loss or impairment of organ function. EIM also reflect the systemic nature of IBD in some patients and have an influence on the treatment choice. Their pathophysiology is largely unknown. It may involve a shared predisposition to develop abnormal inflammatory reactions at different organ levels. The co-existence of other immune-mediated inflammatory disorders (IMIDs) (like ankylosing spondylitis or psoriasis) in individual patients or in affected families is an argument for a genetic predisposition. As a matter of fact, a large number of shared genetic variants have been described in IMIDs. Beyond that, the mechanism by which an intestinal inflammation may trigger remote inflammation in the joints or the skin, for example, remains unclear, even if tissue antigenicity and immune cross-reaction or recirculation of bacterial fragments have been proposed. The European Crohn's and Colitis Organisation (ECCO) has published the first guideline/consensus paper on this topic (Harbord et al. 2016). The aim of the present chapter is to review the most important EIM (a more extensive list is presented in Table 19.1) according to their clinical picture, as they may present to IBD nurses and gastroenterologists in the outpatient or hospitalization setting.

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Table 19.1 Extra-intestinal manifestations of IBD and their prevalence

Affected organ	Extra-intestinal manifestation	Estimated frequency among IBD patients (wide ranges can be observed depending on the definition)
Joints	Axial arthropathies	5–50% (depending on the definition, from ankylosing spondylitis to asymptomatic sacroiliitis) (Harbord et al. 2016; Salvarani et al. 2001)
	Peripheral arthropathies type 1	5–20% (Harbord et al. 2016; Orchard et al. 1998)
	Peripheral arthropathies type 2	5–20% (Harbord et al. 2016; Orchard et al. 1998)
	Enthesopathies and dactylitis	2–4% (Harbord et al. 2016)
Bone	Osteopenia	40–50% (Harbord et al. 2016; Reinshagen 2008)
	Osteoporosis	5–37% (Harbord et al. 2016; Reinshagen 2008)
Eye	Episcleritis	4–12% (Harbord et al. 2016; Larsen et al. 2010)
	Anterior uveitis	4–5% (Harbord et al. 2016; Larsen et al. 2010)
	Posterior and intermediate uveitis	<1% (Harbord et al. 2016; Mintz et al. 2004)
	Scleritis	<1% (Harbord et al. 2016; Mintz et al. 2004)
Mouth	Mouth and labial swelling, deep ulcers and polyps	Rare (Harbord et al. 2016)
Nose	Metastatic Crohn, aseptic nasal septal abscess	Rare (Harbord et al. 2016)
Ear	Sensorineural hearing loss	Rare (Harbord et al. 2016)
Skin	Erythema nodosum	4.2–7.5% (Harbord et al. 2016; Farhi et al. 2008)
	Pyoderma gangrenosum	0.6–2.1% (Harbord et al. 2016; Farhi et al. 2008)
	Sweet syndrome	Not known
Liver and biliary tract	Primary sclerosing cholangitis	4–5% (Harbord et al. 2016; Karlsen et al. 2010)
	Autoimmune hepatitis	<1% (Harbord et al. 2016; Trivedi and Chapman 2012)
	Granulomatous hepatitis	<1% (Harbord et al. 2016; McCluggage and Sloan 1994)
	Portal vein thrombosis	<1% (Harbord et al. 2016; Hatoum et al. 2005)
	Hepatic abscess	<1% (Harbord et al. 2016; Mir-Madjlessi et al. 1986)
	Drug-induced liver toxicity	1–15% (Harbord et al. 2016; Khokhar and Lewis 2010)
	Hepatic amyloïdosis	<1% (Harbord et al. 2016; Greenstein et al. 1992)
Pancreas	Autoimmune pancreatitis	8–16% (including isolated biological or morphological signs) (Harbord et al. 2016; Heikius et al. 1996)
	Drug-induced pancreatitis	0–4% (depending on the drug used) (Harbord et al. 2016; Bermejo et al. 2008)
	Pancreatitis associated with duodenal CD	Rare (Harbord et al. 2016)
Peripheral and central nervous system	Peripheral neuropathy	0.7–2.4% (Harbord et al. 2016; Gondim et al. 2005)
	Demyelinating disorders	<1% (Harbord et al. 2016; Gupta et al. 2005)
	Cerebral sinus venous thrombosis	Rare (Harbord et al. 2016)
Cardiovascular system	Ischemic cardiac disease	OR: 1.19 (95% CI: 1.08–1.31) (Harbord et al. 2016; Singh et al. 2014; Fumery et al. 2014; Kristensen et al. 2013)
	Cerebrovascular accident	OR: 1.18 (95% CI: 1.09–1.27) (Harbord et al. 2016; Singh et al. 2014; Fumery et al. 2014; Kristensen et al. 2013)
	Mesenteric ischaemia	OR: 3.46 (95% CI: 1.78–6.71) (Harbord et al. 2016; Singh et al. 2014; Fumery et al. 2014)
Pulmonary manifestations	Latent interstitial pulmonary involvement	20–55% (Harbord et al. 2016; Bonniere et al. 1986)
	Drug-induced manifestations	Rare (Harbord et al. 2016)
	Bronchiectasis	<1% (Harbord et al. 2016; Black et al. 2007)
	Airway strictures	Rare (Harbord et al. 2016)
	Granulomatous interstitial lung disease/sarcoïdosis	Rare (Harbord et al. 2016)

Table 19.1 (continued)

Affected organ	Extra-intestinal manifestation	Estimated frequency among IBD patients (wide ranges can be observed depending on the definition)
Urogenital manifestations	Renal insufficiency	2–15% (Harbord et al. 2016; Lewis et al. 2013)
	Secondary amyloïdosis	Rare (Harbord et al. 2016)
	Tubulointerstitial nephritis (including granulomatous)	Rare (Harbord et al. 2016)
	Glomerulonephritis (including IgA)	Rare (Harbord et al. 2016)
	Nephrolithiasis (uric acid, calcium oxalate)	Frequent (Harbord et al. 2016)
	Drug-induced (5ASA, ciclosporin)	0–20% (depending on the drug used) (Harbord et al. 2016; Gisbert et al. 2007)
Coagulopathy	Deep vein thrombosis and pulmonary embolism	OR: 2.2 (95%CI: 1.83–2.65) (Harbord et al. 2016; Yuhara et al. 2013)

19.2 Joint Pain and Swelling

Joint pain (arthralgia) may affect any joint in an IBD patient. Arthralgia represents the most frequent EIM of IBD (Salvarani et al. 2001). These joint pains must be defined according to pain characteristics, joint inflammation, affected joints number, size and locations. A first differentiation must be made between mechanic and inflammatory pains. The first usually reflects osteoarthritis, while the second usually reflects inflammatory process. An inflammatory pain is usually present at rest and is associated with morning stiffness and mild improvement in movement, while mechanic joint pain will increase with movement and charge on the joint. Inflammatory pain may also be associated with joint swelling, which is usually not the case in a mechanical pain. A mechanical pain is most often due to osteoarthritis, whose prevalence is not increased in IBD but which is frequent in the general population and thus also in IBD.

An inflammatory pain may reflect joint extra-intestinal manifestation of IBD. This pathology is part of the spondyloarthritis, also grouping psoriatic arthritis, reactive arthritis and ankylosing spondylitis. The pain may affect either peripheral or axial joints (spine and sacroiliac joints). Peripheral arthropathies associated with IBD may be classified into two subcategories: type 1 affecting a small number of big joints and usually evolving in parallel with the intestinal symptoms and type 2 affecting smaller symmetric joints, most often in the upper limb, and evolving independently from the intestinal symptoms (Orchard et al. 1998). Axial arthropathies range from the asymptomatic of radiographic negative sacroiliitis to the most severe ankylosing spondylitis. Classical ankylosing spondylitis represents a minority of the axial arthropathies encountered in IBD, and they are associated with the HLAB27, while the other axial arthropathies associated with IBD are not associated with this HLA (Orchard et al. 2009). Apart from the mechanical pain discussed here above, the differential diagnosis of these joint pains includes lupus-like arthropathies triggered by anti-TNF treatment (Fornaciari et al. 2001) as well as joint pains due to steroid weaning (Fornaciari et al. 2001) or to purine analogue treatment (Hindorf et al. 2009). Arthralgias during purine treatment usually appear during the first 3 months of treatment, they subside beyond these 3 months and if they persist under azathioprine, a change to mercaptopurine may solve the problem. Of note, an infectious arthritis may also occur in an IBD patient, particularly if treated with immunomodulators of biologic treatments. This will usually present as a monoarthritis with swelling, redness and heat of the joint. The patient may also present fever. This presentation should prompt a rapid referral to a rheumatologist. The joint pain must also be differentiated from muscle pain or from enthesopathy. Muscle pain may also be secondary to some treatment in IBD including again purine analogues, while enthesopathies characterized by a pain upon pressure at the insertion of a tendon to the bone have also been recognized as potential EIM of IBD (Palm et al. 2002). Usually, if a first diagnosis of IBD-related joint problems

may be done by the gastroenterologist and the IBD nurse, the patients with axial arthropathies should be referred to a rheumatologist for diagnosis confirmation and optimal management and treatment. While waiting for the rheumatologist appointment, a treatment with first-level painkillers, like paracetamol or even low-dose tramadol, may be attempted. Peripheral arthropathies will also usually improve with the treatment of the intestinal disease. If insufficient and if non-steroidal anti-inflammatory drugs (NSAIDs) can be tolerated by the patient, short courses of NSAIDs may be beneficial. Prolonged treatment with NSAID is not appropriate as they may favour IBD flares or increase disease activity (Felder et al. 2000). Cox-2 selective NSAIDs may be best tolerated in IBD (El Miedany et al. 2006); however some patients might flare up with their IBD in response to those drugs. Beyond this, salazopyrine may be effective for peripheral arthropathies, while it has only marginal effect on axial arthropathies (Chen et al. 2014). Corticosteroids may be effective in peripheral arthritis but less so in axial arthropathies (Braun et al. 2011). The most effective treatment of persisting peripheral or axial arthropathies is anti-TNF. Their effect has mainly been studied in rheumatologic disorder having similarities with IBD-associated joints inflammation, but data are also available in IBD, including small case series, cohort studies and more recently post hoc analysis of large pivotal controlled trials (Van den Bosch et al. 2000). No data is currently available for vedolizumab. If an effect may be expected in arthropathies which are directly linked to the active intestinal inflammation, an independent effect on the joint problem seems unlikely due to the gut selectivity of this drug. No data is currently available for ustekinumab either, but its well-demonstrated efficacy in psoriatic arthritis may suggest the possibility of an impact on other spondyloarthritis including IBD-related.

Key Points

- Arthropathies are the most frequent EIM.
- Peripheral arthropathies usually evolve in parallel to gastrointestinal manifestations and may respond to their treatment as well as to salazopyrine.
- Axial arthropathies evolve independently from gastrointestinal manifestations, are difficult to treat and may require anti-TNF treatment.

19.3 Skin Lesions

The second most prevalent EIM of IBD is represented by skin lesions (Farhi et al. 2008). These skin lesions are of different types. The most two frequent skin lesions are erythema nodosum (EN) and pyoderma gangrenosum (PG). EN presents as a swollen erythematous or blueish lesions, usually 1–2 cm wide, painful upon pressure and most often localized on the lower limbs. These lesions usually appear in parallel to an IBD flare and may be present with other EIM like peripheral arthritis or inflamed eye. Presentation is usually typical and a biopsy not necessary. Erythema nodosum usually lasts for a few days to a few weeks and resolves with the treatment of the intestinal disease (Trost and McDonnell 2005). If extensive, painful and debilitating, a treatment with systemic corticosteroids will usually improve the situation. For recurring severe flares of EN, immunomodulators and anti-TNF may also be effective.

PG is usually a more severe lesion, frequent on the lower limbs (mainly shins) and on scars, like in the peristomal area (Polcz et al. 2011). It presents as a reddish papule or pustule that will soon be ulcerated giving rise to sometimes deep and large purulent excavation. This is a sterile lesion unless secondarily superinfected. In case of doubt, a biopsy can be performed to differentiate from other diseases like necrotising vasculitis or vascular insufficiency. This lesion may be painful and debilitating particularly in the peristomal area where it will interfere with the stoma equipment. It can appear and evolve independently from the intestinal disease and requires specific treatment. Systemic corticosteroids may have some impact, but in refractory lesions, ciclosporin and anti-TNF are the most effective (Brooklyn et al. 2006).

Other types of lesions may occur more seldom, including Sweet syndrome which is an acute neutrophilic dermatosis. Sweet syndrome presents with red inflammatory nodules or papules on the neck, face and upper limbs (Travis et al. 1997). This may be associated with fever.

The location is thus different from EN and the lesions are usually smaller. The lesions are most often associated with active intestinal disease, and the treatment is similar as for EN.

Skin lesions are also the most frequent side-effects of anti-TNF treatment, so it is important to differentiate these treatment effects from an EIM. Xerosis, psoriasiform lesions and eczematiform lesions have been described (Cleynen and Vermeire 2012). These are usually considered as being the consequence of skin paradoxical inflammation. The psoriasiform lesions are most often localized on the scalp, the umbilicus, nasogenial folds and ear pavilion. Palmoplantar pustulosis may also be observed. These lesions may improve upon local treatment (including local steroids) and only require anti-TNF withdrawal in a minority of cases. Severe and refractory lesion may necessitate anti-TNF withdrawal and may persist a long time even after withdrawal.

Key Points

- Most frequent skin lesions associated with IBD are erythema nodosum and pyoderma gangrenosum.
- Erythema nodosum usually evolves in parallel to gastrointestinal manifestations of IBD.
- Pyoderma gangrenosum evolves independently from the gastrointestinal manifestations of IBD and may require ciclosporin or anti-TNF in the most severe presentations.

19.4 Red Eye

IBD patients may present with a red, inflammatory eye. This may correspond to several pathologies, including episcleritis, scleritis and uveitis (Larsen et al. 2010). It is very important to differentiate scleritis and uveitis from the benign episcleritis. Episcleritis is usually self-resolving and is not sight-threatening, while scleritis and uveitis require a specific management by an ophthalmologist as may, if poorly managed, jeopardize the eye and induce persisting damage. The main clinical elements to differentiate these conditions are moderate-severe eye pain, photophobia, blurring and diminished vision observed in scleritis and uveitis. Those symptoms are usually absent in cases of episcleritis, which is characterized by hyperaemic sclera and conjunctiva, itching and burning. Episcleritis is most often associated with active intestinal disease and resolves with it (Mintz et al. 2004). On the contrary, uveitis may appear independently from intestinal inflammation (Lyons and Rosenbaum 1997). Most frequent uveitis is anterior, but intermediate and posterior uveitis are even more serious and sight-threatening (Ernst et al. 1991). Scleritis is also sight-threatening but much more seldom than episcleritis (Sen et al. 2011). According to ECCO guidelines (Harbord et al. 2016), episcleritis may self-resolve, but topical or systemic NSAIDs or topical corticosteroids can be used for symptomatic treatment. Treatment for scleritis or uveitis should be guided by an ophthalmologist and includes topical or systemic corticosteroids, conventional immunomodulators and anti-TNF agents (Levy-Clarke et al. 2014).

Key Points

- Uveitis, scleritis and episcleritis are the most frequent eye manifestations of IBD.
- Episcleritis is usually benign and requires topical treatment.
- Uveitis and scleritis may be sight-threatening and require a specialized management by an ophthalmologist.

19.5 Alteration of the Liver Function Tests and Hepatobiliary Manifestations

Routine blood tests monitoring in IBD include liver function tests. This is to detect side-effects of some IBD treatments like purine analogues, methotrexate or anti-TNF but also to screen for hepatobiliary manifestations of IBD. The most classical, affecting 3–5% of IBD patients, is primary sclerosing cholangitis (PSC) (Karlsen et al. 2010). This condition is generally diagnosed after the detection of cholestasis at the liver function tests. It is rarely diagnosed at a later stage where jaundice or even pruritus is present.

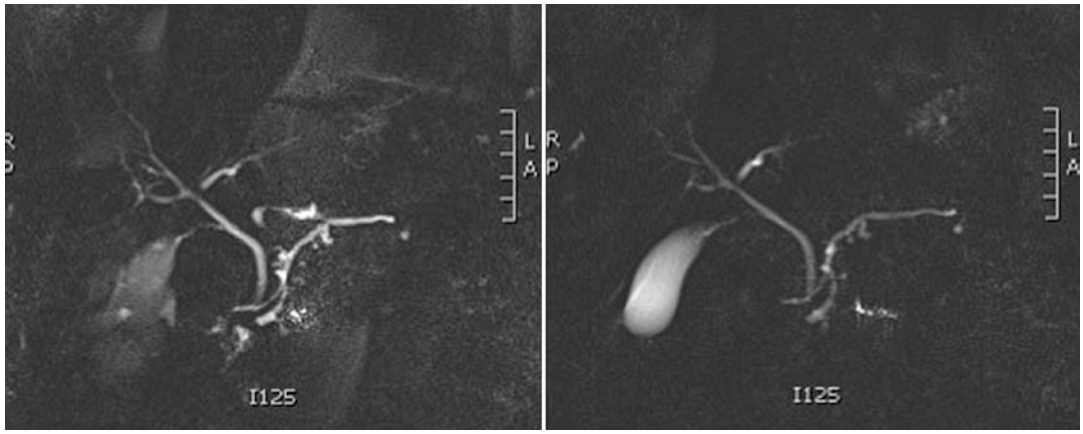

Fig. 19.1 MR cholangiopancreatography: compatible with primary sclerosing cholangitis affecting the intrahepatic small bile ducts, with significant stricture of the main bile ducts and choledocus

The most important differential diagnosis of alteration of the liver function tests in IBD is drug side-effects. Almost all drugs used in IBD can induce either cytolysis or cholestasis. This includes mesalazine, salazopyrine, steroids, purine analogues, methotrexate or anti-TNF (Khokhar and Lewis 2010). A magnetic resonance cholangiography (MRCP) will help make the diagnosis of PSC, by showing alternating strictures and dilatations along the biliary tract (Fig. 19.1). Sometimes these lesions are milder and dominate in the intrahepatic biliary tract. This situation is sometimes called small-duct PSC (Bjornsson et al. 2008). This may have a better prognosis and slower progression. The lesions can even sometimes not be visible at the MR cholangiography, and the diagnosis may require a liver biopsy. Although there is currently no specific treatment effective to stop or even slow down lesions' progression in PSC, this diagnosis is important to make because it is associated with an increased risk of both cholangiocarcinoma and colorectal cancer. This increased risk has an important impact on the surveillance of the patient. For cholangiocarcinoma, liver function tests and Ca19-9 are usually measured every 6 months, while ultrasound and MR cholangiography (first line in some countries or at least in doubt after ultrasound) are performed on a yearly basis. In case of detection of a new and suspect stricture of the biliary tract, an ERCP should be performed with at least brushing or cholangioscopy when available, to exclude (as good as possible) cholangiocarcinoma (Van Assche et al. 2013). For the colorectal cancer prevention, the PSC patients are followed up with full colonoscopy and chromoendoscopy every 1–2 years (Van Assche et al. 2013; Mowat et al. 2011).

Besides PSC and drug toxicity, other causes of alteration of the liver function test in IBD are more seldom. Secondary cholangitis are rare in IBD (infection, ischaemia, immunodeficiency, pancreatic disease, IgG4 disease, etc.) but should be excluded in large duct sclerosing cholangitis. Autoimmune hepatitis may occur independently in association with PSC, giving rise to an overlap syndrome. The diagnosis of associated autoimmune hepatitis may be suspected in case of hypergammaglobulinemia and presence of autoantibodies (ANA, SMA, LKM and more) (Trivedi and Chapman 2012). Portal vein thrombosis may occur following abdominal surgery for IBD or also in the setting of a flare of IBD which is associated with an increased risk of thromboembolic manifestations (Hatoum et al. 2005).

Key Points

- PSC is the most classical liver EIM of IBD.
- PSC is a potentially severe condition that may require liver transplantation.
- PSC is associated with an increased risk of cholangiocarcinoma and colorectal cancer.

19.6 Miscellaneous

Other manifestations are either more seldom or will not present with particular symptoms but rather discovered through blood tests or other explorations made during the routine follow-up of the patient (Table 19.1). Among those are bronchopulmonary, neurological, kidney or pancreatic manifestations (reviewed in Chap. 2). Osteoporosis and venous thromboembolism are also sometimes classified as EIM, while they are actually consequences of the acute and/or chronic inflammation of the intestinal tract and its impact of the bone metabolism for the first and coagulation cascade for the second. Finally, some illnesses like psoriasis or hidrosadenitis (Verneuil's disease) are associated with IBD and thus more prevalent in IBD patients than in the general population but are usually not considered as strict EIM of IBD. The distinction between those entities (EIM or associated diseases) may finally be theoretical.

19.7 Conclusion

EIM affect a large proportion of IBD patients. They may significantly impact their quality of life. They sometimes evolve independently from the gastrointestinal manifestations of the disease and may not respond to treatments given for these gastrointestinal manifestations. Some of them may also have severe presentation and lead to complications. For these reasons, they have to be known and recognized by health-care providers to be adequately managed.

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Penetrating Crohn's Disease and Fistulae

20

Nicola S. Fearnhead

Abstract

Crohn's disease can affect the bowel anywhere in the gastrointestinal tract, but most commonly affects the small bowel and perianal areas, where it may cause fistulae to form. Both enteric fistulae arising from the small bowel and perianal fistulae affecting the anorectum cause significant suffering for patients and are clinically difficult to treat. This chapter covers the manifestations and management options for fistulating Crohn's disease.

20.1 Background

Crohn's disease causes chronic inflammation in the gastrointestinal tract, but its cause is poorly understood. It affects around 115,000 people in the United Kingdom, and the overall incidence is gradually rising. Between one third and half of patients with Crohn's disease will experience a fistula (Schwartz et al. 2002; Molendijk et al. 2014). A fistula is a connection between two organs that are lined by epithelium and arises from an area of Crohn's inflammation in the gastrointestinal tract.

Perianal fistulae are the commonest type, followed by internal intestinal fistulae and enterocutaneous fistulae (Molendijk et al. 2014). Fistulating Crohn's disease tends to cause severe symptoms, such as diarrhoea, malnutrition, weight loss, pain and feculent discharge. The condition is often associated with physical disability and psychological distress, with significant impact on the patient's quality of life. There is also increased likelihood of needing repeated admissions to hospital and surgery.

The optimal strategy for managing fistulating Crohn's disease involves coordinated multidisciplinary management (Gecse et al. 2013). Surgical involvement is essential for initial management of abscesses and controlling infection, to allow subsequent medical therapy to control the inflammatory component of Crohn's disease. Patients with intestinal fistulae frequently require nutritional support.

Further surgical intervention is often required to cure Crohn's fistulae, but there are risks associated with surgical resection of intestinal fistulae, and success rates in sphincter-preserving procedures for perianal fistulae are particularly poor. Many treatments are aimed at controlling symptoms rather than cure, and a significant proportion of patients may need either a temporary or permanent stoma.

20.2 What Is a Fistula?

A fistula is a connection between two organs with an epithelial lining (Sandborn et al. 2003), and the fistula itself will also develop an epithelial lining

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in time. In Crohn's disease, the fistula connects part of the gastrointestinal tract either to another part of the gut or to the skin or to another organ like the bladder, vagina, uterus or fallopian tube.

Penetrating disease is another term used to describe the type of intestinal Crohn's disease that makes fistulae, in contrast to the stricturing (narrowing) type of intestinal disease.

Perianal disease is a specific form of Crohn's disease characterised by fistulae arising from the rectum and anal canal but also characterised by fleshy tags around the anus and fissures. It tends to be worse if there is also active inflammation of the rectum (proctitis).

20.3 Why Do Patients with Crohn's Disease Develop Fistulae?

Crohn's disease is a chronic inflammatory condition affecting the lining of the intestine. It is characterised by formation of ulcers in the lining of the intestine. The inflammation often causes narrowing or scar tissue, but ulceration may also result in localised perforation of the bowel and abscesses outside the bowel. If these abscesses rupture into adjacent organs, or onto the skin around the anus or on the abdominal wall, then a permanent connection from the gut may develop, and this is now a fistula (Panes and Rimola 2017; Siegmund et al. 2016).

The two commonest types of fistulae in Crohn's disease arise from the small or large bowel (intestinal fistulae) or occur around the anus (perianal fistulae).

20.4 Intestinal Fistulae

Intestinal fistulae in Crohn's disease usually present with either an acute episode of intra-abdominal infection or with chronic symptoms of malnutrition, malaise, weight loss and diarrhoea. Diagnosis is usually made with cross-sectional imaging in the form of CT or MRI, together with endoscopic assessment of inflammatory changes.

Table 20.1 Names and types of enteric fistula in Crohn's disease

Name of fistula	Definition
Enteric (or entero-enteric)	Internal fistula connecting two or more parts of the intestine
Enterocolic	Internal fistula connecting small intestine to the colon
Enterocutaneous	Internal fistula arising from the intestine and draining to the skin
Enterovesical	Internal fistula between small intestine and bladder
Enterovaginal	Internal fistula between small intestine and vagina
Colovesical	Internal fistula between large intestine and bladder
Colovaginal	Internal fistula between large intestine and vagina

20.4.1 What Are the Different Types of Enteric Crohn's Fistulae?

The commonest enteric fistulae in Crohn's disease arise from the small intestine, although fistulae arising from the large intestine are also well-recognised (Table 20.1). Fistulae most commonly arise from an area of active Crohn's inflammation (Poritz et al. 2004).

Enterocutaneous fistulae are an important subgroup as these patients suffer significant problems with drainage of bowel contents onto skin and are at high risk of nutritional compromise (Gecse et al. 2013).

20.4.2 How Does Fistulating Intestinal Crohn's Disease Present?

Some patients will present with intestinal fistulae as their very first manifestation of Crohn's disease, while others with known Crohn's disease may develop fistulae as a complication of the disease. In either situation, there is usually an initial illness characterised by flare of luminal Crohn's disease followed by a septic episode with intra-abdominal abscess or phlegmon (an inflammatory mass of bowel, mesentery, omentum and other abdominal organs).

Once the fistula is established, then the symptoms will depend on the anatomy of the fistula (Nielsen et al. 2009).

- When the fistula connects and bypasses segments of bowel, profuse diarrhoea, weight loss and malnutrition are the commonest symptoms.
- Pain is also a common symptom due to the localised inflammation around an internal fistula.
- If the fistula connects part of the bowel with the skin, bladder or vagina, then there will also be discharge of faecal matter to the skin, urine or vagina.
- As small bowel contents contain significant volumes of digestive enzymes, faecal discharge can cause severe skin irritation.
- A fistula into the bladder will typically cause faecaluria (faeces in urine), pneumaturia (air in urine often described as "peeing lemonade") and ascending urinary tract infections.
- A fistula into the vagina causes vaginal irritation, faecal discharge per vagina and urinary tract infections and has a profound impact on quality of life and ability to engage in sexual intercourse.

Most patients will have the diagnosis of intestinal fistula made on cross-sectional imaging with CT or MRI (Hvas et al. 2011). Some patients with intestinal fistulae may be minimally symptomatic; the presence of an incidental fistula on imaging does not require treatment.

An enterocutaneous fistula may also result as the consequence of an anastomotic leak after surgery to resect Crohn's disease affecting the intestine. About one quarter of enterocutaneous fistulae in Crohn's disease arise from surgical intervention (Poritz et al. 2004).

20.4.3 What Are the Treatment Goals for Fistulating Enteric Crohn's Disease?

The aims of treatment in fistulating intestinal Crohn's disease vary at different stages of the disease (Sampietro et al. 2013).

At first presentation, the goals are to:

- Drain internal abscesses or collections
- Consider early bowel diversion with a stoma to help control severe infection
- Bring ongoing inflammation in the bowel lumen under control with medical therapy
- Institute nutritional support
- Protect skin if enterocutaneous fistulae present

In the medium term, the priorities are to:

- Maintain control of luminal inflammation with immunosuppressants
- Consider proximal diversion with a stoma in selected patients
- Optimise nutritional condition

In the longer term, the treatment goals concentrate on improving quality of life while not causing unnecessary harm by:

- Offering delayed surgical resection to heal fistulae (Kosmidis and Anthimidis 2011)
- Maintaining and optimising immunosuppression

These goals are best achieved with treatment delivered within a multidisciplinary team (Gecse et al. 2013; Sampietro et al. 2013) with experience in interventional radiological drainage of abscesses, medical and surgical specialist IBD expertise, dedicated nutritional support teams, specialist nursing colleagues, skilled stoma therapists to manage enterocutaneous fistulae, tissue viability specialists to advise on open abdominal wounds (laparostomy) and gastrointestinal radiologists to help delineate the precise fistula anatomy (Fig. 20.1).

20.4.4 What Is the Role of Acute Surgical Management?

The IBD surgeon plays an important part in the acute management of a patient with intestinal fistula by advising on the best route of drainage of any intra-abdominal infection using a combination of minimally invasive techniques through inter-

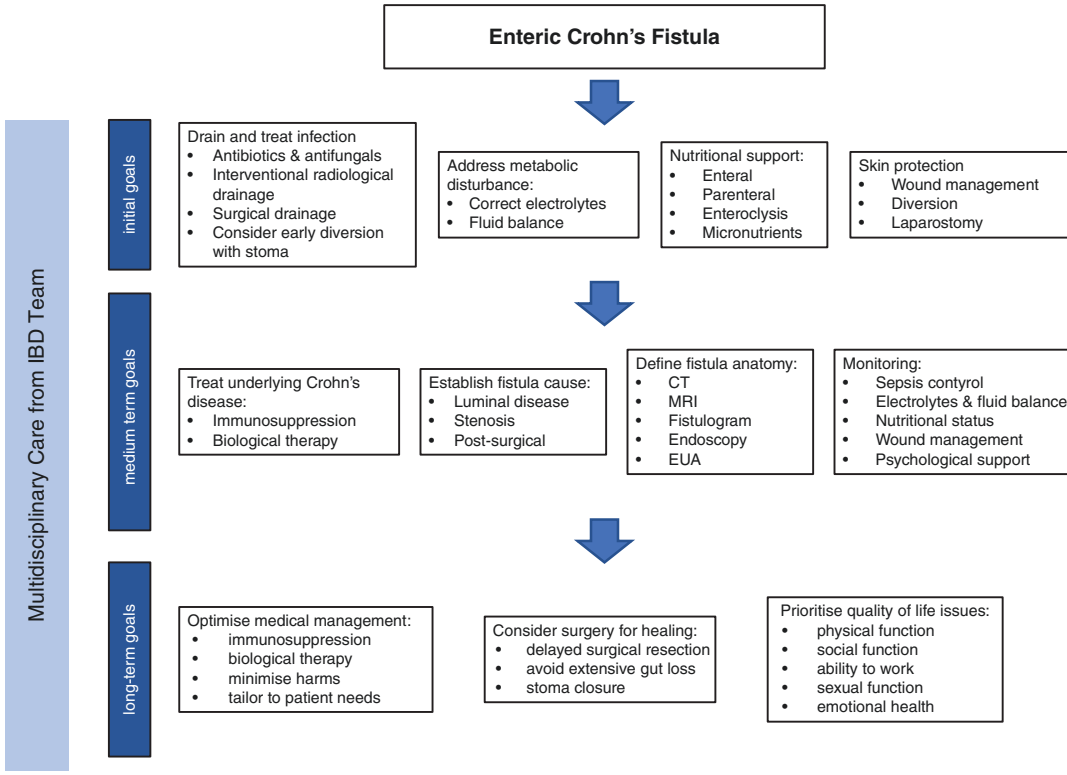

Fig. 20.1 Algorithm enteric fistula

ventional radiology or transluminal approaches with endoscopic ultrasound (Hvas et al. 2011).

As fistulae may be associated with ongoing intra-abdominal infection due to leakage of bowel contents, diversion of the faecal stream with a proximal stoma may be advisable in some patients (Geltzeiler et al. 2015). Surgery to resect bowel should be avoided in the acute stage as there is a very high risk of excessive loss of length of bowel and ultimately short gut syndrome. Resection is reserved for patients with peritonitis due to perforation or life-threatening complications requiring "source control".

20.4.5 What Is the Role of Medical Management?

Antibiotics are an important first line of management in patients with infection due to fistulating intestinal Crohn's disease and should be administered immediately on first presentation. Electrolyte and fluid balance disturbances need proactive correction. Analgesia and nutritional support should be prioritised. Antidiarrhoeal agents (e.g. loperamide, codeine), antisecretory agents (e.g. proton pump inhibitors, somatostatin analogues, octreotide) and hyperosmolar electrolyte solutions may help reduce fistula output (Gecse et al. 2013; Sampietro et al. 2013). Octreotide reduces visceral blood flow and so is now usually omitted in patients with postoperative complications resulting in enterocutaneous fistula formation.

Unlike acute inflammatory exacerbations of small bowel Crohn's disease, steroid therapy is seldom indicated in first presentation of fistulating disease due to the necessity of treating and draining sepsis. Once abscesses have been drained, Crohn's disease should be confirmed endoscopically and histologically in the newly presenting patient or disease activity assessed if the patient already has an established diagnosis (Sampietro et al. 2013; Stidham and Cross 2016). Most gastroenterologists would prioritise bring-

ing any underlying inflammatory component of Crohn's disease under control, but there is no high-quality evidence to guide therapeutic decisions in this situation.

Meta-analysis of subgroups from trials in Crohn's disease suggests there may be a role for thiopurines such as azathioprine and 6-mercaptopurine in some patients with active luminal Crohn's disease and intestinal fistulae (Pearson et al. 1995). Thiopurines may also offer a means of bridging therapy until biological therapy can be introduced. Biological therapy with anti-TNFα agents such as infliximab or adalimumab may be introduced once abscesses are drained and certainly should be considered early in patients with more aggressive luminal disease (Nunes et al. 2010; Gecse et al. 2013; Bor et al. 2015). A small proportion of the patients in the ACCENT II trial on infliximab in patients with perianal Crohn's disease also had enterocutaneous fistulae, but there was no subgroup analysis to guide management in this patient group (Sands et al. 2004).

Optimising medical therapy through monitoring of thiopurine metabolites (Kariyawasam et al. 2017; Goel et al. 2015) and measuring infliximab antibody and trough levels (Nanda et al. 2013; Bor et al. 2017) is an important part of the gastroenterologist's role in managing all patients with Crohn's disease.

Fistulae arising from surgical anastomotic complications are unlikely to benefit from immunosuppression or biological therapy unless ongoing luminal inflammation contributed to the complication.

20.4.6 What Is the Role of Nutritional Support?

Malnutrition is common in patients with intestinal fistulae, either as a consequence of persistent catabolism in the systemic inflammatory response of acute infection or due to loss of absorption of nutrients from an enterocutaneous or internal fistula bypassing significant length of intestine (Sampietro et al. 2013; Lloyd et al. 2006).

Patients need to be assessed for risk of refeeding syndrome on first presentation. Refeeding syndrome is a particular concern in patients with intestinal Crohn's fistulae due to chronic malnutrition. Refeeding syndrome occurs due to depleted electrolyte stores from prolonged starvation, is characterised by low levels of phosphate and magnesium when feeding supplementation is initiated and may manifest as arrhythmias, cardiac failure, neurological symptoms or altered conscious level. Early supplementation with thiamine, vitamin B complex, multivitamins and minerals will help reduce the risk of refeeding syndrome, and close monitoring of biochemistry during nutritional supplementation is essential.

Parenteral (intravenous) nutrition will often be needed due to loss of absorptive capacity from the intestine. The majority of intestinal fistulae will not close with parenteral nutrition and gut rest alone (Poritz et al. 2002), but use of parenteral nutrition may help control volumes of intestinal losses, especially with enterocutaneous fistulae (Gecse et al. 2013).

Enteral feeding or supplementation offers the benefits of mucosal barrier protection and reduced bacterial translocation, and should be instituted whenever clinically possible once infection has been drained and inflammation controlled with medical therapy (Sanchez-Guillen et al. 2016; Lloyd et al. 2006). Elemental diets may be used as a steroid-sparing treatment strategy in some patients with small bowel Crohn's disease.

20.4.7 What Is the Role of Definitive Surgical Management?

Prior to consideration of any surgical procedure to resect the source of the fistula, it is important to have clear delineation of fistula anatomy and accurate assessment of intestinal length and condition from up-to-date imaging (Hvas et al. 2011; Stidham and Cross 2016) with involvement of specialist gastrointestinal radiologists to interpret images from MRI, CT and contrast studies. Recent colonoscopy and other forms of endoscopy such as gastroscopy, enteroscopy or video capsule enteroscopy may also be useful for surgical planning (Stidham and Cross 2016).

Patients should only be considered for definitive surgery once their nutritional status has been restored and ideally at least 3–6 months after their last episode of intra-abdominal infection to allow softening of intra-abdominal adhesions and reduction in risk of inadvertent enterotomy. Specialist stoma counselling is essential as many patients will need either a temporary or even permanent stoma at the time of surgical resection.

The principles of surgical management are resection of the donor segment of the bowel giving rise to the fistula, repair or resection of the recipient end of the fistula and either anastomosis to restore bowel continuity of stoma creation (Coelho et al. 2016; Geltzeiler et al. 2015; Sampietro et al. 2013). In the case of an ECF, the fistula site on the skin will need excision and is often best managed with a suction dressing device due to the presence of chronic infection.

Surgery has significant risks with an appreciable complication rate, including recurrent fistulation (Bellolio et al. 2013). Careful counselling to discuss potential benefits and risks is essential, and must incorporate patient views and considerations. However surgical resection offers the potential for curing a fistula and so may offer the best chance at improving quality of life in the long-term for many patients.

20.4.8 How May the Specialist Nurse Help a Patient with Intestinal Fistula?

There are several roles for the specialist nurse in managing a patient with Crohn's intestinal fistulae:

- Explaining the diagnosis and management of Crohn's disease
- Recognising and escalating concern for initial symptoms and complications
- Counselling about side effects of medications
- Providing details of patient support groups
- Liaising with other members of the IBD multidisciplinary team (Thompson and Epanomeritakis 2008)
- Advising on strategies to minimise fistula output (Thompson and Epanomeritakis 2008)
- Instituting and monitoring nutritional support
- Advising on stoma siting, management and appliances
- Providing psychological support and counselling
- Managing and advising on enterocutaneous fistula drainage and laparostomy appliances (Thompson and Epanomeritakis 2008)
- Tissue viability expertise

20.4.9 Specific Concerns in Managing Enterocutaneous Fistulae

Enterocutaneous fistulae form an important subgroup within Crohn's patients with intestinal fistulae as they are associated with high levels of morbidity and mortality due to complications arising from:

- Septic complications
- Nutritional deficiencies due to intestinal failure
- Excessive fluid loss
- Electrolyte disturbances
- Skin erosion from fistula effluent
- Major psychological burden

The "SNAP" acronym provides a guide to management (Gecse et al. 2013) by prioritising:

- Sepsis management with skin care
- Nutritional support
- Anatomical delineation of fistulae
- Procedure (surgery) to remove fistula

All members of the multidisciplinary team need to be involved in management. Re-feeding of fistula losses into the downstream limb of a defunctioning stoma (Farrer et al. 2015) may sometimes be possible, but many patients require prolonged periods of parenteral nutrition and specialist nursing advice on managing fistula sites and losses.

20.4.10 Managing the Abdominal Catastrophe

One of the complications of both planned and emergency surgery in Crohn's disease is anastomotic leak. Occasionally anastomotic leaks may be managed with bowel rest, antibiotics and drains, usually resulting in enterocutaneous fistula formation. But the majority of patients experiencing an anastomotic leak will require emergency surgery to drain the infection and bring out the bowel ends as stomas. Some will need to have the abdominal wall left open and a laparostomy formed and some will go on to form multiple enterocutaneous fistulae (Thompson and Epanomeritakis 2008).

Patients with abdominal catastrophes have high rates of morbidity and mortality and often have very prolonged and difficult hospital admissions requiring intensive care, nutritional support, multiple surgical and radiological interventions, laparostomy and fistula drainage devices, tissue viability services and psychiatric support.

20.5 Fistulating Perianal Crohn's Disease

One in three patients with Crohn's disease will develop a perianal fistula at some stage (Molendijk et al. 2014), although recent evidence suggests that the incidence may have fallen with introduction of biologic therapy (Gottgens et al. 2017). For some patients, developing a fistula may be the first sign of Crohn's disease (Singh et al. 2004).

The condition is distressing and debilitating for patients. Common symptoms include perianal pain, discharge from the fistulae, offensive odour and leakage of stool (Solomon 1996). There is significant negative impact on the patient's ability to function as a human being:

- Inability to work or carry out normal roles, e.g. childcare and housework
- Inability to function socially, e.g. unable to go out, meet friends or socialise
- Inability to be intimate or have a sexual relationship
- Reduction in overall quality of life
- Major psychological burden

While the physical symptoms may predominate, there may also be secondary effects from treatment that may exacerbate symptoms further, e.g. surgery to control infection and promote fistula healing may in turn also impair continence mechanisms (Keshaw et al. 2010; Brochard et al. 2017).

20.5.1 How Does Fistulating Perianal Crohn's Disease Present?

As a perianal fistula starts with development of a perianal abscess that then discharges to leave a fistulous connection between the anus and the perianal skin or vagina, first presentation is typically with swelling and pain from a perianal abscess, followed by discharge of pus or faecal drainage from the fistula site.

Fistulating perianal Crohn's disease in several contexts:

- New onset perianal disease in a patient known to have luminal Crohn's disease
- Perianal abscess or fistula as first presentation of Crohn's disease
- Recurrent perianal Crohn's disease after period of remission
- Persistent suppurating fistulating Crohn's disease

As perianal abscesses are common in the general population due to cryptoglandular sepsis, and just a small proportion of perianal abscesses are due to Crohn's disease, there may be a significant delay in recognising and treating the cause of perianal fistula in the patient who is not yet known to have Crohn's disease. Clinicians need to recognise other clinical or perianal features suggestive of perianal Crohn's disease (Solomon 1996) and consider the diagnosis early to avoid undue suffering due to delays in implementing appropriate treatment for patients with perianal Crohn's fistulae.

20.5.2 What Are the Different Types of Perianal Crohn's Fistulae?

The following definitions are used when describing fistula tracks (Table 20.2).

There are several classification systems based on:

- Anatomical configuration of fistulae (Parks et al. 1976)
- Combined index including discharge, type of perianal disease, induration, pain and restriction of activity (Irvine 1995)
- Fistula drainage assessment (Present et al. 1999)
- MRI criteria of anatomical configuration and inflammatory activity (Van Assche et al. 2003).

Perianal fistulae are usually best classified as "simple" or "complex", where simple refers to a low fistula with a single external opening, without evidence of ongoing abscess, rectovaginal fistula and anal stenosis (Sandborn et al. 2003). Proctitis may also be present, and its presence is a poor prognostic sign (Lee et al. 2017a) (Fig. 20.2).

20.5.3 What Are the Treatment Goals for Fistulating Perianal Crohn's Disease?

The overarching aims of treatment in fistulating perianal Crohn's disease are to:

- Drain and prevent infection
- Control inflammation
- Prevent recurrent infection
- Minimise fistula drainage
- Maintain remission
- Improve quality of life (Gecse et al. 2013)

These goals are best achieved with treatment delivered within a multidisciplinary team with expertise in medical and surgical treatment of fistulating perianal Crohn's disease supported by specialist nursing colleagues and gastrointestinal radiologists (Gecse et al. 2014; Morar et al. 2015).

Management of fistulating perianal Crohn's disease is typically with a combination of medical and surgical treatments (Yassin et al. 2014). Surgery has two main roles in the management of perianal Crohn's disease: controlling infection in the first instance and later as an adjunct to medical therapy to minimise recurrent infection, to reduce drainage and occasionally to cure fistulae (Gecse et al. 2014; Tozer et al. 2015; Lee et al. 2017b). Medical therapy is primarily aimed at controlling inflammation to induce remission of Crohn's disease in the short term and maintaining remission in the longer term (Gecse et al. 2013).

Patient expectations will direct whether therapy should be aimed at alleviating symptoms or trying to achieve cure, and indeed these expectations may change over time. Clinicians caring for

Table 20.2 Definitions used in describing perianal Crohn's fistulae

Term	Definition
Primary track	Principal connection arising from within anorectal canal and connecting to an external opening on perineum
Secondary track	Additional track extending from a primary track, but not arising within the anorectal canal, and draining to another external opening on perineum
Sinus or tract	A blind-ending sump draining into a primary or secondary fistula track
Subcutaneous	Tracking just underneath the skin
Submucosal	Tracking just underneath the mucosal lining of the rectum
Inter-sphincteric	Tracking from the anorectal canal across the internal anal sphincter and then between the internal and external sphincters, but not across the external sphincter, to drain onto the perianal skin
Trans-sphincteric	Tracking across both the internal and external sphincter muscles i.e. the fistula tracks from the anorectal canal across both internal and external sphincter to drain onto the perianal skin
Supra-sphincteric or supralevator	Tracking from the anorectal opening through levator muscle of pelvic floor to open on the skin, i.e. fistula track crosses above and outside sphincter muscles
Rectovaginal	Fistula with dual openings in anorectal canal and in vagina
Retrorectal	Lying in space behind rectum and above pelvic floor
Pelvic	Lying in space within pelvic cavity

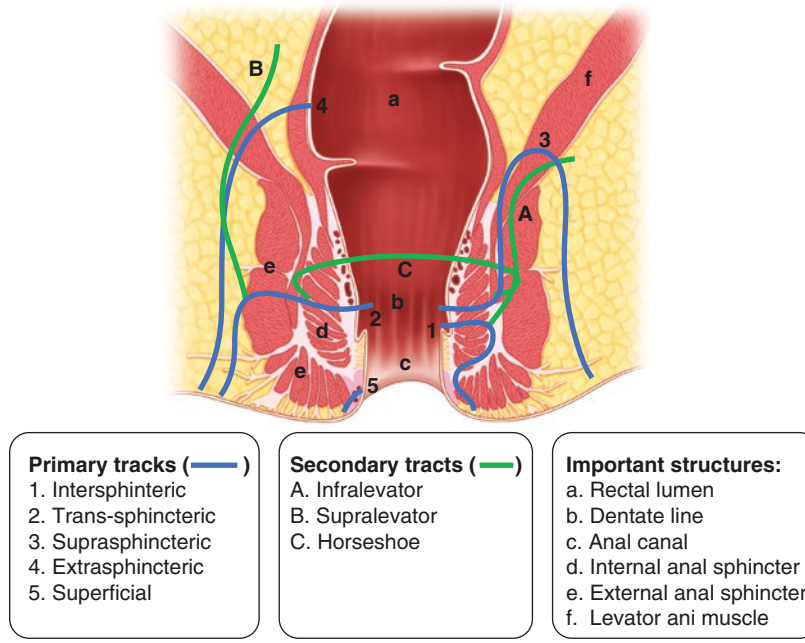

Fig. 20.2 Perianal Crohns fistula

patients with perianal Crohn's disease need to accommodate patient preferences in all aspects of multimodal treatment. Awareness of poor outcomes overall has led to patient and clinicians prioritising research into ways of improving outcomes for patients with perianal Crohn's fistulae (Tiernan et al. 2014; Hart et al. 2017; McNair et al. 2017) (Fig. 20.3).

20.5.4 What Is the Role of Acute Surgical Management?

On first presentation with perianal sepsis, the surgeon's role is to drain infection properly and minimise tissue destruction while preserving the function of the anal sphincter complex and sensitive anoderm. If a fistula is seen at the time of drainage of sepsis, a seton may be placed (De Groof et al. 2016; Lee et al. 2017a; Lee et al. 2017b). Otherwise further examination under anaesthesia will be required at a later date for placement of draining seton(s) by an experienced colorectal surgeon (Lee et al. 2017a).

Where a patient with new onset fistulating perianal disease presents with perianal sepsis, the specialist surgeon may recognise pathognomonic combination of fleshy anal tags, associated fissures or complex fistulae that suggest a new diagnosis of fistulating perianal Crohn's disease (Solomon 1996).

If a patient with perianal Crohn's disease continues to have pain or purulent discharge from poorly controlled fistula drainage, it is essential to establish long-term drainage with setons and local drains both to prevent further tissue loss from undrained infection and also to allow safe initiation of biological therapy (Tozer et al. 2011).

Magnetic resonance imaging (MRI) of the perineum may aid identification of occult fistulae or sources of ongoing sepsis (Borley et al. 1999; Mullen et al. 2011). It may also be used to ensure that all infection is adequately drained and to assess response to medical therapy (Gligorijevic et al. 2010; Karmiris et al. 2011; Schwartz et al. 2015; Thomassin et al. 2017).

20.5.5 What Is the Role of Medical Management?

Once perianal sepsis is controlled and diagnosis of Crohn's disease is confirmed if necessary, the

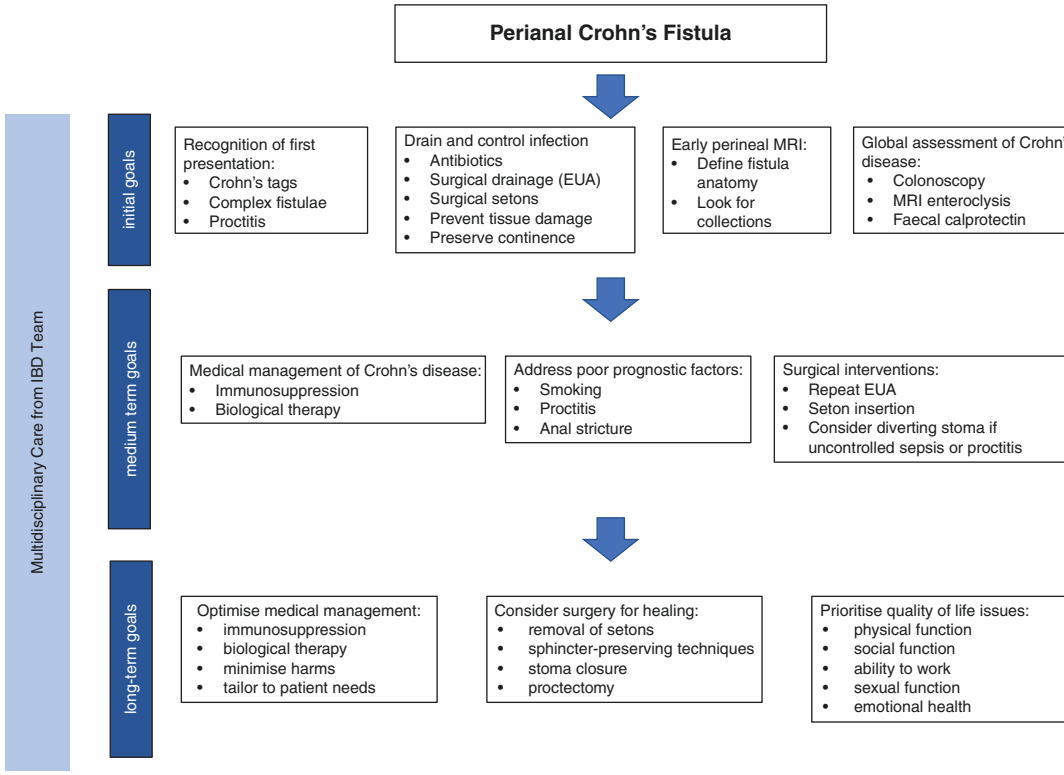

Fig. 20.3 Algorithm perianal fistula

priority shifts to control of the underlying inflammatory disease and especially of proctitis if present (Gecse et al. 2014). Medical treatment with a combination of thiopurine immunosuppression, e.g. azathioprine and mercaptopurine (Pearson et al. 1995), and biological therapy with anti-TNFα agents such as infliximab, adalimumab or certolizumab (Present et al. 1999) is initiated either through a top-down or step-up approach.

After induction of biologic therapy, setons may be removed to allow a chance of fistula healing (Present et al. 1999), but ongoing biological therapy is essential to maintain this response. There is evidence from randomised trials suggesting that healing may be achieved in around a third of patients maintained on biological therapy, but long-term remission is less than 20% (Sands et al. 2004; Colombel et al. 2007; Schreiber et al. 2011).

Optimising medical treatment through measurement of drug metabolites and monitoring of biological therapy with trough levels and antibody titres is a crucial aspect of the gastroenterologist's role in managing fistulating perianal Crohn's disease (Gecse et al. 2014).

20.5.6 What Is the Role of Definitive Surgical Management?

Chances of fistula cure may be enhanced with surgical attempts at repair if carried out on a background of optimised medical therapy (El-Gazzaz et al. 2012). Given the chronic relapsing nature of Crohn's disease and the high risk of diarrhoea at any time, surgical procedures that preserve sphincter function should be offered in the first instance. Patients need to be counselled about the chances of cure and the potential consequences of failure. For this reason, long-term drainage setons are still widely used in the United Kingdom as a permanent solution for symptom control rather than attempting fistula cure.

Front-running curative surgical options include advancement flaps, fibrin glue, fistula plugs, ligation of the inter-sphincteric fistula track (LIFT) and adipose-derived stem cell injection coupled with sutured closure of the internal fistula opening (Nasseri et al. 2016; Panes et al. 2016; Lee et al. 2017a). The over-the-scope clip (OTSC)® and video-assisted anal fistula treatment (VAAFT) have only been used in fistulating perianal Crohn's disease in small numbers (Lee et al. 2017a). All procedures have relatively low success rates.

An algorithmic approach to surgical repair may offer better chances of successful and sustained healing. Prognostic factors for healing include the absence of proctitis, normal body mass index and non-smoking status, but overall prognostic factors are poorly understood (Gecse et al. 2014; Lee et al. 2017a).

Diverting stoma may offer significant benefit to selected patients and should be considered for symptomatic patients in the presence of intractable symptomatic perianal disease or proctitis or failure to adequately control perianal sepsis (Kasparek et al. 2007; Sauk et al. 2014; Tozer et al. 2015). Proctectomy is a good option for some patients, and a permanent stoma should not be viewed as technical failure as it may significantly improve quality of life in selected patients (McNair et al. 2017).

20.5.7 How May the Specialist Nurse Help the Patient?

As with intestinal fistulae, the specialist nurse may fulfil several roles in caring for the patient with perianal Crohn's fistulae (Hernandez-Sampelayo et al. 2010; Greveson and Woodward 2013), including:

- Explaining the diagnosis and management of Crohn's disease
- Prescribing, administering and monitoring medical therapies
- Providing details of patient support groups
- Liaising with other members of the IBD multidisciplinary team
- Advising on protection of perianal skin with barrier creams and pads
- Explaining operative procedures
- Advising on perineal hygiene with setons and after surgical procedures
- Stoma siting and counselling if required
- Providing psychological support and counselling

20.5.8 Specific Concerns in Managing Rectovaginal Fistulae

Some women with fistulating perianal Crohn's disease may develop a fistula between the anorectum and the vagina. Rectovaginal fistulae are particularly distressing for the patient due to persistent feculent discharge into the vagina having a significant impact on social and sexual function and consequent reduction in quality of life (Milito et al. 2017).

Rectovaginal fistulae hardly ever close with medical management alone, and surgery to repair rectovaginal fistulae has low success rates (Manne et al. 2016). Failure of surgical repair may result in further deterioration in symptoms if there is additional loss of tissue, and ultimately stoma rates are high in this group of patients.

There are several techniques used in Crohn's rectovaginal fistula, and surgical recommendations vary according to anatomical position, length and width of the fistula, integrity and quality of the perineal tissues, surgical experience and patient preferences. Approaches include transanal, transperineal, transvaginal and trans-abdominal approaches, aimed either at primary repair or interposition of native tissue or biological mesh. Management of rectovaginal fistulae in Crohn's disease should be confined to specialist centres (Lee et al. 2017a).

20.5.9 Managing the Perineal Catastrophe

Some patients with long-standing or poorly controlled fistulating perianal Crohn's disease (often termed "pepperpot bottom") may develop

intractable pain, sepsis, feculent drainage and incontinence. The primary goal of treatment for such patients is palliation of symptoms.

Biological therapy is usually ineffective in this scenario. Topical metronidazole may offer some temporary improvement in symptoms. For many patients, a defunctioning stoma and involvement of pain specialists may help (Kasparek et al. 2007; Sauk et al. 2014; Tozer et al. 2015). In others, proctectomy with permanent stoma may be a better option still, often with plastic surgical flap reconstruction of the perianal tissues, due to the degree of tissue damage and size of the perineal area affected by draining fistulae (Tozer et al. 2015; Lee et al. 2017a).

In patients suffering with perineal catastrophe from fistulating perianal Crohn's disease, it is important that clinicians convey that having a permanent stoma is not a sign of failure but offers a realistic opportunity for true palliation of intractable symptoms and potential improvement in quality of life (McNair et al. 2017).

20.6 Summary

- Fistulating disease is a source of significant morbidity for patients with Crohn's disease and often has a significant negative impact on quality of life.
- Intestinal fistulae may present with pain, malaise, weight loss and diarrhoea. Management requires drainage of infection by radiological or surgical means, consideration of proximal diversion in selected patients, initiation of immunosuppression or biological therapy, nutritional support and delayed surgical resection.
- Fistulating perianal Crohn's disease manifests as painful abscesses and discharge in the perianal area. Initial surgical approaches prioritise drainage infection and minimise recurrence by placement of seton drains. The mainstay of medical treatment is biological therapy with or without thiopurine immunosuppression. Subsequent surgery may be aimed at trying to cure fistulae, but many patients choose to live with long-term setons.
- Stomas may facilitate bringing fistulating disease under control and should not be viewed as failure or a last resort as patients may experience significant improvement in quality of life after stoma creation.
- Successful management requires careful integration of expertise from all members of the multidisciplinary inflammatory bowel disease team. A patient-centred focus is essential.

20.7 Resources

Living with a Fistula (Crohn's & Colitis UK information for patients) http://s3-eu-west-1.amazonaws.com/files.crohnsandcolitis.org.uk/Publications/fistula

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Opportunistic Infections

21

Serena R. Martin and Robert V. Bryant

Abstract

The treatment of inflammatory bowel disease (IBD) has been revolutionised over the past decade by the increasing use of immunomodulators and biologic therapy. Immunosuppression associated with use of these agents introduces the potential for opportunistic infection, which is a key safety concern for IBD patients and their carers. An opportunistic infection is one that is caused by a microorganism that is not harmful under ordinary circumstances but which causes serious disease in a predisposed person with a reduced capacity to fight the infection. Viral, bacterial, parasitic and fungal infections have all been associated with the use of immunosuppressive therapy in IBD. Opportunistic infections in IBD are associated with appreciable morbidity and mortality, because they are often difficult to recognise, potentially serious, and hard to treat effectively. The IBD nurse can play an important role in preventing opportunistic infections, through identification of those patients at risk. Moreover, the IBD nurse is integral to the implementation of screening and vaccination programmes for opportunistic infections in IBD patients, as well as in providing education and counselling around this important topic.

21.1 Introduction

The treatment of inflammatory bowel disease (IBD) has evolved with increasing use of immunomodulator and biologic therapy. Immunosuppression associated with use of these agents introduces the potential for opportunistic infection (OI), which are appreciable causes of morbidity and mortality in IBD. IBD nurses play a key role in the prevention and recognition of OIs, through identification of those patients at risk and recognition of early clinical signs. Moreover, IBD nurses are integral to prevention through education, screening and implementation of vaccination programmes.

21.2 What Is an Opportunistic Infection and What Are the Risk Factors?

OIs are those caused by microorganisms that would ordinarily have limited or no capacity for infection but which are able to cause serious

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disease as a result of predisposing conditions or treatment (Rahier et al. 2014).

While patients with IBD have been found to have aberrant gut mucosal immune responses, this does not necessarily translate to defective systemic immunity (Rahier et al. 2014). It has not been shown that IBD is a risk factor for infection per se, but rather patients with IBD can become immunocompromised due to the effects of medications, malnutrition, ageing and comorbidities (Connell et al. 2010). In particular, IBD patients treated with immunosuppressant medications have an increased risk of OI, which poses a challenge to healthcare providers given the increasingly widespread and long-term use of these therapies. The risk factors for infection in IBD patients may be broadly characterised as those external to the patient (immunosuppressant therapy, exposure to pathogens) and inherent to the patient (age, comorbidity, malnutrition) (Table 21.1, Fig. 21.1).

21.2.1 Inherent Risk Factors for Infection

Age The elderly are at increased risk of developing OI due to diminished function of both the innate and adaptive immune systems associated with ageing, a phenomenon termed 'immunosenescence' (Gavazzi and Krause 2002). Advancing age has been identified as an independent risk factor for infection-related hospitalisation in patients with IBD, and patients aged over 50 years have been shown to have an increased risk of developing OI (odds ratio (OR) 3.0; 95% confidence interval (CI), 1.2–7.2, compared to patients ≤24 years of age) (Cottone et al. 2011). The risk of OI in IBD patients of advanced age is further compounded by immunosuppressive therapy (Cottone et al. 2011).

The opposite extreme of age is also a risk factor OIs. Paediatric patients with very early-onset IBD are at higher risk of OI, which is contributed to by underlying immune defects predisposing to IBD in this group (Uhlig 2013).

Table 21.1 Risk factors for opportunistic infection in IBD

Domain	Risk factor
Intrinsic	Older age
	IBD disease activity and complicated disease
	Malnutrition
	Medical comorbidities
Extrinsic	Exposure to pathogens (particularly in endemic areas)
	Immunosuppressive therapy • Biologic therapy • Immunomodulator therapy (thiopurines, methotrexate) • Corticosteroid therapy

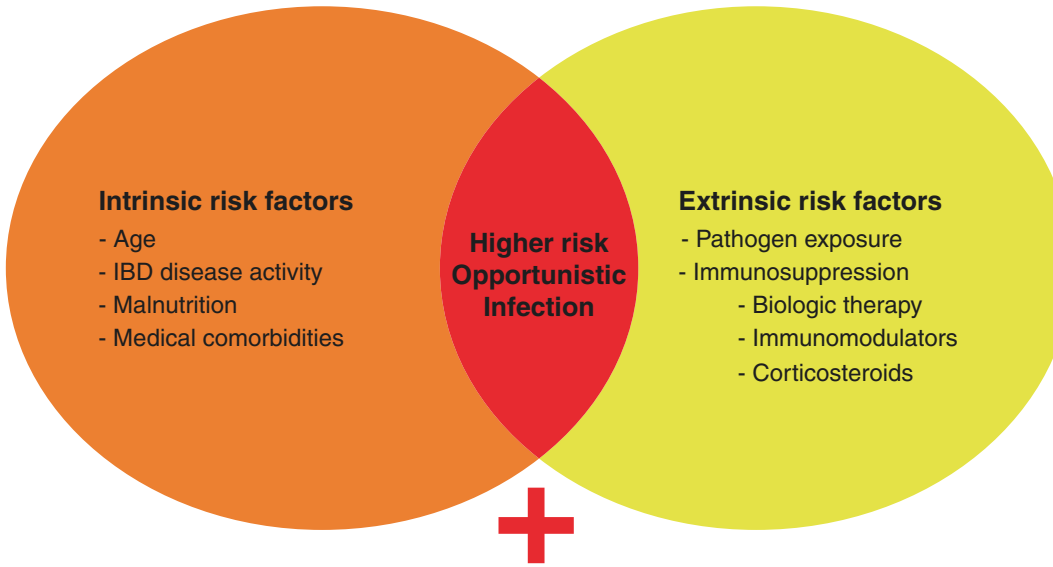

Fig. 21.1 Risk factors for opportunistic infection in IBD

Disease Activity Serious infections in patients with IBD can be a consequence of complications of disease, particularly penetrating complications leading to abscess formation and ensuing abdominal, pelvic or perianal sepsis (Sandborn 2010). Concurrent use of immunosuppressant therapy may worsen outcomes of infection, predisposing to uncontrolled sepsis in this setting.

Malnutrition A poor nutritional state deprives the immune system of the components required to mount an effective immune response (Gerasimidis et al. 2011). Nutritional deficiencies are common in IBD, particularly in Crohn's disease, and tend to be of multifactorial aetiology, relating to anorexia and reduced oral intake, malabsorption (particularly in extensive small bowel disease), drug-nutrient interaction and postsurgical states (small bowel obstruction or resection and/or short gut syndrome) (Valentini and Schulzke 2011). Both micro- and macronutrient deficiencies are common and may go unrecognised in clinical practice without careful screening and dedicated dietetic input (Rahier et al. 2014). Malnutrition in IBD has been shown to increase the risk of hospitalisation for infection (Ananthakrishnan and McGinley 2013).

Medical Comorbidities In IBD, the presence of medical comorbidities has been shown to increase the risk of hospitalisation related to infections (Ananthakrishnan and McGinley 2013). As extrapolated from other chronic illnesses, the greatest additional risk of OI is imparted by chronic lung disease, alcoholism, organic brain disease and diabetes mellitus (Rahier et al. 2014; Doran et al. 2002).

21.2.2 External Risk Factors for Infection

Exposure to Pathogens Exposure to pathogens obviously represents a risk factor for opportunistic infections and is particularly relevant to immunocompromised patients who reside in or visit endemic areas of infection (Abitbol et al. 2016; Byun et al. 2015).

Immunosuppressive Therapy Susceptibility to infection, whether viral, bacterial, parasitic and fungal infection, is increased with the use of immunosuppressive therapy. The type of opportunistic infection may vary depending on the class of immunosuppressant used; corticosteroid therapy may be more associated with fungal infection, thiopurines with viral infections and antitumour necrosis factor (anti-TNF) therapy with mycobacterial infections (Toruner et al. 2008). There is however a large amount of overlap in the types of infections associated with particular therapies, and the picture is further clouded by common concurrent use of these medications. A simple premise is that the risk of infection in IBD is increased with use of combination immunosuppressive therapy. The risk of infection associated with use of a single immunosuppressive agent increases substantially when two or more drugs are used in combination (OR 2.9, 95% CI 1.5–5.3; OR 14.5, CI 4.9–43; respectively) (Toruner et al. 2008).

Corticosteroids A total daily dose equivalent of ≥20 mg prednisolone for ≥2 weeks is associated with an increased risk of infection in IBD (Rahier et al. 2014). Corticosteroid therapy also increases the risk of *Clostridium difficile* infection threefold compared to other immunosuppressant agents in patients with IBD (Schneeweiss et al. 2009). Corticosteroid use can also cause reactivation of *Mycobacterium tuberculosis* (TB) and hepatitis B virus (HBV) infections. Corticosteroid therapy is associated with increased postoperative infectious complications (Post et al. 1991). Overall, corticosteroid therapy poses a high risk of side effects including infection yet does not achieve mucosal healing, and its long-term use in IBD should be avoided.

Thiopurine Therapy Patients with IBD taking thiopurine therapy, including azathioprine, mercaptopurine or thioguainine, are at increased risk of infection, particularly of viral aetiology (Rahier et al. 2014). Primary Epstein-Barr virus (EBV) infection in seronegative patients with IBD on thiopurine therapy is associated with 100-fold increased risk of haemophagocytic lymphohistiocytosis (haemophagocytic syndrome) (Biank et al. 2011). EBV is also associated with

lymphoproliferative disorders (such as non-Hodgkin's lymphoma) in IBD patients on thiopurine therapy (Linton et al. 2013). Patients on thiopurine therapy are more susceptible to the common cold and seasonal influenza. There is conflicting evidence as to whether thiopurines impart greater risk of infection with *Cytomegalovirus* (CMV) (Hradsky et al. 2015; Bonta et al. 2016).

Antitumour Necrosis Factor Alpha (Anti-TNF) Therapy Anti-TNF therapy, including infliximab, adalimumab and golimumab, has been associated with higher rates of serious infection in patients with IBD (Shah et al. 2017). Anti-TNF therapy acts by binding to tumour necrosis factor alpha, a pro-inflammatory cytokine, thereby diminishing inflammation. The TREAT Registry in Crohn's disease showed that although the risk of serious infection is increased with anti-TNF therapy, the risk is lower than that associated with corticosteroid therapy (Lichtenstein et al. 2006; Lichtenstein et al. 2012). Overall, the risk of infection with the use of anti-TNF therapy may be higher in patients with UC than with CD (relative risk (RR) 1.2, 95% CI 1.0–1.3 vs. RR 1.1, 95% CI 0.8–1.5; respectively) (Shah et al. 2017). There remains debate as to whether perioperative anti-TNF therapy is associated with an increased risk of postoperative infection (Waterland et al. 2016).

Anti-TNF therapy has traditionally been considered a risk factor for intracellular pathogens, including mycobacteria and invasive fungal infections. *Mycobacterium tuberculosis* (TB) is a well-recognised potential complication of anti-TNF therapy, both with regard to increased susceptibility for acquisition of TB and reactivation of latent TB infection. Even if initial TB screening results are negative, TB can arise during treatment with anti-TNF therapy, prompting calls for serial rescreening for TB during therapy for those at risk of occupational or endemic exposure (Abitbol et al. 2016). Reactivation of latent TB will generally occur during the first year of anti-TNF treatment (Papay et al. 2012). Chronic hepatitis B virus (HBV) infection can also be exacerbated by anti-TNF therapy and can result in an acute hepatitis flare when anti-TNF therapy is stopped. Patients should therefore be screened for HBV and receive prophylactic antiviral treatment if required before commencing anti-TNF therapy (Connell et al. 2010).

Anti-integrin Therapy The use of anti-integrin therapy in the treatment of UC and CD carries theoretical risks of opportunistic infection in IBD (Shah et al. 2017; Luthra et al. 2015). Anti-integrin therapies inhibit the binding of leukocytes to receptors in the gut, thereby diminishing inflammation. Natalizumab was the first anti-integrin therapy trialled in Crohn's disease but was withdrawn from the market due to risks associated with the universally fatal condition progressive multifocal leucoencephalopathy (PML), associated with latent JC virus infection (Bloomgren et al. 2012; Sandborn et al. 2005). Vedolizumab and etrolizumab are newer anti-integrin therapies demonstrating higher gut specificity that have not been associated with PML (Vermeire et al. 2014; Colombel et al. 2017). Systematic review data have shown that although absolute numbers of infection are slightly higher in patients treated with anti-integrin therapy versus placebo, the difference is not statistically significant (Shah et al. 2017; Luthra et al. 2015). Rates of minor infections (in particular upper respiratory tract infections and enteric infection) may be increased in patients on vedolizumab therapy (Colombel et al. 2017).

Learning Box 21.1

1. Opportunistic infections are infections caused by microorganisms that are generally not harmful under ordinary circumstances but which cause serious disease in a predisposed person with a reduced capacity to fight the infection.
2. IBD patients are at increased risk of opportunistic infection due to extrinsic and intrinsic factors leading to an immunocompromised state, including medications, malnutrition, ageing and medical comorbidities.

3. Medications that increase the risk in of opportunistic infection in IBD patients include corticosteroids, thiopurines, antitumour necrosis alpha factor therapy and anti-integrin therapy.
4. The risk of opportunistic infection increases with use of combination immunosuppressive therapy.

21.3 What Are the Microorganisms That Cause Opportunistic Infection in IBD?

21.3.1 Viruses

Hepatitis B Virus Hepatitis B virus (HBV) is a hepatotropic DNA virus belonging to the Hepadna virus family. Progression from acute to chronic HBV infection varies depending on age of acquisition, with increased rates of chronic infection associated with a younger age of acquisition (particularly vertical transmission). Early-phase chronic HBV infection results in high viral replication and associated active liver disease, whereas later-phase chronic HBV infection results in lower viral replication and minimal hepatic injury (Rahier et al. 2014).

Patients who have evidence of active HBV infection (hepatitis B surface antigen positive (HBsAg+)) are at greatest risk of reactivation with use of immunosuppressive therapy. Although rare, reactivation of occult HBV infection (hepatitis B core antibody positive (HBcAb+) but HBsAg−) has been reported (Madonia et al. 2007; Morisco et al. 2011). The risk of HBV reactivation is highest in patients receiving combination immunosuppressive therapy (Morisco et al. 2011). A flare of HBV infection or reactivation in immunosuppressed patients can lead to liver decompensation, with deranged liver function tests (transaminitis) and the reappearance of high circulating levels of HBV DNA (Rahier et al. 2014).

Hepatitis C Virus Hepatitis C virus (HCV) is a hepatotropic RNA virus belonging to the *Flaviviridae* family. Acute HCV infection is frequently asymptomatic, while chronic HCV infection can lead to cirrhosis and hepatocellular carcinoma. Chronic HCV infection develops in roughly 85% of cases of HCV infection. The majority of cases of HCV infection are transmitted parenterally, although sexual, perinatal and sporadic transmission is possible but far less common (AASLD/IDSA HCV Guidance Panel 2015).

Human Immunodeficiency Virus The human immunodeficiency virus (HIV) belongs to the human retrovirus family. Although not truly an opportunistic infection, infection with HIV can cause immunosuppression and complicate management of IBD. HIV infection causes a progressive deficiency of T-helper cells and subsequent impairment of T-cell-mediated immune response, leading to an increased risk of developing OIs. Transmission occurs via sexual and parenteral routes, as well from mother to infant via intrapartum, perinatal or breast milk transmission in the absence of highly active antiretroviral therapy (HAART) (Rahier et al. 2014). Concurrent HIV infection influences the course of IBD, with a tendency to fewer IBD flares over time (Viazis et al. 2010). Although experience is limited, immunosuppressive therapy is not necessarily contraindicated in IBD patients with HIV infection, particularly in those on HAART with well-controlled HIV infection (Rahier et al. 2014).

Herpesvirus Herpes simplex virus transmission is transmitted via intimate or sexual contact, with type 1 (HSV-1) most often causing orofacial herpes and type 2 (HSV-2) genital herpes. HSV can cause also severe disease, including keratitis, encephalitis and retinitis. Primary and recurrent flares of herpes are more frequent in immunocompromised patients. Although such flares are usually mild, disseminated HSV has been reported, causing hepatitis, colitis or pneumonitis (Rahier et al. 2014).

Cytomegalovirus Cytomegalovirus (CMV) belongs to the *Herpesviridae* family. Infection with CMV is ubiquitous, with transmission in early life via childbirth, breastfeeding, close contact and sexual contact, resulting in 80% of the adult population having antibodies to CMV. Initial infection can be asymptomatic or cause mononucleosis-type symptoms including fever, fatigue and colitis

(Baniak and Kanthan 2016). Following initial symptomatic infection, it enters a latent period, where it remains for the lifetime of the host.

Immunomodulation can cause reactivation of latent CMV infection (Beswick et al. 2016). CMV infection can cause hepatitis, colitis, oesophagitis, pneumonia, encephalitis and retinitis (Rahier et al. 2014). In the setting of colitis, particularly steroid-refractory colitis, CMV is frequently present in the sites of inflamed mucosa, which makes it difficult to determine whether the CMV is causing disease or merely a bystander (Romkens et al. 2016). The presence of CMV in steroid-refractory colitis is associated with poorer outcomes and higher rates of colectomy, however antiviral therapy if often unhelpful (Beswick et al. 2016). Discriminating true CMV colitis is best undertaken using histology with immunohistochemistry from colonic biopsy tissue, which allows identification of those patents most likely to benefit from antiviral therapy (Beswick et al. 2016).

Epstein-Barr Virus Epstein-Barr virus (EBV), also a form of herpesvirus, is ubiquitous, with around 90% of the adult population demonstrating antibodies to the virus. Primary childhood EBV infection is often asymptomatic or mild, whereas primary adolescent EBV can result in mononucleosis syndrome including fever, sore throat and lymphadenopathy (Linton et al. 2013). Mild hepatitis including jaundice is common, as well as hepatomegaly, splenomegaly and maculopapular rash. Serum lymphocyte and monocyte counts are typically elevated. Acute symptoms generally resolve within a month; however fatigue can persist. In rare cases, death can occur due to splenic rupture, airway obstruction, haemophagocytic syndrome or neurological complications (Rahier et al. 2014). After primary infection, EBV enters a latent stage, evading recognition by cytotoxic T cells and coexisting with the host immune system within latently infected circulating B-lymphocytes (Linton et al. 2013). Immunosuppressed patients with IBD are at risk of both primary infection and reactivation of EBV. There is a link between EBV and the development of haemophagocytic lymphohistiocytosis as well as lymphoma in immunosuppressed patients, particularly for those patients on thiopurine therapy (Linton et al. 2013).

Varicella Zoster Virus Primary varicella zoster virus (VZV) infection is nearly always symptomatic, resulting in the 'chickenpox' vesiculo-pustular rash and fever. In adults, primary VZV infection can cause pneumonitis, which is potentially fatal. Latent VSV resides lifelong in the dorsal root ganglia, with reactivation of VZV infection manifesting as shingles (zoster), a painful vesicular rash manifest in a dermatomal distribution (Rahier et al. 2014). Primary infection with VZV, as well as reactivation, is more severe in immunocompromised patients (Cullen et al. 2012; Kopylov et al. 2012).

Human Papillomavirus (HPV) HPV is the most common sexually transmitted infection worldwide. There are over 40 types of HPV, with a spectrum of disease from anogenital warts to high-grade dysplasia or carcinoma of the cervix or anus (Rahier et al. 2014). There is an increased rate of reported abnormal cervical smears associated with HPV infection in patients with IBD on immunosuppressive therapy (Kane et al. 2008).

Influenza Virus The two most common types of influenza virus that causes disease in humans are types A and B. Although the incidence of influenza infection in immunosuppressed patients with IBD does not seem to be increased, the severity of infection may be amplified, with a higher consequent risk of complicated infection and death (Rahier et al. 2014).

21.3.2 Bacteria

Clostridium difficile *Clostridium difficile* is a gram-positive anaerobic spore-forming bacterium, with spores transmitted via the faecal-oral route. *Clostridium difficile* infection (CDI) typically presents with watery diarrhoea, malaise, abdominal pain, fever and leucocytosis. Patients with IBD, particularly those on immunosuppression, are predisposed to CDI. CDI is associated with an increased risk of hospitalisation, surgery and mortality in patients with IBD (Law et al. 2017; Trifan et al. 2014). IBD in itself is a risk factor for acquiring CDI, which may be further compounded by antibiotic and corticosteroid use (Schneeweiss et al. 2009).

Mycobacterium tuberculosis *Mycobacterium tuberculosis* (TB) is an aerobic bacillus that causes caseating granuloma formation. TB typically infects the lungs, particularly the lung apices, but can also cause disseminated disease ('miliary TB'). The incidence and prevalence of TB in IBD patients are variable depending on population, background, underlying disease and treatment. TB has been found to be one of the most common serious OIs to develop in IBD patients treated with anti-TNF therapy (Byun et al. 2015; Ford and Peyrin-Biroulet 2013).

Streptococcus pneumonia Patients on immunosuppressive therapy, particularly older patients, are at higher risk of developing pneumococcal infections (Rahier et al. 2014). Pneumococcal infection can lead to pneumonia or meningitis, with or without bacteraemia.

Legionella pneumophila *Legionella pneumophilia* is a gram-negative bacterial infection that is spread by inhalation of infected water droplets from a contaminated source. Respiratory infection with *L. pneumophilia* is called 'Legionnaires' disease' and should be considered as a differential diagnosis in immunosuppressed patients presenting with respiratory symptoms.

Salmonella **Species** *Salmonella* species, in particular *Salmonella enteritidis* and *Salmonella typhi*, are aerobic gram-negative bacteria, spread via consumption of contaminated food. Infection begins in the gastrointestinal tract but can disseminate leading to sepsis, meningitis, urinary tract infection or arthralgia. *S. typhi* causes 'typhoid fever', characterised by high fevers, rash and abdominal pain. Patients taking immunosuppressive medication are at increased risk of severe *Salmonella* infections (Rahier et al. 2014).

Listeria monocytogenes *Listeria monocytogenes* is a bacterial infection primarily transmitted by ingestion of contaminated food, causing 'listeriosis' characterised by central nervous system disease (meningitis, encephalitis, abscess) and bacteraemia. Immunosuppressive therapy increases the risk of developing *Listeria* infection, particularly the use of anti-TNF therapy (Rahier et al. 2014).

Nocardia **Species** *Nocardia* species are gram-positive rod-shaped bacteria that are ubiquitous soil organisms, spread by inhalation or traumatic introduction. *Nocardia* species are of low virulence but in immunocompromised patients can cause opportunistic infection. *Nocardia* infection can cause a range of manifestations including pneumonia, local skin infections and central nervous system infection (including encephalitis and brain abscess formation).

21.3.3 Parasitic and Fungal Infection

Fungi are commonly found in soil and animals. There have been fatal cases of invasive fungal infections in IBD patients undergoing immunosuppression therapy (Rahier et al. 2014).

A higher rate of *Pneumocystis jirovecii* infection has been reported in IBD patients taking corticosteroid therapy, either alone or in combination with other immunosuppressants (Long et al. 2013). There are also case reports of invasive infection with *Candida* species and *Aspergillus* species in immunosuppressed patients with IBD.

Parasitic infection has been reported in patients with IBD receiving immunosuppressive therapy, particularly those travelling to regions with higher endemic risk (Rahier et al. 2014). *Strongyloides stercoralis* infection is associated with non-inflammatory diarrhoea, however in immunocompromised patients can cause overwhelming infection due to the ability to replicate via autoinfection. *S. stercoralis* can persist indefinitely in the host patient and lead to hyperinfection years later when host immunity is reduced (Rahier et al. 2014).

Learning Box 21.2

- Opportunistic infections are caused by viral, bacterial, fungal and parasitic microorganisms.
- Specific opportunistic infections of concern in IBD include *Mycobacterium tuberculosis*, varicella Zoster, hepatitis B virus, Epstein-Barr virus, cytomegalovirus and *Clostridium difficile*, which may complicate immunosuppressive therapy and may mimic an IBD flare.

21.4 How to Detect, Prevent and Treat Opportunistic Infections in People With IBD?

21.4.1 Clinical Detection of OI

Recognition of OI can be difficult in the context of non-specific symptoms, but with a healthy index of suspicion and appropriate testing, timely diagnosis is possible. IBD nurses are in a unique position to assist with detection of OIs in patients with IBD given their close contact with patients and 'frontline' role in patient care. IBD nurses need to be attuned to symptoms that could be consistent with an OI, including unexplained fever, cough, rash or gastrointestinal upset, particularly in immunosuppressed patients or those at risk. Any concerning symptoms for OI should be discussed by the IBD nurse with a medical officer and appropriate assessment and management undertaken per specialist advice.

Learning Box 21.3

- IBD nurses are uniquely positioned at the 'frontline' of patient care to assist with recognition of opportunistic infections.
- Symptoms of opportunistic infections may be non-specific such as fever, cough, rash or gastrointestinal upset but can progress quickly in immunocompromised patients, and identification requires a healthy index of suspicion.
- Prompt assessment and treatment of opportunistic infections are necessary, and concerns as to suggestive symptoms should be reported to the treating medical team without delay.

21.4.2 Screening Tests

Screening tests for the presence of certain infections are recommended for people with IBD prior to the commencement of immunosuppressive therapy. The ideal time to perform screening tests for infection is at diagnosis of IBD, which facilitates timely administration of the necessary vaccinations and implementation of preventative strategies prior to commencement of any immunosuppressive therapy (Mazzola et al. 2017). Although screening guidelines for underlying infection in IBD may vary worldwide, particularly in regions of endemic infection, a guideline is proposed in Table 21.2. A robust clinical history should accompany screening tests to assist with interpretation of pretest probability of infection.

Screening for TB prior to anti-TNF therapy is noteworthy given the magnitude of associated risk. Screening guidelines vary around the globe, often reflecting background incidence of TB infection and BCG vaccination rates. Screening can include a tuberculin skin test or interferon gamma release assay (IGRA) depending on availability, accompanied by a plain chest radiograph. A careful and robust clinical history, focussing on current or past endemic, travel or occupational exposure, is an essential (and often missed) aspect of TB screening. Anti-TNF therapy can be initiated in patients who require treatment for TB in special cases but only in collaboration with a treating infectious disease specialist (Connell et al. 2010). Repeat screening for TB is also recommended for IBD patients treated long term with anti-TNF therapy (Abitbol et al. 2016).

International guidelines recommend that all IBD patients should be screened for HBV and HCV, and all Hepatitis B surface antigen (HBsAg)-positive IBD patients should receive antiviral prophylaxis before starting immunosuppressive medications (Rahier et al. 2014; Chaudrey et al. 2015). Screening for HIV is also recommended for adolescent and adult patients with IBD, particularly before commencement of immunomodulation, with retesting indicated at regular intervals for at-risk patients. Screening should also be conducted for VZV immunity (positive IgG status), given the potential for severe primary infection while on immunosuppression, as well as the necessity to give the live VZV vaccine *prior* to commencement of immunosuppressive therapy. Young IBD patients in particular should be screened for EBV serostatus prior to commencing immunosuppression

Table 21.2 Screening for infection in patients with IBD

Infection	Clinical features	When	Screening tests
Human immunodeficiency virus (HIV)	Fever, fatigue, lymphadenopathy, sore throat, rash, arthralgia, diarrhoea, weight loss, headache, mucocutaneous ulceration	Diagnosis/prior to immunosuppression Retest if risk exposure	HIV antibody • If positive, test HIV viral load and CD4 count
Hepatitis C virus infection (HCV)	Jaundice, nausea, dark urine, right upper abdominal pain, pale stools, pruritus, fatigue, confusion, fever, muscle/joint ache	Diagnosis/prior to immunosuppression Retest if risk exposure	HCV antibody • If positive, test HCV RNA
Hepatitis B virus infection (HBV)	Anorexia, nausea, vomiting, right upper abdominal pain, fatigue	Diagnosis/prior to immunosuppression Retest if risk exposure	HBV surface antigen (sAg), surface antibody (sAb), core antibody (cAb) • If HBsAg positive, test HB 'e' antigen and HBV DNA
Hepatitis A virus (HAV)	Nausea, vomiting, anorexia, fever, malaise, abdominal pain, dark urine, pale stools, jaundice, pruritus	Consider prior to immunosuppression in those planning travel to endemic areas	Hepatitis A virus antibody
Varicella zoster virus (VZV)	Varicella: Fever, malaise, pharyngitis, generalised vesicular pruritic rash Zoster: Painful, unilateral vesicular rash (dermatomal distribution)	Diagnosis/prior to immunosuppression[a]	VZV antibody (IgG)
Epstein-Barr virus (EBV)	Malaise, headache, fever, tonsillitis/ pharyngitis, cervical lymphadenopathy, fatigue, hepatitis	Diagnosis/prior to immunosuppression[b]	EBV antibody (IgG)
Human papilloma virus (HPV)	Cutaneous warts, anogenital warts/ epithelial lesions	Prior to immunosuppression[b]	Cervical 'pap' smear testing
Herpes simplex virus (HSV)	Vesicular lesions to oral mucosa/ genitals/ other cutaneous sites, ocular infection, neurologic symptoms, fever, malaise	Diagnosis/prior to immunosuppression	Clinical history
Mycobacterium tuberculosis (TB)	Fever, pleuritic/retrosternal pain, bronchial lymphadenopathy, fatigue, cough, arthralgia, pharyngitis, pneumonia, dyspnoea, anorexia	Diagnosis/prior to immunosuppression Repeat screening recommended at intervals during immunosuppression Repeat screening following travel to endemic area or possible exposure	Combination screening: • Clinical history • Interferon gamma release assay (IGRA) • Tuberculin skin test • Plain chest radiograph
Cytomegalovirus (CMV)	Fever, dermatologic rash, diarrhoea, fever, abdominal pain	Flare of colonic IBD	Colonic tissue biopsy histology and immunohistochemistry or polymerase chain reaction
Clostridium difficile	Diarrhoea, colitis, abdominal cramping and bloating	Flare of colonic IBD	*C. difficile* toxin A/B enzyme immunoassay, or glutamate dehydrogenase antigen
Strongyloides stercoralis	Persistent GI/cutaneous/pulmonary symptoms, eosinophilia	Consider in immunosuppressed patients returning from an endemic area	*Strongyloides* serology

[a]Test in those patients without a clear history of VZ infection or prior vaccination
[b]Consideration for testing is recommended. Based on ECCO Opportunistic Infections Guidelines (Rahier et al. 2014)

Table 21.3 Vaccinations in IBD quick reference tool (for adult patients who have received full childhood vaccinations)

Vaccine	When	Live vaccine	Safe on immunosuppression	Safe in pregnancy
Pneumococcal	Five yearly	No	Yes	Only if clinically indicated – not routine
Influenza injection	Annual	No	Yes	Recommended
Influenza nasal spray	Annual	Yes	No	Recommended
Tetanus and diphtheria (Td)	Ten yearly	No	Yes	Recommended: Each pregnancy, preferably 27–36/40 weeks gestation
Pertussis (with tetanus and diphtheria) (DTaP)	Ten yearly Replace 1 Td booster with DTaP	No	Yes	Recommended: Each pregnancy, preferably 27–36/40 weeks gestation
Human papillomavirus (HPV2 for females only, HPV4 male and female)	Females and males aged 11–26 Three dose series	No	Yes	Not recommended
Meningococcal (MCV4/ MPSV4-preferred)	Five yearly	No	Yes	Only if clinically indicated—not routine
Hepatitis B	At diagnosis/prior to immunomodulation	No	Yes	Only if clinically indicated—not routine
Hepatitis A	As required	No	Yes	Only if clinically indicated—not routine
Varicella	Two doses, minimum 3 weeks prior to immunomodulation if inadequate immunity	Yes	No	Contraindicated—if not immune give post pregnancy
Zoster	Single dose in patients over 60 years	Yes	No	Contraindicated
Measles, mumps, rubella (MMR)	Minimum 6 weeks prior to immunosuppression if inadequate immunity	Yes	No	Contraindicated—if not immune give post pregnancy

Table References (Chaudrey et al. 2015; Council AGNHaMR 2015)

(Linton et al. 2013). Screening for HSV is not necessary prior to immunomodulation; however a thorough history should be taken including previous evidence of oral, labial, genital or ophthalmic lesions.

Screening for infection is indicated in the event of a flare of IBD, particularly for *C. difficile* infection and CMV infection in the setting of colonic disease (Table 21.3) (Rahier et al. 2014).

21.4.3 Prevention, Vaccination and Management

Preventative measures to reduce the risk of OI are an important part of management of patients with IBD receiving immunosuppressive therapy (Table 21.4). Both vaccination and provision of appropriate advice to reduce risk of infection are extremely important for all patients IBD (Rahier et al. 2014; Chaudrey et al. 2015).

21.4.3.1 Vaccination

Vaccination can significantly reduce the risk and incidence of opportunistic infection in IBD patients yet has been found to be frequently overlooked and underutilised in practice (Table 21.3) (Kotton 2010; Gupta et al. 2011). Awareness of the need for vaccination in IBD patients varies widely amongst gastroenterologists, and despite recommendations, compliance with vaccination schedules may be suboptimal (Walsh et al. 2013).

Vaccination is less effective when administered to already immunocompromised patients,

Table 21.4 Prevention and treatment of infection in IBD patients

Infection	Vaccination	Transmission	Prevention/prophylaxis	Treatment
Hepatitis B (HBV)	Yes	Blood, body fluid contact, sexual, peripartum	Standard precautions, vaccination	Antiviral medication, hold IMM in acute HBV cases
Hepatitis C (HCV)	Yes	Blood, body fluid contact, sexual, peripartum	Standard precautions	Antiviral medication
Human immunodeficiency virus (HIV)	No	Blood, body fluid contact, sexual, peripartum	Standard precautions	Highly active antiretroviral medication, consider holding IMM
Cytomegalovirus (CMV)	No	Body fluid contact	Standard precautions	Antiviral medication, hold IMM in severe colitis cases
Herpes simplex virus (HSV)	No	Lesion exudate contact, sexual	Standard precautions	Antiviral medication, hold IMM in severe cases
Varicella zoster (VZV/chickenpox/shingles)	Yes	Respiratory droplet, lesion exudate contact	Transmission-based precautions, vaccination	Antiviral medication, hold IMM
Meningococcal (Neisseria meningitidis)	Yes	Contact, droplet	Transmission-based precautions, vaccination	Antibiotic therapy
Epstein-Barr virus (EBV)	No	Oral and pharyngeal fluid contact	Standard precautions	Antiviral medication, haematology management for lymphoma, hold IMM
Human papilloma virus (HPV)	Yes	Contact, sexual	Standard precautions, vaccination	Dermatology management for cutaneous warts, oncology management for HPV-associated carcinoma
Influenza virus	Yes	Respiratory secretions, contact/droplet	Transmission-based precautions, vaccination, consider chemoprophylaxis	Antiviral medication
Mycobacterium tuberculosis (TB)	No	Respiratory secretions, droplet	Transmission-based precautions	Infectious diseases management—antibiotic therapy, hold anti-TNF therapy
Streptococcus pneumonia	Yes	Respiratory droplet/contact	Transmission-based precautions, vaccination	Antibiotic therapy, hold IMM
Legionella pneumophilia	No	Contaminated water, droplet	Standard precautions	Antibiotic therapy, hold IMM
Salmonella enteritidis/typhimurium	No	Contaminated food/water, faeces, contact and droplet	Transmission-based precautions, food hygiene and choice	Antibiotic therapy, hold IMM
Listeria monocytogenes	No	Contaminated food, contact	Standard precautions, food hygiene and choice	Hold anti-TNF therapy
Nocardia species	No	Contaminated soil, contact	Standard precautions, skin hygiene	Antibiotic therapy, cease anti-TNF therapy
Clostridium difficile	No	Faecal-oral contact	Transmission-based precautions	Antibiotic therapy, faecal microbiota transplant, consider holding IMM
Candida albicans	No	Contact	Standard precautions, consider prophylaxis	Antibiotic therapy
Aspergillus	No	Contaminated soil, respiratory	Standard precautions, consider prophylaxis	Antibiotic therapy
Pneumocystis Jirovecii	No	Respiratory secretions, contact/droplet	Standard precautions, prophylaxis for triple IMM	Antibiotic therapy
Strongyloides stercoralis	No	Faeces, contact	Standard precautions	Antibiotic therapy

Table key and references: *IMM* immunomodulator, *anti-TNF* antitumour necrosis alpha therapy (Chaudrey et al. 2015; Council AGNHaMR 2015)

emphasising the imperative for screening and vaccination at diagnosis prior to commencement of immunosuppressive therapy (Andrade et al. 2015). Nonetheless, inactivated vaccines are still valuable for patients who are already immunosuppressed, providing important protection to most recipients (Chaudrey et al. 2015; Kotton 2010). Live vaccines should not be administered to patients receiving immunosuppressant therapy, including VZV, oral polio, measles/mumps/rubella and yellow fever. Conversely, inactive vaccines including pneumococcal pneumonia and influenza are safe, as are booster vaccinations of diphtheria, tetanus and poliomyelitis (inactive form) (Hagihara et al. 2014).

Immunisation against HBV is recommended in all patients with IBD. Screening for HBV should be performed at diagnosis of IBD, given that immunosuppression has been shown to reduce the efficacy of the HBV vaccine (Andrade et al. 2015).

Patients who have not been previously infected with VZV (IgG negative) should complete the two-dose course of vaccine at least 3 weeks before commencing immunomodulation. Subsequent vaccinations should only be given 3–6 months after immunomodulation has ceased.

It is recommended that household contacts of immunocompromised patients should also be vaccinated in line with recommended guidelines, so as to reduce the risk of transmission of infection. In the instance of live vaccination of household contacts, there is a small risk of transmission to immunocompromised patients, which can be at least partially mitigated by careful exposure precautions postvaccination (Chaudrey et al. 2015; Kotton 2010).

Pregnancy safety categories apply to all vaccines and should always be considered. Immunocompromised parents caring for infants and children also need to be mindful of inadvertent exposure to live vaccines given to their offspring as part of routine childhood vaccination programmes. Moreover, where a pregnant mother receives biological therapy (anti-TNF therapy) in pregnancy, the newborn should not receive live vaccines within the first year of life (Damas et al. 2015).

21.4.3.2 Other Methods of Prevention

Other methods of prevention of infection in patients with IBD receiving immunosuppression include advice as to risk avoidance. Reduction of exposure to infection may be achieved by hand-washing, careful food and personal hygiene and safe sex practices and barrier contraception. Prevention of 'food poisoning' infections such as *Listeria* and *Salmonella* species requires diligent attention to food handling and choice. This includes avoiding unpasteurised milk and cheese, uncooked meat and eggs, raw vegetables and raw seafood. There are no vaccines available for fungal or parasitic infections, making preventive measures necessary (Rahier et al. 2014).

Prophylaxis against opportunistic infection is an important strategy for patients at risk. All hepatitis B surface antigen (HBsAg)-positive IBD patients should receive antiviral prophylaxis before starting immunosuppressive medications (Rahier et al. 2014). Post-exposure VZV prophylaxis in cases where high-risk patients who are not immunised, seronegative and pregnant and/or immunosuppressed have had significant exposure to VZV should also be given via administration of varicella zoster immunoglobulin. In patients receiving triple immunosuppression, with one of these being a calcineurin inhibitor or an anti-TNF agent, standard prophylaxis against *Pneumocystis jirovecii* with co-trimoxazole is indicated (Rahier et al. 2014).

For female patients with IBD receiving immunosuppressive therapy, more frequent cervical 'pap' smear is recommended (Connell et al. 2010). Reducing long-term corticosteroid exposure is a key strategy to reducing infection risk in IBD patients, including the risk of *C. difficile* infection.

21.4.3.3 Management of Infection

An extremely important part of timely recognition of OI is patient education as to concerning symptoms and access to medical services. Many OIs require a multidisciplinary team input, including a specialist infectious disease physician. For patients on immunosuppression diagnosed with an OI, immunosuppression is typically held or ceased and directed therapy administered.

21.4.4 Travelling IBD Patients

Due to recent developments in treatment options for patients with IBD, overall health, motivation and fitness for travel have improved, meaning that the number of IBD patients travelling internationally has increased (Baaten et al. 2011). IBD patients are at increased risk of acquiring opportunistic endemic infections when travelling overseas, particularly if they are immunosuppressed. For IBD patients travelling to developing countries, special consideration and advice are necessary. Particular attention needs to be paid to the risk of travel-related skin infection and gastroenteritis, both of which have been found to be more common in patients who are immunosuppressed with IBD (Baaten et al. 2011). Preparation of IBD patients for travel is imperative to reduce the risks of OI while abroad.

1. *Travel medicine specialist consultation*. Consultation with a travel medicine specialist is recommended before travel to regions of endemic infection, particularly for immunocompromised patients.
2. *Travel vaccinations*. Non-live vaccines may reduce the risk of endemic infections for patients with IBD travelling abroad. Travel medicine specialists can advise as to the appropriate vaccination schedule depending on the countries being visited. Vaccination regimens for developing countries may include hepatitis A virus, *Salmonella typhi*, yellow fever, rabies, Japanese encephalitis (Table 21.5).
3. *Antimicrobial prophylaxis*. Malarial prophylaxis for travel to endemic regions is recommended. Additionally, it is recommended that IBD patients travel with antibiotics such as azithromycin or ciprofloxacin for treatment of traveller's diarrhoea (Kotton 2010).
4. *Precautions while travelling*. Immunocompromised patients should avoid insect bites, which may transmit disease, as well as infestation with scabies (Rahier et al. 2014). Patients should be educated as to diligent food, water and personal hygienic measures that should also be undertaken to reduce the risk of travel-related skin infection and gastroenteritis, both of which have been found to be more common in patients who are immunosuppressed with IBD (Baaten et al. 2011).
5. *Travel insurance*. Patients with IBD should ensure that they have taken appropriate steps to obtain travel insurance to cover them in the instance of flare of their disease while travelling. Travel insurance covering pre-existing conditions may not be possible for all patients, and it is important that patients explore the health systems of their destinations prior to departure. There is reciprocity of healthcare provision between some countries, meaning

Table 21.5 Travel vaccines and IBD

Illness	Vaccine	Use in immunosuppressed patients	Use in pregnancy
Hepatitis A	Injection	Safe-waning immunity noted	Not routinely recommended
	Gamma globulin	Consider if strongly immunosuppressed	Not routinely recommended
Japanese encephalitis	Injection	Likely safe	Not routinely recommended
Polio	Injection	Likely safe	Not routinely recommended
	Oral live vaccine	Contraindicated (patient and household contacts)	Not routinely recommended
Rabies	Injection	Likely safe	Can be given
Tuberculosis	BCG live attenuated bacterial—injection	Contraindicated	Contraindicated
Typhoid	Vi capsular polysaccharide	Likely safe, less immunogenic	Contraindicated
	Oral live attenuated bacterial	Contraindicated	Contraindicated
Yellow fever	Live attenuated injection	Contraindicated	Contraindicated

Table key and references: (Council AGNHaMR 2015)

that treatment can be provided without out-of-pocket expense.

6. *Medications and infusions while travelling*. Patients with IBD requiring infusions while abroad should consult with their IBD specialist prior to departure. They may be able to facilitate an appointment at a specialist centre where their infusion may be given. Patients with IBD should travel with a letter from their doctor outlining their medical history and medication requirements. This documentation is imperative and is particularly important for airplane travel as well as for navigating customs. Patients should advise airlines if they need to carry syringes or injecting pens prior to travel.
7. *Returning travellers*. There is also an increased risk of TB infection for patients who travel to countries where it is endemic, and screening on return is recommended (Papay et al. 2012). Immunosuppressed patients travelling to developing countries are at increased risk of parasitic infection and should be screened via stool culture for enteric pathogens and microscopy for ova, cysts and parasites in cases of ongoing diarrhoea (Rahier et al. 2014).
8. *IBD travel information*. There are several useful resources for travelling IBD patients including the IBD passport (www.ibdpassport.com).

21.4.5 Elderly Patients

The percentage of newly diagnosed IBD patients aged over 60 years is estimated to be around 10%. Clinical management of older patients is challenging due to a number of factors including competing comorbidities, polypharmacy and a higher potential for medication-related adverse events. Advanced age has been found to independently predispose IBD patients to infection, with infections increasing mortality for elderly patients requiring hospitalisation. Elderly patients are at significantly increased risk of developing OIs when treated with oral corticosteroids. A careful risk/benefit assessment is required prior to corticosteroid use in this group, and if deemed necessary, corticosteroid use should be used for the shortest duration possible (Brassard et al. 2014).

Learning Box 21.4

1. Ideally, assessment and screening for opportunistic infections should occur at diagnosis of IBD.
2. Opportunistic infection preventative measures include vaccination of the patient and household contacts, handwashing, food hygiene, safe sex practices and diligent food handling and choice.
3. Early assessment, diagnosis and treatment of immunosuppressed patients with opportunistic infections is vital.
4. Prevention of opportunistic infection is particularly important for elderly patients with IBD, patients on combination immunosuppression, as well as for immunosuppressed patients with IBD travelling to developing countries.

21.5 Summary

Patients with IBD may be at increased risk of OI, largely due to the effect of immunosuppressive medications required for therapy. The potential for OI is a key safety concern for patients with IBD and their carers. Screening, chemoprophylaxis, vaccination and preventative behaviours are all strategies that can be used to reduce the risk OI in IBD patients. The IBD specialist nurse, as part of the multidisciplinary healthcare team, can play a key role in the implementation of such strategies to mitigate risk of OI, in turn leading to improved patient outcomes.

21.6 Key Resources

- European Crohn's and Colitis Organisation. Second European evidence-based consensus on the prevention, diagnosis and management of opportunistic infections in inflammatory bowel disease (Rahier et al. 2014)
- Update on vaccinations in inflammatory bowel disease (Chaudrey et al. 2015)
- IBD passport website for travelling IBD patients – www.ibdpassport.com

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Cancer

22

Vito Annese and Anita Cserbane

Abstract

- The lifetime risk of cancer is on the rise owing to increasing life expectancy and the increased incidence associated with advanced age.
- In general, when cancer develops or recurs in IBD patients, this may be related to the chronic intestinal inflammation, have no link with IBD or its treatment, and/or may be potentially influenced by the immunosuppressive drugs.
- Health-care providers caring for patients with IBD are often faced with the challenges of managing the disease in patients with history of neoplastic disease or those who develop cancer for the first time.
- Few consensus guidelines and studies are available on the management of IBD patients with history of cancer. Most of the clinical data on the potentially detrimental effects of immunosuppressant therapy derives from observational studies of patients with rheumatologic diseases or solid organ transplants.
- This chapter will offer (a) an understanding into the background cancer risk in IBD patients and (b) analysis and discussion of the risk of cancer related to IBD therapy and, finally, (c) suggest some clues for a multidisciplinary management.

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22.1 Introduction

Because of the long disease life span, health-care givers treating IBD can frequently be faced with a previous or incident cancer history. This can be related to the specific background cancer risk in that subject related to aging, familiar/genetic factors, or ongoing chronic inflammation. However, a potential influence of some therapeutic agents should also be considered. This situation, in the absence of controlled trials and few open series reports available, raises issues such as correct screening, prevention, and surveillance but also eventual modification or adaptation of the medical management. The insights and recommendations reported in this chapter are mainly derived from a recent consensus guideline effort of the European Crohn's and Colitis Organisation (ECCO) (Annese et al. 2015).

22.2 Background Risk of Cancer in IBD

Two recent meta-analyses of population-based cohorts have calculated the increased risk of

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colorectal cancer (CRC) in patients with IBD (Jess et al. 2005, 2012). The excess for CRC for patients with ulcerative colitis (UC) has been estimated at a standardized incidence ratio [SIR] of 2.4, with increased risk for young age at diagnosis [SIR = 8.6] and extensive colitis [SIR = 4.8]. Other important risk factors are a family history of CRC and primary sclerosing cholangitis, particularly in UC (Brentnall et al. 1996). The CRC cancer risk is at 1.9 for Crohn's disease (CD), whereas the risk for small bowel cancer is 27, although the absolute risk is low (Jess et al. 2005). Of note, IBD patients tend to develop CRC at younger ages than non-IBD patients (Ording et al. 2013). However, no effect of IBD on patient survival for CRC has been consistently demonstrated (Ali et al. 2011).

In patients with CD, adenocarcinoma complicating perianal or enterocutaneous fistula tracts can occur but is rare (Laukoetter et al. 2011), and the same is true for patients with UC and ileal pouch-anal anastomosis (IPAA) (Branco et al. 2009).

The overall risk of extraintestinal cancer in patients with IBD is not increased relative to the general population; however, analysis by individual cancer sites shows that CD patients are more likely to develop cancers of the upper gastrointestinal tract, lung, urinary bladder, non-Hodgkin lymphoma, and non-melanoma skin cancers, whereas UC is associated with an increased risk of liver-biliary tract cancers and leukemia (Pedersen et al. 2010; Biancone et al. 2012; Lees et al. 2009; von Roon et al. 2007; Askling et al. 2005).

IBD are associated with an increased risk of non-melanoma skin cancers and the risk further increased with aging (Long et al. 2010, 2012a; Singh et al. 2011a; Ha and Katz 2013; Lanoy and Engels 2010).

22.2.1 Management

Surveillance colonoscopy programs reduce morbidity and mortality due to CRC by detecting cancer at an earlier stage with better prognosis or by detecting and resecting dysplasia, reducing CRC incidence. Benefit estimated in years of life saved may be much greater in colitis patients than for general population screening because IBD-CRC tends to occur earlier in life and modeling has evaluated that life saved per case screened ranges from 1.2 to 5 years in UC patients, compared to 1.2–4 months in general population screening (Collins et al. 2006; Provenzale et al. 1998). The reduced CRC incidence seen in recent studies may be the evidence that surveillance is effective, although other potential factors, including better disease control, may be relevant.

As duration of disease is a major risk factor for the development of IBD-CRC, it is rational to propose a screening colonoscopy when the risk starts to increase, i.e., after 8–10 years from the onset of disease (Eaden et al. 2001). This initial colonoscopy also aims to reassess the extent of disease, since this parameter also impacts on the risk of CRC. Nevertheless, the appropriateness of screening colonoscopy as a way of reassessing disease extent and potential risk has not been formally established. The surveillance schedule should consider the risk for dysplasia to progress to CRC between two surveillance interventions. However, the timing of dysplasia progression is not known in IBD. Therefore, intervals between repeat surveillance colonoscopy should be prospectively adjusted to each patient taking into consideration CRC risk factors and previous endoscopic findings. Disease extent should be taken as the most extensive histologically confirmed inflammation from all previous colonoscopies. A proposal of risk stratification and different time intervals of surveillance colonoscopy has been proposed by the British Society of Gastroenterology and agreed in a consensus guideline effort of the European Crohn's and Colitis Organisation (ECCO) (Cairns et al. 2010; Annese et al. 2013; Magro et al. 2017) (Table 22.1).

In recent years, endoscopic equipment, patient preparation, and diagnostic technique have advanced considerably. High-resolution equipment improves image quality and may improve dysplasia detection rate (Toruner et al. 2005). The dysplasia yield from surveillance colonoscopy can be improved by spraying dyes that highlight subtle changes in the architecture of the colonic mucosa (Subramanian et al. 2011; Wu et al. 2012). This holds true for all dysplastic lesions, the proportion of targeted lesions and the proportion of flat lesions detected. With this method, random biopsies of apparently normal mucosa are of negligible additional value.

Table 22.1 Suggested interval for surveillance colonoscopy in IBD

Risk strata	Risk Factors	Timing
High risk	Stricture or dysplasia detected within the past 5 years, PSC, extensive colitis with severe active inflammation, or a family history of CRC in a first-degree relative at <50 years	Every year
Intermediate risk	Extensive colitis with mild or moderate active inflammation, post-inflammatory polyps, or a family history of CRC in a first-degree relative at 50 years and above	Every 2–3 years
Low risk	All the other situations	Every 5 years

PSC primary sclerosing cholangitis, *CRC* colorectal cancer

Comparable diagnostic yields from chromoendoscopy have been obtained with both methylene blue and indigo carmine (Rees et al. 2016). Achieving optimal colonic preparation is needed for chromoendoscopy, and longer withdrawal time yields higher adenoma detection rates in non-IBD patients (Toruner et al. 2005).

In general, there are no specific screening and prevention recommendations for extraintestinal cancers except for stopping smoking, annual skin screening, and adequate sunblock protection. This is particularly important for IBD patients, particularly those taking thiopurines (Ortiz and Grando 2012; Elwood and Jopson 1997; O'Donovan et al. 2005).

22.2.2 Risk of Cancer in IBD Key Points

- Patients with IBD have roughly a twofold higher risk of colorectal cancer compared to background population, further increased by disease extension, disease duration, young age at diagnosis, family history, and primary sclerosing cholangitis.
- Patients with UC have also a higher risk for liver-biliary cancers and leukemia, whereas those with CD are more likely to develop cancers of the upper GI tract, lung, urinary bladder, non-Hodgkin lymphoma, and non-melanoma skin cancers.
- Adequate, timely, and technically performed surveillance colonoscopy reduces morbidity and mortality due to colorectal cancer.
- Besides the general standard recommendations for other cancers, stopping smoking, annual skin screening, and sunblock protection are also advisable.

22.3 Therapy for IBD and Risk of Cancer

Cancers caused by immunosuppressant drugs represent a minority of the incident cancers observed in patients with IBD.

22.3.1 Thiopurine

Thiopurines can promote cancer in several different ways, such as carcinogenic mutations of cell DNA, impaired tumor cell immune surveillance, and reduced number and/or function of immune cells, and facilitate the proliferation of cells with microsatellite instability. However, several studies conducted in referral centers and adequately powered nationwide studies have suggested that cancer risk in general is not increased (Annese et al. 2015). In a recent meta-analysis, the overall SIR for lymphoma considered in the population studies was significantly increased in IBD patients receiving thiopurines, (5.7, 95% CI 3.2–10.1), but not in former users or patients who had never used these drugs (Kotlyar et al. 2015; Beaugerie et al. 2009). The absolute risks were globally higher by a factor of 2–3 in men compared with women, irrespective of age and drug exposure. The highest absolute risks for lymphoma (any type) were found in patients over 50 (2.6/1000 patient-years) and in males under the age of 30 (estimated crude risk: 1–2/1000 patient-years). In two studies that considered the potential impact of treatment duration, the SIR for lymphoma attributable to thiopurine exposure did not appear to increase substantially beyond the first year of treatment. Thiopurines may also increase the long-term risk

of acute myeloid leukemia and severe myelodysplastic syndromes (Lopez et al. 2014).

Hepatosplenic T-cell lymphomas (HSTCLs) occur almost exclusively in males under the age of 35 who are exposed to thiopurines (Kotlyar et al. 2011). In this subgroup of the CESAME (Cancers et Surrisque Associé aux Maladies Inflammatoires Intestinales En France) study population, the absolute risk for HSTCL was approximately 0.1/1000 patient-years in individuals treated with thiopurines alone and 0.3/1000 patient-years for those treated with thiopurines and anti-TNF agents. In the latter group, over 80% of the cases of HSTCL occur after the first 2 years of combination therapy. The risk can therefore probably be reduced by limiting the duration of combination therapy in this population to 2 years, whenever possible (Beaugerie 2013).

Data suggesting an excess risk of non-melanoma skin cancer (NMSC) in IBD patients being treated with thiopurines have emerged from several studies conducted in the last 5 years and a recent meta-analysis, which found a pooled adjusted HR for NMSC in thiopurine-treated IBD patients of 2.3 (Ariyaratnam and Subramanian 2014). The carcinogenic effect of thiopurines has been attributed to increased UVA-induced DNA damage and increased production of reactive oxygen species in skin epithelial cells. Interestingly, the CESAME study found a significant excess risk of NMSC in IBD patients with past exposure to thiopurines, suggesting that the carcinogenic effect of these drugs might persist after withdrawal (Peyrin-Biroulet et al. 2011). However, this persistent risk was not noted in a nested case-control study in the Manitoba population or in US Veterans Affairs database (Singh et al. 2011a, b).

22.3.2 Anti-TNFα

Inhibition of TNF-alpha has been hypothesized to increase the overall cancer risk, possibly in combination with impaired immune surveillance of tumor cells. Since 1995, several studies have investigated the cancer risk associated with TNF-alpha antagonists used in IBD. Most patients treated with these agents in these studies also used (or had used) thiopurines, so it is difficult to attribute the findings to anti-TNF therapy alone. In addition, most of the studies were not adequately powered to demonstrate a mild anti-TNF-induced increase in the overall risk of cancer. More recently an adequately powered nationwide study in Denmark has confirmed the data of meta-analysis and pooled analysis for either infliximab or adalimumab excluding an excess of risk (Nyboe Andersen et al. 2014; Williams et al. 2014; Osterman et al. 2014).

It is not clear whether concomitant anti-TNF treatment increases the risk of thiopurine-associated lymphoma, except for the hepatosplenic T-cell variety. In two nationwide cohort studies and in a meta-analysis, the absolute risk of lymphoma in patients receiving TNF inhibitors and thiopurines was similar in that of patients treated with thiopurines alone (Lichtenstein et al. 2014; Herrinton et al. 2011).

Data of possible risk of NMSC during anti-TNF are contrasting and not conclusive (Annese et al. 2015). The incidence of melanoma is increasing in developed countries. The results of a recent meta-analysis indicate that the risk of melanoma is mildly increased (37%) in IBD patients, independent of the use of biologic therapy (Singh et al. 2014). In a large nested case-control study performed with data from a large health insurance claims database, the use of TNF-alpha antagonists was independently associated with an increased melanoma risk in patients with IBD (OR = 1.9; 95% CI, 1.1–3.3) (Long et al. 2012b), but in a Danish cohort, the adjusted odds ratio was nonsignificant (Long et al. 2012a). The most recent systematic reviews in the field of rheumatology indicate that the risk of melanoma in patients with rheumatoid arthritis (RA) exposed to anti-TNF agents is slightly higher than that of patients receiving conventional disease-modifying antirheumatic drugs (Ramiro et al. 2014).

22.3.3 Methotrexate and Cyclosporine

Reliable data regarding risk of cancer and therapy with methotrexate and cyclosporine in IBD are lacking. Data on methotrexate related to rheumatologic experience do not report an excess risk of solid cancer or hematological malignancies. Calcineurin inhibition is associated with an unequivocal excess risk of cancer in the posttransplant state but is

generally dose and duration dependent and, therefore, is not an issue for IBD.

22.3.4 Management

The characterization of lymphomas diagnosed in patients with IBD has distinguished three types of lymphomas that are attributable to thiopurine use:

(a) Posttransplant-like lymphomas, which can develop in any patient with chronic latent EBV infection and seropositivity – in other words, the majority of teenagers and almost all adults over the age of 30.
(b) Post-mononucleosis lymphomas, which occur exclusively in males who convert from being EBV-seronegative.
(c) Hepatosplenic T-cell lymphomas, which occur mainly in men under the age of 35 who receive thiopurines, alone or with anti-TNF agents, for more than 2 years. Caution in the indication and duration of thiopurine therapy should be used in these circumstances (Annese et al. 2015).

Risk factors for skin cancers include smoking, older age, male gender, fair skin type and eyes, red hair, cumulative sun exposure, a childhood history of painful or severe sunburns, outdoor occupation and family history of skin cancer, Caucasian race, geographic area, atypical moles, and several genetic factors. They should be evaluated when immunosuppressant therapy is being considered for a patient with IBD (Annese et al. 2015). Given the background excess risk of skin cancers associated with various immunosuppressants, drugs other than anti-TNF agents and calcineurin inhibitors might be safer for use in melanoma survivors and patients at high risk for these tumors. Alternatives to thiopurines should also be considered in patients with histories of more aggressive NMSC.

22.3.5 Therapy for IBD and Cancer

- No increase of solid tumors has been linked to specific therapy in IBD; however, based on the long-standing experience in posttransplant patients, prolonged use of thiopurines or calcineurin inhibitors is associated with cancer recurrence.
- Thiopurines increase significantly the risk of lymphoma, although the absolute risk is small. They also increase the risk of very rare and frequently lethal hepatosplenic T-cell lymphoma.
- A clear increased risk of non-melanoma skin cancers is also associated with the use of thiopurines, with a possible carry-on effect also after withdrawal.
- It is still not clear whether anti-TNF agents increase in association with thiopurines the risk of lymphoma and when given alone the risk of melanoma.

22.4 Management of IBD Patients with History of Cancer

For patients who have apparently been cured of cancer, the risk of local recurrence or metastatic spread of the original neoplastic disease must always be considered. In addition, data from registries in the SEER program suggest that individuals who survive cancer are 14% more likely to develop a second malignancy than those in the general population and the development of a first cancer during childhood increases the lifelong risk of a second malignancy by sixfold (Curtis et al. 2006).

For gastroenterologists and nurses caring for patients with IBD, managing the disease in patients with a history of cancer or those who develop neoplastic disease for the first time can be challenging. Oncologists are often uncertain on how to deal with IBD in their cancer patients. The best course involves joint management by specialists from both fields with case-by-case decision-making based on the characteristics and expected evolution of the index cancer, the probable impact of IBD therapy on cancer evolution, and the intrinsic severity of the IBD. In IBD patients with a history of cancer, the risk of developing new or recurrent cancer is increased twofold relative to that of IBD patients who have never had cancer, regardless of whether they receive an immunosuppressant.

In this context, three major questions arise: first, what effects (if any) have the medical therapies prescribed for IBD on the progression or recurrence of cancer? Second, how should medical therapy for IBD be managed for patients with a history of cancer, newly diagnosed cancer, or recurrent neoplastic disease? Third, what effects (if any) do the treatments used for cancer have on the course of concomitant IBD?

Clinical data on the potentially detrimental effects of immunosuppressant therapy come mainly from observational studies of patients with rheumatologic disease or solid organ transplant recipients. Regarding the use of thiopurines, the risk of recurrence exceeded 20% for patients who had had melanomas or NMSCs and was highest (54%) in the 2 years following completion of chemotherapy, decreasing progressively thereafter (to 33% at 2–5 years and 13% after 5 years) (Penn 1997). However, as shown in Table 22.2, the relative risk of cancer recurrence in the renal transplant recipients studied varied with the type of cancer (Penn 1993). In the CESAME study, the authors concluded that while prior cancer increases the risk of new/recurrent incident cancer in IBD patients, immunosuppressant therapy has no real impact on this risk. These findings should be considered with caution, however, because the subset of patients with previous cancer in this cohort was relatively small (Beaugerie 2014).

Table 22.2 Risk of cancer recurrence (adapted from Penn I) (Penn 1997)

Risk	Organ/type of cancer
Low (<10%)	Incidental asymptomatic renal tumor Lymphomas Testicle Uterine cervix Thyroid
Intermediate (11–25%)	Uterine body Colon Prostate Breast
High (>25%)	Bladder Sarcoma Melanoma and NMSC Myeloma Symptomatic renal carcinoma

Data on anti-TNF therapy in IBD patients with histories of cancer come exclusively from small case series, mostly unpublished yet. Preliminary data on immune-mediated inflammatory diseases and IBD demonstrate no obvious excess risk of developing a second (new or recurrent) cancer while being treated with anti-TNF therapy (Annese et al. 2015); in contrast, a predictive statistical model based on the Adverse Event Reporting System of the US Food and Drug Administration estimated that the risk of a second cancer increased 11-fold after about 10 years of anti-TNF therapy (Stobaugh et al. 2013).

There are no solid data of how to manage IBD patients with newly diagnosed or a history of cancer. Treatment decisions require close collaboration between gastroenterologists and oncologists, and they must be based on a thorough knowledge of the individual case, including the activity of the IBD, concomitant therapy, patient age, and the type and stage of the cancer. The development of a second neoplasm in cancer survivors is one of the most serious and lethal complications of cancer therapy. These tumors account for about 18% of the incident cancers in the United States. In general, thiopurines, calcineurin inhibitors, and anti-TNF agents should be stopped at least until cancer therapy is completed. Conversely, 5-aminosalicylates (5-ASA), nutritional therapies, and local corticosteroids (e.g., budesonide) can be safely used in patients with active IBD and a history of malignancy. For more severe flares that do not respond to these treatments, anti-TNF agents, methotrexate, a short course of systemic corticosteroids, and/or surgery should be considered on a case-by-case basis. Regardless of the expected duration of the immunosuppressant drug withdrawal period, the choice of an immunosuppressant drug that can be initiated or resumed after a completed cancer therapy must be based on the type of cancer.

The decision to resume immunosuppressant therapy in a patient who has had cancer should be carefully evaluated, case by case, in a multidisciplinary fashion. Emphasis should be placed on the individual risk of cancer recurrence (Table 22.2), the potential risk posed by each immunosuppressant drug in the setting of the specific cancer history, and most importantly the amount of time

that has passed since the completion of cancer therapy. Based on data in transplant recipients, physicians should consider delaying the resumption of immunosuppressant therapy for IBD in patients being treated for cancer, because of the risk of recurrent neoplastic disease, for 2 years following the completion of cancer treatment. The delay can be extended to 5 years if the cancer is associated with an intermediate or high risk of recurrence.

22.5 Influence of Chemotherapy on IBD Course

Limited evidence indicates that IBD can be aggravated by hormonal therapy, chemotherapy-induced mucositis, or immune system-activating therapy, alone or in combination (Annese et al. 2015). In patients with active disease at cancer diagnosis, remission can be induced and maintained thanks to the immunosuppressant effects of cancer treatment (despite withdrawal of immunosuppressant therapy for IBD). The impact of targeted anticancer therapy on IBD remains unknown.

22.5.1 Management of IBD Patients with History of Cancer

- Patients with IBD with current or previous history of cancer should be treated in a multidisciplinary fashion with the oncologist and often on case-to-case basis.
- In general, besides the risk of cancer recurrence, individuals who survive to cancer are 14% more likely to develop a second malignancy, and the lifelong risk is increased by sixfold when first cancer developed during childhood.
- Thiopurines, calcineurin inhibitors, and anti-TNF agents should be stopped at least until cancer therapy is completed. Conversely, 5-aminosalicylates and local corticosteroids (e.g., budesonide) can be safely used.
- The decision to resume immunosuppressant therapy should be taken in a multidisciplinary fashion by evaluating the clinical situation, kind of cancer, cancer therapy-free intervals, and risk of each immunosuppressant.

22.6 Summary

IBD are lifetime diseases with frequent need of immunomodulators and biologic therapy. Since the life expectancy is generally unchanged, patients are exposed to a background risk of cancer development, in some cases increased because of the underlying disease (i.e., colorectal cancer). In addition, some cancers are more frequently induced because of the ongoing therapy (i.e., lymphomas and NMSC by using thiopurines). Therefore, health-care providers are often faced with situations of managing the medical therapy of these patients with a previous or current medical history of cancer. Due to the lack of controlled trials and few case series in IBD, most information is derived by rheumatologic or posttransplant experience. A careful multidisciplinary evaluation is the key, with a case-by-case evaluation of risk/benefit ratio.

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Part V

The Patient in…

The Newly Diagnosed Patient

23

Charlotte Mullin, Kate Griffiths, and Lydia White

Abstract

This chapter aims to explore the implication of a diagnosis of inflammatory bowel disease and the effect that a diagnosis of a lifelong chronic condition can have on a patient. This involves exploring patients' expectations of the service and support they should receive as demonstrated through a local departmental survey and service review. This allows services to be adapted to best support these patients and make goals for practical management.

This will be broken down into:

- New diagnosis state of mind
- Patient expectations after a diagnosis of chronic illness
- Supporting adherence and good clinical outcomes
- Reviewing at the point of first diagnosis
- Practical management of a newly diagnosed IBD patient
- An audit of practice
- Service redevelopment
- Chapter conclusion

23.1 Introduction

Inflammatory bowel disease (IBD) is estimated to affect five million people in the world today (European Federation of Crohns and ulcerative Colitis Associations (EFFCA) 2018). As it is a lifelong condition, patients should be empowered to understand their diagnosis and its management, through adequate education and support (IBD Standards Group 2013). This can be a steep learning curve, and establishing what is the right support is therefore essential for patients at initial diagnosis (Whayman et al. 2011). Providing appropriate education and support allows patients to achieve the best quality of life possible, and will help them to adapt to the psychological and social effects of IBD (IBD Standards Group 2013). Ensuring that patients have a positive experience of their care and that the care given is safe is vital in providing a high-quality service (National Institute for Clinical Excellence (NICE) 2014). The IBD nurse specialist has long been seen as pivotal in improving disease management, compliance and patient satisfaction (Nightingale et al. 2000), and is therefore an integral player in the multidisciplinary team, in order to provide this appropriate support and education.

23.2 New Diagnosis State of Mind

With a diagnosis of a chronic illness power, responsibility and control are important in the process of psychological ownership, and what

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this means for a patient's state of mind and their identity or sense of "self" (Winkelman et al. 2005). Every individual experience will be different and personal examples allow health professionals to better understand the psychological impact: One source speaks about a personal example of receiving a prostate cancer diagnosis, in that he endeavoured to *"take control away from the disease and to 'own' it"* (Karnilowicz 2011). He says that his initial diagnosis was a *"journey of discovery",* and that the epiphanic moment of diagnosis was a significant life event which leads to recognising that psychological ownership was integral to his recovery and re-building his lost identity. (Generally psychological ownership has not been studied extensively in contemporary health and cultural psychology but instead has been investigated mainly in reference to owning possessions (Pierce et al. 2003)). However, they go on to say that the experience of identifying with, and owning a disease, is fixed on the idea of control. The greater the level of control may, in turn, result in an enhanced sense of responsibility in order to improve, maintain and protect one's identity (Pierce et al. 2003).

It is also important to consider that professionals and patients often interpret the reality of illness differently. Specialists in possession of expert knowledge have power and control (Foucault 1980). This power difference is especially evident in the health industry (Tang and Anderson 1999). Although both are very dated studies, there is minimal further research found on this topic. With loss of personal power to one's sense of "self" there comes vulnerability and effect on how one perceives their own identity and changes in how one perceives identity could include feelings of increased inadequacy, decreased value and influence in their community (Karnilowicz 2011; Lundwall 2002). Illness can either dominate a patient's identity and permeate all aspects of their life or it can effect only part of their self (Kralik et al. 2004). These shifts in identity and struggle for self-preservation are an ongoing process for patients and it's important that the health care professional (such as the IBD nurse) can recognise this struggle and perspective in order to best support the patient (Karnilowicz 2011).

23.3 Patient Expectations After a Diagnosis of Chronic Illness

Research has shown that patients have certain expectations when they are diagnosed with a chronic condition. Research from the 1990s found that 60% of patients expected advice from a trained advisor, and 86% expected advice on the same day of their diagnosis (Probert and Mayberry 1991). This research remains relevant especially in the absence of significant research. However, more recent guidelines do support high expectations. The British Society of Gastroenterology (British Society of Gastroenterology (BSG) 2004) suggests that patients now expect the emotional impact of their diagnosis to be taken into account. They want written and audio-visual material and the opportunity to meet a non-medical member of staff such as a clinical nurse specialist.

23.4 Supporting Adherence and Good Clinical Outcomes

There has been a lot of research into patient recall and what factors have an impact on the amount of information patients remember. To add to this, the matter of communication is often a challenge for IBD newly diagnosed patients particularly. They are often diagnosed in the endoscopy department after sedation. Although there is no specific research linked to recall after sedation, one can expect that accurate recall and understanding will likely be limited. Patients recall around 50% of information received at diagnosis (Kessels 2003). This figure is supported by the majority of all recall data. Research has also looked specifically at the amount of information forgotten and remembered incorrectly. In fact, up to 40–80% of information provided by a health care professional may be forgotten immediately

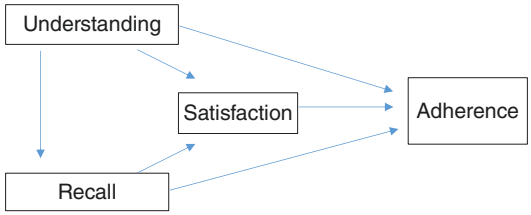

Fig. 23.1 Leys model of interaction. Adapted from: Ley (1988). Psychology and medicine series. Communicating with patients: Improving communication, satisfaction and compliance. New York, NY, US: Croom Helm

or remembered incorrectly (Kessels 2003; Robert 2004).

Despite these disappointing figures, and the additional challenge of post-sedation patients, it is important to persevere towards finding ways to help towards adequate understanding and recall. There have even been studies which link recall with understanding and ultimately compliance (Vermiere et al. 2001; Schillinge et al. 2003). Although study sizes were relatively small at 74 and 150 respectively, both studies concluded that poor communication leads to poor recall and then poor compliance. So better recall would improve understanding and adherence, which is a key aim in managing chronic conditions and good clinical outcomes (see also Chap. 32).

Leys model of interaction (Ley 1988) (Fig. 23.1) diagrammatically represents these links and notably also includes patient satisfaction:

23.5 Support at Diagnosis

According to the UK IBD standards Group (IBD Standards Group 2013), patients diagnosed at Endoscopy, at a clinic consultation or during an acute admission should all be reviewed by the IBD multidisciplinary team (which includes an IBD nurse), and all IBD patients admitted to hospital should be notified to an IBD specialist nurse. At this initial meeting, all IBD patients should be provided with information about the IBD service and how it can be accessed. There should be a clear rapid access process for patients to receive specialist advice and support by the end of the next working day, and patients should be provided with educational literature including disease education, treatment options and self-management strategies (IBD Standards Group 2013).

23.6 An Audit of Practice

In 2015 at the Oxford University Hospitals trust it was recognised that patients may not consistently get this level of support. Therefore it was decided to implement a project to review and direct changes. From an audit of notes, and a patient survey over a 6-month period the team were encouraged that important information was retained by some patients and the input of the IBD nurse specialist was valued. However it also directed service changes.

Results are summarised as follows:

1. *Logistics*: Where the patient saw the IBD nurse:

   Results from the logistics section gave evidence of the range of locations that patients are being reviewed at diagnosis and raised concerns. It was felt that the best location for privacy was in outpatient department consultation rooms. The outpatient department and endoscopy department were equally likely areas for seeing a newly diagnosed patient. A second concern raised was that several patients were still not being given the opportunity to meet an IBD nurse at diagnosis and were relying on telephone consultations to receive information about their diagnosis. Although telephone consultations are convenient, communication is limited by the loss of non-verbal, or para-verbal cues natural to a face to face meeting. Given the importance of understanding and engagement highlighted by the research discussed earlier, it was felt this

may not be appropriate for this initial consultation.

2. *Information received*: What the patient remembers about their diagnosis:

   Results from this section showed:

   – 100% of respondents were able to mark where their bowels were affected, on a picture of the digestive tract.
   – 100% of respondents received a Crohn's and Colitis UK pack (which is an information pack about IBD written by the UK-wide charity), and had said that they had read the written information provided.
   – 80% of respondents said that they had searched for additional information (i.e. on the internet).
   – 70% of respondents felt that the amount of information they received was "just right". The remaining patients said that they couldn't remember (rather than the information was inadequate).
   – 70% of respondents were aware of the advice line and most had used it since their diagnosis.

3. *Further education*: Patient views on further education at diagnosis

   Results from this section showed:

   – 40% of respondents felt that they would have benefited from further education at the time of their diagnosis. Some of those that initially answered "no" to requiring further education at diagnosis then went on to suggest that they would have liked to attend a dedicated education clinic.
   – 60% of respondents said that they would attend a designated education clinic with an IBD nurse, 20% were unsure, and 20% said they wouldn't want to attend.
   – The majority of patients said that they would like to be seen for further education within 1 month of their diagnosis and would prefer a one-to-one session, rather than a group education session.

4. *Overall experience*: Satisfaction with service received and comments

   – 90% of respondents felt that they were listened to (10% marking "can't remember")
   – 100% of respondents found the experience either 'very helpful' or 'helpful'
   – "*I was looked after with dignity and care*"
   – "*Put me at ease and gave me time to ask questions*"
   – "*A positive experience at a difficult time*"
   – "*The information pack was very useful, the nurse talked me through everything*"

23.7 Audit Conclusion: Service Redevelopment

The theoretical work around information and recall was put together with the information gleaned from service audit and patient survey in order to develop a new clinic and an overall change in service design for newly diagnosed patients. The "New Diagnosis Clinic" was the main addition to the service flow. It consists of protected appointments for patients to have adequate time for lengthy discussion if needed (Fig. 23.2). Depending on the level of experience and qualification of the IBD nurse this may include an element of clinical review and even prescribing, ensuring there are no delays in follow-up treatment. The clinic is also during a time slot alongside medical clinics for additional support and advice as needed.

As the diagram details, information leaflets are provided for patients to take away and read and it is ensured that patients have Advice Line details if needed between times. There are also key activities that can be accomplished in the process, such as doing vaccination screening, and both visits are supported by documentation to accurately record and prompt. This documentation includes key subjects for discussion. These topics, with a diagram of the gut for illustration, were then reflected in the service introduction booklets so patients can write, draw and keep their own notes. The topics most frequently discussed, felt to be "essential" by the

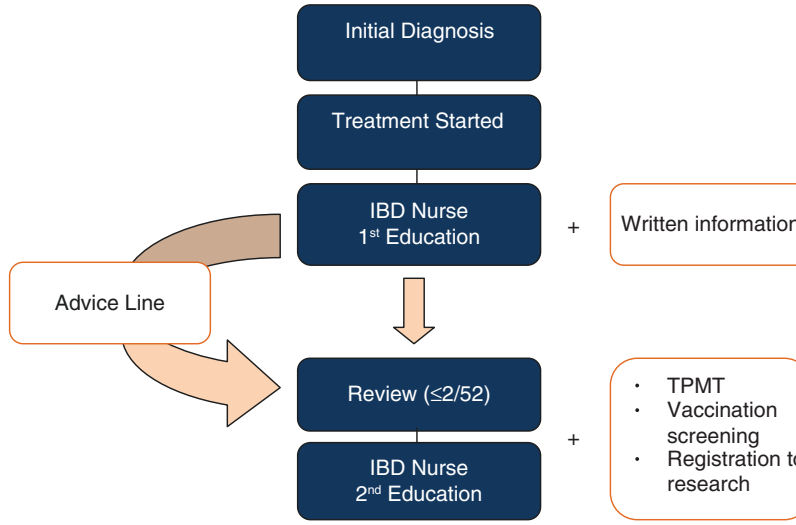

Fig. 23.2 New Service Design

clinical team, and those most asked by patients accumulate to:

- Diagnosis/distribution
- Lifelong
- Remitting/relapsing
- Treatment: Medical/surgical
- Diet
- Causes
- Contact/management
- Smoking
- Pregnancy/fertility
- Travel

Table 23.1 details just a few tips that an IBD nurse may find helpful when communicating with a newly diagnosed patient about these subjects. The two additional points at the end of the table will additionally help inform care decisions of patients going forward. As discussed, it is important to remember that recall for patients in hospital can be challenging particularly if too much information is involved or is poorly presented.

With two points of contact (the initial diagnosis and then the New Patient clinic), it is possible to be flexible with when and how things are discussed. Not all points need to be discussed in one single setting and things can be discussed to a greater or lesser degree as led by the patient.

23.8 Conclusion

The research overview at the start of this chapter suggested how recall and understanding are key to patient satisfaction and adherence. It also recognised how challenging this process is in a real world setting where the location or timing of an interaction with a patient may be less than ideal, such as after a colonoscopy. While guidelines advocate IBD nurse involvement at this stage they are not explicit about how this best occurs but local hospitals can use tools such as audit and survey to consider what changes might be beneficial in their services. The ultimate aim, in any setting, should be to ensure patients a timely and adequate allowance for questions, further education. With this they can begin their lifelong management with a good foundational understanding. It is hoped that their journey with this chronic condition can then begin from a supported and positive mind-set.

Table 23.1 Discussion tips for newly diagnosed IBD

Key topic	Discussion tips
Diagnosis/ distribution	– Use a diagram and indicate the area – Discuss inflammation in the lining of the gut. Can link this to the immune system and how it works
Lifelong	– Once you have it, it is for life – Give an example. (e.g. diabetes)
Remitting/ relapsing	– Symptoms will come and go – Treatment aims to get and keep them in well (like normal) – Consider introducing terms such as "remission" and "flare" – Importance of not stopping treatment when feeling well
Treatment: medical and surgical	– It may take time to find what works for you – Surgery can be a good option when needed
Diet	– There is no diet "for" IBD – A good healthy diet is best
Causes	– We don't know why IBD happens: Not your fault – Immune system + Genetics + Environment
Contact/ management	– Advice line contact details – Clinic appointments and how the process works
Smoking	– Are you a smoker? – Drives Crohn's disease; makes it worse
Pregnancy/fertility	– You are still able to have healthy babies – Best pregnancy is when you are well SO – Take your medication (the correct type)
Travel	– You can still travel – You need to prepare and have insurance – Resources such as www.ibdpassport.com
Past medical history	– Will have been covered in detail by medical review but a quick question on this is not out of place especially if immunosuppression might be indicated soon: e.g., anything in the past (such as cancers, immune disorder)
Flu vax/ Pneumovax (and other)	– Appropriate vaccinations to the country – If LIVE vaccinations use caution (immunosuppression likely) – Opportunistic infection checklist is helpful via resources such as the ECCO website: e-guide.ecco-ibd.eu
Other discussion	– Always give the patient an opportunity to ask any other question or return to a subject that may worry them

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Fertility, Pregnancy, and Lactation

24

J. van der Giessen and C. J. van der Woude

Abstract

Inflammatory bowel disease (IBD) is a chronic disease of the gastrointestinal tract that affects men and women in their young and reproductive years of life. Anxieties about potentially harmful medication, the effect of pregnancy on disease, the effect of disease on the fetus, and the potential of passing on of disease to offspring result in a relatively high "voluntary" childlessness in young women with IBD. A careful consultation with the parents-to-be on these justified concerns is necessary and involves a proactive approach.

24.1 Introduction

In this chapter different aspects of reproduction and pregnancy in women with IBD will be discussed.

Since IBD affects men and women in their reproductive years of life, questions arise around fertility and the possible effect of IBD itself or medication. Furthermore, the effect of IBD on pregnancy and the use of medication during pregnancy and lactation are discussed in this chapter.

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24.2 Fertility in IBD Females

Learning Targets

- Women with quiescent IBD are as fertile as the general population.

Medication prescribed for the treatment of IBD is not associated with lower fertility rates in IBD females compared to the general population. It is known that if patients are in remission, the females are as fertile as the general population (Hudson et al. 1997); however fertility might be reduced in patients with:

- Active Crohn's disease
- Pelvic or abdominal surgery for IBD [e.g., ileal pouch-anal anastomosis (Cornish et al. 2007; Waljee et al. 2006; Rajaratnam et al. 2011)]

Reasons for this decreased fertility probably include induction of inflammation to the ovaries and fallopian tubes in active Crohn's disease and the occurrence of dyspareunia when there is active perianal disease (van der Woude et al. 2015). Further, surgical interventions for IBD may cause tubal adhesions. Patients who have an ileal pouch-anal anastomosis (IPAA), or pouch surgery, have higher rates of tubal obstruction, hydrosalpinx, and destruction of the fimbria, all of which can lower fertility. In the case of an IPAA, patients who underwent a laparoscopic intervention have a

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lower infertility rate than patients who underwent open surgery (Beyer-Berjot et al. 2013).

24.3 Preconception

Learning Targets

- Counseling of IBD patients with a pregnancy wish should focus on the importance of disease remission before conception.
- Preconception care leads to less disease relapse during pregnancy.
- Lifestyle advice is part of counseling (e.g., stop smoking, use of folic acid).

Timely preconception counseling in patients with an active pregnancy wish has been shown to result in less relapses during pregnancy. This is related to medication adherence during pregnancy (de Lima et al. 2016a).

In addition to emphasizing the importance of medication adherence, it is advised to discuss the following factors during preconception counseling:

- The importance of a sustained remission of, at least, 6 months prior to conception
- Risk-benefit of current meds and possible adjustments
- Lifestyle advice such as cessation of smoking, alcohol use, and supplementation of folic acid
- Information about the heredity of IBD
- The effect of medication on breastmilk
- And the mode of delivery as advised with regard to the disease location

Since disease activity increases the risk of relapse during pregnancy and negatively influences fertility, it is advised to strive for a (sustained) remission of approximately 6 months prior to conception (van der Woude et al. 2015; Nguyen et al. 2016). In the majority of patients, medication is needed to accomplish sustained remission, and appropriate treatment of IBD should be maintained to reduce the risk of disease activity during pregnancy. To increase the adherence and correct usage of IBD medication during pregnancy, personalized consultation is of great importance.

General lifestyle advice is also part of a preconceptional care and should include counseling about supplementation of folic acid, cessation of smoking, and alcohol use.

An additional serious concern for IBD patients is the risk of their offspring developing the disease. Children of parents with IBD have an increased risk of developing IBD. When one parent is affected with IBD, the overall risk for their children is 2–13 higher than the general population (Orholm et al. 1999). When both parents are affected, the risk becomes much higher, around 30% (Bennett et al. 1991).

Further, mode of delivery and breastfeeding should be discussed during counseling. Active perianal disease is an indication for a cesarean section. Overall mode of delivery is subject to a multidisciplinary approach and primarily decided by an obstetrician on individual basis.

24.4 Pregnancy

Learning Targets

- There is a higher risk of adverse pregnancy outcomes in case of disease activity during pregnancy.
- Most IBD medication can be used during pregnancy and outweighs the risks of a flare.

During pregnancy acute disease flares carry a high risk of adverse maternal and fetal outcome. Disease activity at time of conception and during pregnancy is associated with a higher rate of spontaneous abortion, preterm delivery, thromboembolic events, emergency cesarean section, and low birth weight. According to current European guidelines, appropriate treatment of IBD should be maintained in those patients who wish to conceive, in order to reduce the risk of flares during pregnancy (van der Woude et al. 2015).

24.4.1 Medication

Below different IBD medications are discussed in further detail.

24.4.1.1 Aminosalicylates

Aminosalicylates are considered low-risk medication during pregnancy (Rahimi et al. 2008). However, sulfasalazine interferes with the resorption of folic acid which is important for women to take before and during the first 12 weeks of pregnancy. Therefore, it is advised to change to other IBD medication before pregnancy or increase the dose of folic acid to 2 mg/day (Norgard et al. 2001). Medication containing dibutyl phthalate coating should be avoided during pregnancy (van der Woude et al. 2015; Hernandez-Diaz et al. 2013). Animal studies showed an increased risk of malformation in the male urogenital tract and a possible association with precocious puberty (Hernandez-Diaz et al. 2013; Jurewicz and Hanke 2011).

24.4.1.2 Corticosteroids

Corticosteroids (CS) are used most often in the case of a disease relapse and can be used during pregnancy. CS cross the placenta, but the placenta is able to convert the medication into a less active metabolite by the enzyme 11-hydroxygenase. Studies show conflicting data regarding risk of malformations when mothers used corticosteroids during pregnancy. In one study the risk for orofacial malformations was increased in the children of mothers receiving corticosteroids in the first trimester (Carmichael et al. 2007; Park-Wyllie et al. 2000), but the risk was small and other studies did not report malformations (Lin et al. 2014; Ban et al. 2014; Hviid and Molgaard-Nielsen 2011). There are also no reports on adverse pregnancy outcomes due to budesonide (Beaulieu et al. 2009). Hydrocortisone, betamethasone, and dexamethasone should be avoided, since they are longer-acting medicine and less efficiently metabolized by the placenta.

There are reports of neonatal adrenal suppression when there is exposure to corticosteroids in utero (Homar et al. 2008). Therefore it is advised to consult a pediatrician who is able to examine the cortisol levels of the newborn.

The risk of maternal complications such as gestational diabetes and hypertension seems to be increased during pregnancy (Martel et al. 2005). Follow-up by a gynecologist/obstetrician is therefore necessary.

Overall the use of corticosteroids during pregnancy is of low risk, but risks and benefits should be considered when prescribing these medications.

24.4.1.3 Immunomodulators

Thiopurines are considered of low risk, and it is advised to continue these medications during pregnancy. Azathioprine and 6-mercaptopurine are converted into the active metabolite 6-TGN and 6-MMP. It was shown that 6-TGN crosses the placenta (de Boer et al. 2006). Recent studies reported no adverse pregnancy outcomes for children exposed to thiopurines in utero (Kanis et al. 2017; Casanova et al. 2013; Coelho et al. 2011; Shim et al. 2011). Limited data for 6-TG as a medicine is known; however it is transferred across the placenta.

Use of methotrexate (MTX) is prohibited. MTX is teratogenic and therefore contraindicated, at least, 6 months prior to conception and during pregnancy (Kozlowski et al. 1990). In the unfortunate case that MTX is not stopped before pregnancy, the drug needs to be stopped immediately, and high-dose folate should be started. Further counseling with an obstetrician to discuss therapeutic abortion should be considered.

24.4.1.4 Anti-TNF Agents

Most commonly prescribed biologicals are infliximab (IFX) and adalimumab (ADA). These two IgG1 antibodies cross the placenta in the second and third trimester of pregnancy (Kane and Acquah 2009). Although exposure to IFX or ADA does not seem to increase the risk of adverse pregnancy outcomes, the long-term effect on children who were exposed in utero remains unknown. Therefore, discontinuation of the treatment during pregnancy might be considered to limit this intrauterine exposure. If the disease is in sustained remission, it is possible to stop these agents around week 20 of pregnancy. Stopping anti-TNF therapy during second and third trimester does not increase the flare rate (de Lima et al. 2016b).

It is advised to measure cord blood levels. Anti-TNF cord blood levels are dependent on the stop

week of the anti-TNF. However, when anti-TNF is continued, the drugs levels of the infant will exceed the levels measured in the mothers (Zelinkova et al. 2011). These high levels of anti-TNF in the fetal blood do not seem to have an influence on the pregnancy outcome (Zelinkova et al. 2013). In the first year of life, there is also a normal growth and development of the children (Mahadevan et al. 2012). The achievement of milestones in children exposed to anti-TNF agents, thiopurines, or combination therapy was similar or better than the cohort who was not exposed to medication (Mahadevan and Sandler 2014). For monotherapy with anti-TNF, no increased infection rate in the infants has been reported. In the case of combination therapy with anti-TNF and thiopurine, there was a higher rate of infection in the infants (Mahadevan et al. 2012). It is recommended to follow up drug levels every 3 months, until drug levels are undetectable. When levels are still detectable, infants should be considered immune suppressed. Therefore administration of live vaccines should be avoided in the first 9 months of life, and it is advised to not bring the children to daycare until drug levels are acceptable.

Thalidomide use has been associated with fetal malformations and neonatal mortality rate of 40% (Smithells and Newman 1992). Therefore thalidomide is contraindicated during pregnancy.

Golimumab data on pregnancy outcomes are limited, but because of the similarity of the safety profile to other anti-TNF, it is considered of low risk.

Certolizumab pegol (CZP) is transferred across the placenta by passive diffusion. Due to this mode of action, the levels of CZP reaching the fetus are probably much lower when compared to ADA and IFZ. No increase in adverse pregnancy outcomes was found when using CZP (Clowse et al. 2015).

24.4.1.5 Anti-integrins

Vedolizumab is an IgG1 antibody and will be actively transferred across the placenta during the second and third trimester. The data on outcome of children exposed to vedolizumab is very limited. One report, limited by sample size and follow-up, showed the outcomes of 24 women exposed to vedolizumab during pregnancy, which identified no new safety concerns (Mahadevan et al. 2017). Vedolizumab is gut specific which leads to the hypothetical concern that there might be an increased risk of gastrointestinal infections, such as rotavirus in the infants.

24.4.1.6 Anti IL-12/IL-23 Agents

Ustekinumab has just recently been added as treatment medication for IBD. It has been available for the treatment of psoriatic arthritis and psoriasis for a couple of years, and the experience of this medication in pregnancy is from case studies around psoriasis and psoriatic arthritis (Rocha et al. 2015; Adrulonis and Ferris 2012; Alsenaid and Prinz 2016; Sheeran and Nicolopoulos 2014). No adverse pregnancy outcomes were noted in these cases. Rheumatologists give the advice that, since there is limited evidence, alternative medicine should be considered during pregnancy (Gotestam Skorpen et al. 2016).

24.5 Lactation

Learning Targets

- Breastfeeding is possible for women with IBD (also when taking IBD medication).
- Women with IBD might have concern about the transfer of medication into breastmilk.
- Data on transfer of medication into breastmilk is sparse, and long-term studies need to be done.

In general breastfeeding is supported because there are many advantages for the mother and child and is not associated with a higher chance of relapse in women with IBD (Barclay et al. 2009). It is known that IBD women breastfed their baby for a shorter period compared to the general population (Bergstrand and Hellers 1983). Reasons for this are concerns about the transfer of medication into the breastmilk and fatigue of the mother. In Table 24.1 the different IBD medication and their risk during lactation are shown. It is important to note that for some drugs there is limited data.

Table 24.1 IBD drugs and their risk during lactation

Drugs		Risk during lactation
Aminosalicylates		
• Mesalazine	Very little excretion into milk	Low risk
• Sulfasalazine		Lows risk
Corticosteroids		Low risk
• Prednisone		
• Prednisolone	Delay breastmilk for 4 h	
• Budesonide	Very little excretion into milk	
Thiopurines		
• Azathioprine (AZA)	Undetectable or low levels	Low risk
• 6-mercaptopurine (6-MP e.g., mercaptopurine)	Undetectable or low levels	Low risk
• 6-thioguanine (6-TG)		Limited data available, probably low risk
Methotrexate		High risk, do not use
Anti-TNF		
• Adalimumab	1/100 of the maternal drug levels detected	Low risk
	1/200 of the maternal drug levels detected	Low risk
• Infliximab		Limited data available, probably low risk
• Thalidomide		Limited data available, probably low risk
• Golimumab	Not detectable	High risk, do not use
• Certolizumab pegol		Low risk
Vedolizumab		Limited data available, probably low risk
Ustekinumab		Limited data available, probably low risk

Aminosalicylates and corticosteroids are excreted into breastmilk but are considered of low risk (Diav-Citrin et al. 1998; Ost et al. 1985; Habal et al. 1993). Small concentrations of thiopurine have been detected in breastfed babies from mothers who were using thiopurines (AZA/6-MP), but there were no adverse outcomes detected in these children (Gardiner et al. 2006; Angelberger et al. 2011). For 6-thioguanine (6-TG), this data is not available, but by mode of action, it is considered of low risk.

Studies on IFX and ADA showed no impact on the infection rate in the infants, although the medicines are excreted into breastmilk in small quantities (Ben-Horin et al. 2011; Ben-Horin et al. 2010).

So far only animal studies have reported on vedolizumab and ustekinumab. These medicines are considered of low risk by their mode of action (Martin et al. 2010; Takeda 2014), but in the absence of sufficient data, it is advised to not breastfeed infants when mothers take vedolizumab or ustekinumab.

24.6 Conclusion

All clinicians, including IBD nurses, have a role in advising patients with IBD having children.

The key messages are:

Fertility

- Women with quiescent IBD are as fertile as the general population.

Preconception

- All women of reproductive age should receive preconception counseling.
- Conception occurring at a time of active disease increases the risk of persistent activity during pregnancy.

Pregnancy

- There is a higher risk of adverse maternal and fetal outcome in case of disease activity during pregnancy.

- Appropriate treatment of IBD should be maintained in those patients who wish to conceive, in order to reduce the risk of flares during pregnancy.

Lactation

- Breastfeeding is possible for women with IBD (also when taking IBD medication), but data on transfer of medication into breastmilk is sparse and long-term studies need to be done.

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Young IBD

25

Vikki Garrick

Abstract

To help set the context for this chapter, consider the following clinical situation:

Clinical Conundrum

You are in clinic and a young mother comes into the room. She has 3 children with her, aged 2 years, 6 years and 8 years. The 6 year old has just been diagnosed with Crohn's disease. You are seeing them at clinic to give disease education to her and the child and commence Exclusive Enteral Nutrition (EEN).

How do you approach this?

This chapter aims to support nurses managing children and families with IBD by providing practical advice on how to deal with situations like the one described in the 'Clinical Conundrum' box above. For the purposes of this chapter, we will use the term 'children and young people' (CYP) to encompass paediatric and adolescent patients. Specifically, we will address:

- Differences in disease phenotype in the CYP population
- Medical priorities
- Nursing priorities
- Transition

25.1 Introduction

Young people with inflammatory bowel disease (IBD) require a different approach to nursing management than their adult counterparts. The reasons for this stem from the fact that they are not yet fully developed as adults either physically or mentally and this has an effect on their ability to live with and manage a chronic disease (IBD Standards Group 2013; Mowat et al. 2011). For this reason, the UK National Standards dictate that children and young people with IBD should be cared for (at least in part) by a paediatric gastroenterology team (IBD Standards Group 2013). The aim of this approach is to provide appropriate and holistic management of the young person and their family through the delivery of family-centred care. In essence, this means that healthcare professional input should encompass the entirety of the family—specifically parents and carers (Coyne et al. 2011).

25.2 Phenotype and Incidence

Learning Targets

- Be aware of the aetiology of Inflammatory Bowel Disease.
- Understand the differences in adult and paediatric phenotype.

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- Understand the importance of a holistic approach to management.

The phenotype of IBD in CYP is different from that in adult IBD. Specifically, colonic CD is more common at diagnosis, and pancolitis is more likely with a diagnosis of paediatric UC. This differs for the adult phenotype where small bowel CD is more common at diagnosis and distal disease (left-sided disease) is more common in UC (Van Limbergen et al. 2008).

The most common age at diagnosis of IBD peaks at between 15 and 29 years (Hovde and Moum 2012), and the incidence of paediatric IBD diagnosis is on the increase (Benchimol et al. 2011). The detrimental effects of chronic disease on the developing young adult are well documented in the literature (Smith and Gettings 2016; Triantafillidis et al. 2013), so it is vital therefore that the CYP has both early and appropriate medical and nursing management at diagnosis and afterwards. IBD teams must be aware of the potential problems which may occur if the CYP is not managed holistically. Historically, clinical consultations have been the domain of the medical profession alone; however, with the implementation of advanced nursing roles (such as the IBD nurse specialist), this has become less so (Betz 2013; Dowling et al. 2013; O'Connor et al. 2013). An appreciation of the psychological and emotional status of the CYP is crucial to the implementation of an effective management plan for the young person, and the IBD nurse is fundamental to this process.

Learning Targets

- IBD phenotype in CYP is likely to be more extensive.
  - Crohn's: more likely to have colonic disease at diagnosis.
  - Ulcerative colitis: more likely to have pancolitis at diagnosis.

- The incidence of IBD in CYP is increasing.
- Management plans for the CYP with IBD should be holistic.

25.3 Medical Priorities

Learning Targets

- Be aware of the therapeutic options for managing IBD.
- Understand the role of exclusive enteral nutrition in CYP management.
- Be aware of the need for a holistic approach to the implementation of management strategies.

The principles of medical management in the CYP are the same as those for the adult population, specifically induction and maintenance of remission. This is achieved using both medical and surgical approaches where appropriate (Turner et al. 2012; Ruemmele et al. 2014).

Exclusive enteral nutrition (EEN) is an effective induction therapy (Ruemmele et al. 2014), although it's exact mechanism of action is unknown. It is thought to have an effect on the gut microbiota, essentially 're-programming' the bacteria within the bowel to interrupt the inflammatory process (Critch et al. 2012). The treatment course for EEN is 6–8 weeks (Ruemmele et al. 2014); however, despite the limited side-effect profile and positive effect on nutritional imbalance, many patients find it too challenging to comply with, and this is cited as a major drawback to this therapy (Rubio et al. 2011). Of note, the implementation of robust patient support mechanisms during this therapy increases compliance and may have a beneficial effect on patient outcomes (Garrick et al. 2011). The IBD nurse is well placed to facilitate these support

mechanisms and improve the likelihood of successful therapy.

Corticosteroids are the most common choice for induction therapy in adult medicine predominantly because of their anti-inflammatory properties. While this is an effective induction agent, the side-effect profile is significant and includes weight gain, acne, mood swings and poor bone health (BMJ Group and Pharmaceutical Press 2014). For this reason, guidelines now specifically advise against corticosteroid therapy as a long-term treatment option (Mowat et al. 2011; Ruemmele et al. 2014). In particular, the use of steroid therapy in the CYP group is likely to be very challenging due to the negative effect on body image—specifically weight gain and acne. The nurse should be aware of these issues and their likely effect on the young person's psychological health when counselling them and the family on the pros and cons of medical therapies.

Maintenance of remission strategies focus on reducing long-term immune activity, the purpose of which is to produce a prolonged period of remission through immunosuppression (Mowat et al. 2011; Ruemmele et al. 2014). There are several immunosuppressant therapies available for the management of IBD, most commonly used are thiopurines (azathioprine and 6 mercaptopurine) and methotrexate. The pharmacology of these medicines will have been covered in previous chapters.

Biologic therapy is an established part of the therapeutic strategy (Fell et al. 2015; Kammermeier et al. 2016). To date, infliximab and adalimumab are the most commonly used anti-TNF-alpha therapies in the paediatric setting within the UK; however many more biologic therapies targeting other cytokine pathways are being used in adult IBD management. Licencing issues prevent the rapid implementation of these therapeutic options in the paediatric arena; however many clinicians will prescribe 'off licence' providing the evidence base exists for their use.

Management of patients on these medications requires a significant degree of coordination and review, and as such, many IBD nurse services have developed 'biologic services' in order to safely monitor this patient group (Greveson and Woodward 2013). The practical aspects of biologic therapy can make it challenging to manage from a family-centred perspective. If the CYP is having infusions every 8 weeks, family life can be very challenging to arrange, particularly if there are siblings and one or both parents work.

The principles of family-centred care are therefore vital to managing this patient group, specifically those of partnership and collaboration (Kuo et al. 2012). From a practical perspective, infusions should be arranged at a time which is suitable for the healthcare system *and* the family. The nurse managing these patients must therefore be aware of any additional family pressures and design holistic care pathways to support them in collaboration with the CYP and their family.

Learning Targets

- EEN is the preferred induction agent in CYP CD management.
- EEN therapy requires formalised nursing support to ensure success.
- Immunosuppression dose is the same as for adults.
  - Azathioprine: 2.5 mg/kg
  - Methotrexate: 15 mg/m^2
- The practicalities of biologic therapy can be challenging from the perspective of family-centred care. A holistic approach to this is vital.

25.4 Nursing Priorities

Learning Targets

- Understand the concept of family-centred care.
- Understand the need for effective communication with the CYP and parents.
- Apply strategies for effective communication with all age groups.

25.4.1 Family-Centred Care

The nursing management of the CYP with IBD is fundamentally different from that of managing adults with IBD. This is predominantly due to the requirement for a family-centred approach to patient management. This approach is best illustrated with a case study which will highlight the fundamental principles (below):

Case Study

Clare is a 14-year-old girl in her third year of high school and is the eldest of four children. She has had Crohn's disease for 4 years and has recently had to be escalated to biologic therapy.

Dad works away from home and mum has a part-time job. Clare is having infliximab infusions in hospital, and mum is struggling to rearrange work, arrange childcare for the siblings and attend hospital with Clare for her infusions. Clare's younger sibling has also received an appointment in the Children's hospital from a different specialty on a different day, and mum is not able to manage this as well as Clare's next infliximab infusion.

The IBD nurse met with mum to discuss the issues which were important to mum. These were:

- Attending both appointments—they were equally important to her
- Managing childcare for hospital attendance
- Negotiating with her employer for regular time out to attend with Clare for infliximab
- Clare missing school

The IBD nurse contacted the specialty medical staff who were going to review Clare's sibling and rearranged the appointment for the same day as Clare's infliximab infusion. Play specialist staff were arranged to sit with Clare, while mum attended the appointment with her sibling.

Further infliximab appointments were arranged on the day that mum did not work so that she did not have to arrange time off for every hospital attendance. Further IBD reviews were arranged on days where mum was available. If this were not possible, as much notice as possible was given so that mum could arrange childcare for Clare's siblings.

The IBD nurse contacted Clare's school to make them aware of the practicalities of Clare's medical therapy. They were then able to provide schoolwork for Clare to complete while she was having her infusions in the hospital so that she did not fall behind academically.

The above clinical scenario illustrates how a family-centred approach addresses all aspects of the patient and family—not just the clinical issues. Clare's mum was becoming increasingly stressed by trying to manage both appointments and childcare. Through using a family-centred approach, the IBD nurse was able to resolve the issues which were important to mum and fundamental to the continued smooth running of family life. Working in partnership with the child and family is fundamental to the ethos of family-centred care (Coyne et al. 2011; Kuo et al. 2012), and this can only be achieved by taking a holistic approach to CYP patient management. Family life is busy, and parents often take on the responsibility for the child's IBD in addition to all of this. Through effective communication between the healthcare provider and the family, a highly stressful situation was avoided, and both parties had their respective needs met—Clare had her infliximab at the correct time, and her sister went to her appointment with mum.

25.4.2 Effective Communication

Although effective communication with the parent is vital, this must also be the case with the

CYP themselves. Young people often feel excluded from their consultations with healthcare professionals as the conversation is aimed at the parent and not the young person themselves (Taylor et al. 2010). In these situations, the onus of care remains with the parent, and the nurse must work to encourage the young person to be 'in control' of their own disease. In other words, by encouraging the young person to be actively involved in decisions about their healthcare needs, the IBD nurse can foster a positive therapeutic relationship with the CYP which will stand them in good stead for further interactions.

This is particularly relevant to the adolescent age group when the young person is exploring their identity, forging key relationships and becoming more emotionally mature (Hilliard et al. 2011; McCartney 2011). Displays of challenging behaviour and family conflict are not unusual as the young person tries to assert their independence. In addition, adolescence is a time when risk-taking behaviours such as smoking, experimenting with alcohol and engaging in sexual activity are common. When these 'normal' changes are combined with the burden of a chronic illness, the outcome can be challenging for both patients and those caring for them (Comeaux and Jaser 2010; Forman and Woods 2011). Specific neurobiological changes occur during puberty; in particular the 'socioemotional' and 'cognitive control' areas of the brain have an effect on risk-taking behaviour. Since both of these areas develop at different stages in adolescence, it is likely that risk-taking behaviours in this age group become magnified as one area of the brain matures before the other. In effect, adolescent patients take part in risk-taking activities without having the emotional maturity to fully assess the potential consequences of their actions (Comeaux and Jaser 2010).

In addition, many adolescent patients with chronic disease may receive suboptimal education on lifestyle issues due to the disease-focussed nature of their interactions with healthcare professionals. Healthcare professionals must therefore be aware of these differences and specifically address lifestyle issues during the consultation with the adolescent (McCartney 2011; Forman and Woods 2011; Greenley et al. 2010).

25.4.3 Concordance ('Adherence' Is Also Used in This Context)

For the reasons discussed above, non-adherence (poor concordance) with medical therapies is common in this patient group and in chronic disease management, and this is further exacerbated during adolescence (Hilliard et al. 2011; Stepansky et al. 2010). Issues around adherence should therefore be identified and addressed during consultation with the CYP. As with Clare's mother in the earlier clinical scenario, often the key concerns for the CYP are not clinically related and therefore may go unidentified if specific questions are not asked. Addressing lifestyle issues is fundamental to any consultation and adolescent patient; however, there are techniques which can be used to encourage the CYP to engage in the conversation. Asking questions in a non-confrontational manner sends the message that you are gathering information only—no judgements are being made. Here are some examples:

Confrontational	Non-confrontational (preferred)
Do you smoke?	How many cigarettes would you have when you are out with your friends?
Do you drink?	Do your friends drink? If yes, how many nights a week would you have alcohol with your friends? What would you drink?
Are you sexually active?	Do you have a boyfriend? How long have you known him for? How did you meet? Are you sleeping with him?

Furthermore, the nurse should be able to advise and guide the CYP if some identified behaviours are detrimental to their physical or mental health. It is important to remember that an adolescent patient is not a small adult. They are a paradox of cognitively developed but socially underdeveloped young people, and this should be at the forefront of the healthcare professional's mind when consulting with them.

25.4.4 Younger Children

Equally, the younger patient can be a challenge to deal with in terms of cooperating with procedures, taking medicines and engaging with healthcare professionals. The same principles apply for communicating with younger age groups (e.g. those patients under 10 years old). Younger patients respond well to information displayed as pictures or in an interactive manner (Koller and Goldman 2012). The nurse should be able to communicate directly with the child even for a short time during the consultation. Practical tips for this include:

- Get down to eye level with the child (sit on the floor if needed).
- Ask them questions about themselves, e.g., What school do you go to? What is your teacher's name? What is your favourite colour?
- Books with pictures encourage interaction.
- Colouring pens and paper encourage interaction—draw a colon!
- Use simple language, e.g., Colon = tube/snake/wiggly worm.
- Include siblings if they are in the room.
- Use rewards when things go well (star charts, stickers).

Younger patients often display anxiety when they come to the clinic because they may have had difficult experiences there before. Unfortunately, having IBD means that hospital attendance is likely to be a significant part of their life, so it is important that fears and anxieties are identified and allayed where possible. The nurse plays a vital role in this process and can draw on other resources to support the younger child and family with this. Specifically, play therapy is an effective way of helping the younger child understand what is happening to them (Koller and Goldman 2012; Axline 2012)—many children's hospitals have access to this service. Another approach is to plan interventions wherever possible. For example, if the child needs blood samples taken, it is often best to make them aware that this will be happening before they come to the clinic so that they are prepared for it. Flexibility is key to maintaining engagement, so unless the timing of the specific investigation is absolutely vital, it is often more effective to give the child some time to prepare and rearrange a suitable date.

25.4.5 Patient Education

Patient information must be appropriately tailored to the individual needs of the young person and their family, and this will change as they grow and develop into young adults. As a result of this CYP, patients often require several information and teaching sessions as their needs and ability to process information develop. This is best illustrated by considering the following situations—consider the 'age and stage' of the CYP for each situation and think about how you would approach it in terms of setting, language used or whether parents are present or not:

- Explain Crohn's disease to a 5-year-old starting EEN for the first time.
- Counsel a 10-year-old starting thiopurine therapy.
- Counsel a 15-year-old starting methotrexate.

It is clear from the above that a 'one-size-does-not-fit-all' approach is vital if communications with the various age ranges of the CYP patient group are to remain effective. The IBD nurse must therefore be highly skilled in managing this and keeping lines of communication open for the CYP and family (O'Connor et al. 2013). Suggested approaches to the above situations are described below:

- *Explain Crohn's disease to a 5-year-old starting EEN for the first time*:
  - Bring parents into the room.
  - Use the appointment for discussion only—no bloods, no medicines, nothing invasive for the child.
  - Relaxed atmosphere.
  - Use colouring pens/books to explain how the gut works.

  - If discussing a nasogastric tube (NGT), bring a toy with one attached (teddy bear/doll).
  - Simple language—'magic milk', 'tube into your tummy', 'make your tummy feel better'
- *Counsel a 10-year -old starting thiopurine therapy*:
  - Bring parents into the room.
  - Use the appointment for discussion only—no bloods, no medicines, nothing invasive for the young person.
  - Relaxed atmosphere—perhaps a visit at home.
  - Find out what the young person already knows—ask if they understand why they are seeing you today.
  - Address the issues identified by the previous question.
  - Can they swallow pills? Do you need liquid medications?
  - Use clear language—'medicine once a day', 'you need blood tests'.
- *Counsel a 15-year-old starting methotrexate*:
  - Ask if they would like parents in attendance.
  - Use the appointment for discussion only if possible. If other investigations are needed, ask the patient if they are happy to have bloods done, have medicines, etc.
  - Address them directly at all times—bring parents in if necessary, but focus on the young person.
  - Find out what they already know about their visit to you.
  - Ask them if they have any anxieties about the new medications.
  - Address these—even if they have no direct clinical relevance.
  - Demonstrate the injection. Give them a practice pen if possible.
  - Discuss practicalities and effect this may have on their lives—specifically blood monitoring and pregnancy. Arrange administration out with school hours and locally where possible.

It is clear from the evidence above that consultation with the CYP group is often more complex than with an adult; for these reasons, longer appointment times are often necessary. IBD is currently a lifelong condition. It is vital therefore that healthcare professionals are aware of the age and stage of the patient sitting with them and can tailor their consultation style appropriately to fit the needs of the CYP and family.

To complete this section on nursing priorities, consider now how you would approach the initial clinical conundrum illustrated at the start of the chapter:

Clinical Conundrum

You are in clinic and a young mother comes into the room. She has three children with her, aged 2 years, 6 years and 8 years. The 6-year-old has just been diagnosed with Crohn's disease. You are seeing them at clinic to commence exclusive enteral nutrition (EEN).

How do you approach this?

25.5 Conclusion

This chapter has been designed to illustrate the main differences in the management of children and young people with IBD. The delivery of family-centred care means that a more flexible and holistic approach is necessary as the young person moves through the paediatric healthcare setting and into the adult setting. Healthcare professionals should be aware of the different approaches needed to manage this patient group and, perhaps most importantly, that they are not small adults but in fact a specific patient group with specific healthcare needs.

25.6 Resources

- Dr. Mike Evans explains IBD. YouTube video https://www.youtube.com/watch?v=Keqzt83KMVA
- 'What's up with Adam?' graphic novel by Dr. Falk

- 'The Gooey, Chewy, Rumble, Plop Book' by Steve Alton and Nick Sharrat
- ECCO website**:** https://www.ecco-ibd.eu/
- Crohn's and Colitis UK**:** https://www.crohnsandcolitis.org.uk/
- ESPGHAN website: http://www.espghan.org/
- RCN Nurse Network**:** https://www.rcn.org.uk/
- RCN IBD Nurse Network: https://www.facebook.com/groups/RCNIBDNetwork/

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Transition

26

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Abstract

There are several definitions of transition when used in a healthcare setting. Essentially they all cover the same principles of the process being planned, appropriately timed and flexible. Many models of transition exist which focus on either healthcare professional-driven approaches or patient-driven approaches. However none of these illustrate the specific *processes* involved in implementing the various models. This section will describe one model of transition (the sequential model) and the practical application of that process within a healthcare organisation.

Learning Targets

- Understand the need for transition
- Understand the difference between transition and transfer
- Understand the principles of effective transition
- Apply a transition model practically

Transition can be a challenging time for both the young person and their parents. It is for this reason that appropriate preparation is vital, and this should include both the young person and their parents. The previous chapter has already outlined the differences between the adolescent patient and the younger (paediatric) patient in terms of cognitive ability and emotional development. Transition should not be chronologically set; rather it should be a fluid process which supports the young person as they move from paediatric to adult services (van Rheenen et al. 2017).

26.1 Introduction

Several factors should be considered when preparing the young person and family for transition to adult services (Brooks et al. 2017). Specifically these are:

- A flexible approach to timing (not during exams or a disease flare)
- Identification of a named transition coordinator (most commonly the IBD nurse)
- Formal assessment of transition readiness
- An individualised approach to the programme
- The provision of disease-specific information to the young person and family

The practical application of these principles is discussed later in the chapter; however what is clear from the evidence is that poor transition results in unfavourable outcomes for the young people involved. In particular; poor disease control, increased 'unscheduled care' attendance (i.e. A & E or GP's), poor attendance at outpatient clinics,

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poor compliance with medications and an increase in adverse events (i.e. unplanned surgery, use of steroid therapy) (van Rheenen et al. 2017; Brooks et al. 2017). Clearly this will have a significant impact on both the CYP and the healthcare systems supporting them, so IBD teams looking after this patient group must be cognizant of the importance of setting up robust transition processes.

The first stage of this is to encourage the young person to come into the clinic room alone. It can be overwhelming for a young person to do this, particularly if their parent has always been there with them and spoken for them. Consultation style is important in these cases.

26.2 Consultation Style

One of the many challenges faced when managing the adolescent patient is encouraging them to engage in their medical management plan. Specifically, remembering to take medications can be problematic, and this (concordance) has been addressed in the previous chapter. From a practical perspective, framing questions in a non-confrontational manner is helpful in these situations:

Confrontational	Non-confrontational (preferred)
Do you take all of your medicine?	How often would you forget to take your medicine in a week?

This approach is showing the young person that it is 'normal' for them to forget meds and also leads to opening a conversation about ways in which we can help support them with this. The healthcare professional should remember that compliance with medications can be poor for many reasons and it is important to address the cause for this before a management plan can be put in place (McCartney 2011; Greenley et al. 2010a). Often the young person may just forget to take meds—this is relatively easy to deal with. If however the young person is not taking meds because of concerns about side effects or because they do not understand the importance of it, then a session around drug and/or disease education would be a better solution.

It is important to remember that teenagers live very much in the present, so explaining things in a way which relates to their 'here and now' is much more likely to have an effect on their behaviour than projecting potential outcomes for them when they are in their 20s or 30s (Greenley et al. 2010b). Often there can be conflict between parents and teenagers regarding lifestyle issues and taking responsibility for their condition—again this is to be expected, and using motivational consultation techniques can help with this. Focussing on the positives is often a better way to manage potential conflict in the consultation room.

Framing taking responsibility for medications or arranging blood monitoring around increasing independence may be a better way of ensuring this happens, rather than merely 'telling' them that it is necessary. Approaching consultations with the young person during the process of transition in this manner is likely to encourage continued engagement in services.

26.3 The Transition Process

The timing and age of the young person at transition is variable, and guidance exists to help support healthcare professionals in designing transition programmes (van Rheenen et al. 2017; Brooks et al. 2017). As with managing the adolescent patient, the key to a robust transition process is flexibility. Many hospitals will transfer a patient with a letter—this is not transition.

Transition is a process—not an event. It requires an approach which focuses on two key areas:

1. Appropriate preparation of the young person and family at a time where their condition is stable and it is not a significant time in their lives.
2. Appropriate service infrastructure to ensure that the young person is fully supported during the process of change and has moved on. Most patients transition at around 16 years although this is variable. For many patients, this is in the middle of their school exams, and optimal timing (i.e. not just before) is vital here.

In the UK, some centres offer transition into a 'young adult' clinic where the age range covers 16–24 years and acts as a 'bridge' to adult services (Brooks et al. 2017). It is usually arranged

in the adult setting and is designed to support the young person as they evolve into adulthood. This approach aims to encourage independence and self-management over a longer period of time. However, this method will of course only be effective if the necessary infrastructure is in place within the healthcare organisation to support the process.

For the purposes of this chapter, we will now discuss one particular model used within the UK to illustrate the practical implications of the transition process. This is a sequential model called the 'Ready, Steady, Go' model which is split into three stages: 'Ready' (stage 1), 'Steady' (stage 2) and 'Go' (stage 3) (Nagra et al. 2015). Details of how these stages are implemented may vary across various centres, so one specific model which uses these principles (the Glasgow model) will be described as an illustration of the application of the 'Ready, Steady, Go' approach.

26.4 Ready (Stage 1)

Preparation begins at around age 14 years. The concept of transition is introduced in the clinic where the young person is able to ask questions about the process and the healthcare team can assess whether the young person and family are happy (and ready) to begin. Many units then contact the young person directly by letter to formalise the beginning of the process. This is worth mentioning, as in many paediatric centres, the young person is not contacted directly—almost all of the contact goes to the parent, so this is an immediate change for them. This communication introduces the concept of increasing independence in the form of coming into the clinic room alone, arranging repeat prescriptions and arranging blood monitoring.

During this stage, the young person is seen alone in the clinic in the first instance, and the parents are brought into the consultation afterwards. The young person is given documentation to help move them forward in the process of independent management. The documentation is colour coded to act as a pictorial reference to their stage in transition—a traffic light system is used. Stage 1 is red, stage 2 is amber and stage 3 is green. Stage 1 can take anything from 6 months to 2 years to complete and is entirely dependent on the young person and family. Readiness for transition is assessed at each clinic visit, and, as illustrated in the principles above, a flexible approach is necessary.

26.5 Steady (Stage 2)

The next stage is arranged in the paediatric setting and is led by the paediatric team. The adult team (physician and IBD Nurse) attend the Children's Hospital and sit in on the consultation with the young person. This means the young person's first encounter with the adult team is in an environment which is familiar to them. During this appointment, the adult team are introduced to the young person and their family.

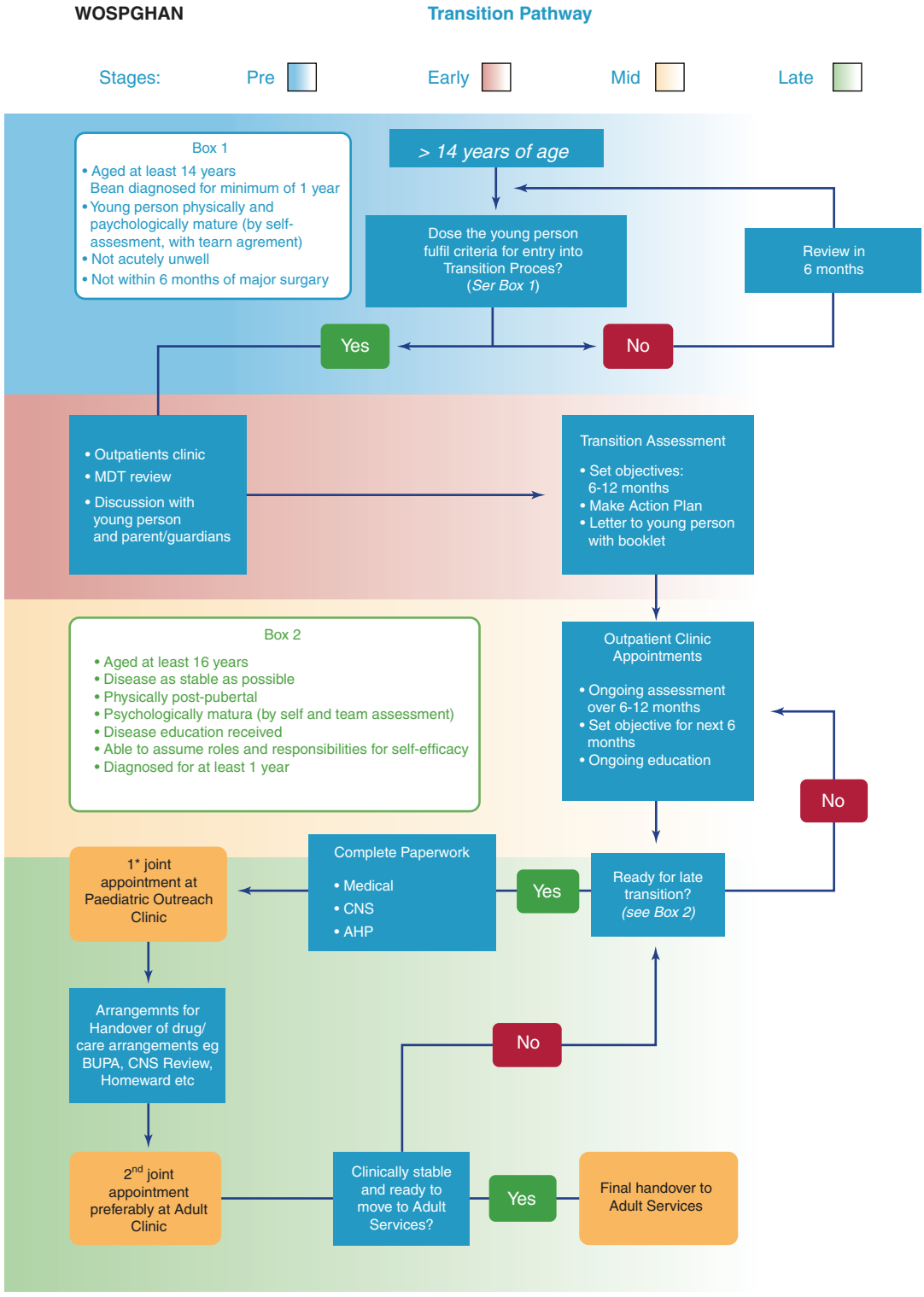
Again, the transition documentation is completed, and the transition readiness is reassessed to ensure the young person and their family are ready to move to the final stage. The individualised approach necessary for the transition process may mean that progress to stage 2 may have to be delayed if the young person's circumstances have changed. For example, if school exams are imminent, their disease has flared, or their lifestyle choices have altered.

26.6 Go (Stage 3)

The final stage occurs in the adult setting with the paediatric team in attendance. This consultation is led by the adult team, and this is usually where new contact details are handed over (by the adult service) and the young person is formally 'discharged' from the paediatric service. Again, this is a flexible process requiring regular review and assessment of transition readiness before it can be completed. This may mean that a young person has to stay in the paediatric setting for slightly longer until they are fully prepared to move on. One example of this is whether the young person has reached full maturity in terms of growth and pubertal development. If this is not the case, transition should be postponed and further referral within paediatrics arranged.

This Glasgow model is illustrated below:

APPENDIX A


WOSPGHAN
Transition Pathway
Stages:
Pre
Early
Mid
Late
Box 1
• Aged at least 14 years Bean diagnosed for minimum of 1 year
• Young person physically and paychologically mature (by self-assesment, with tearn agrement)
• Not acutely unwell
• Not within 6 months of major surgary
> 14 years of age
Dose the young person fulfil criteria for entry into Transition Proces? (Ser Box 1)
Review in 6 months
Yes
No
• Outpatients clinic
• MDT review
• Discussion with young person and parent/guardians
Transition Assessment
• Set objectives: 6-12 months
• Make Action Plan
• Letter to young person with booklet
Box 2
• Aged at least 16 years
• Disease as stable as possible
• Physically post-pubertal
• Psychologically matura (by self and team assessment)
• Disease education received
• Able to assume roles and responsibilities for self-efficacy
• Diagnosed for at least 1 year
Outpatient Clinic Appointments
• Ongoing assessment over 6-12 months
• Set objective for next 6 months
• Ongoing education
No
Complete Paperwork
• Medical
• CNS
• AHP
Yes
Ready for late transition? (see Box 2)
1* joint appointment at Paediatric Outreach Clinic
Arrangemnts for Handover of drug/ care arrangements eg BUPA, CNS Review, Homeward etc
No
2nd joint appointment preferably at Adult Clinic
Clinically stable and ready to move to Adult Services?
Yes
Final handover to Adult Services

The Glasgow transition model. Taken from the WoSPGHAN Transition Guideline 2015 (West of Scotland Paediatric Gastroenterology, Hepatology and Nutrition)

26.7 Setting Up Clinics

Managing adolescent patients and the challenges associated with it is well documented (Greenley et al. 2010b; Forman and Woods 2011; Louis-Jacques and Samples 2011), so interested personnel are vital to ensuring that the transition process works. Flexibility, understanding and empathy with the adolescent mindset are key to ensuring both the young person and the parents feel supported during the process.

Practical challenges to setting up clinics have included ring-fencing specific time within job plans to ensure the transition clinic is run as its own entity and patients are not simply 'slotted in' to existing adult clinics. As previously stated, best practice would suggest that longer appointment times are allocated to ensure that the young person and their parents feel appropriately supported during the process (van Rheenen et al. 2017; Brooks et al. 2017). Slotting these appointments into adult clinics may not be practical or possible, and any team considering setting up transition clinics should be cognizant of this. The Glasgow model uses six slots each lasting 30 min.

On a more practical level, the room has to be big enough to fit up to seven members of staff comfortably (adult team physician and nurse, paediatric team physician and nurse, two parents and young person); otherwise the young person and their family may feel overwhelmed.

As has been illustrated above, a supportive local organisational infrastructure has to be in place for the transition process to flow smoothly. In addition adult personnel who are interested in adolescent patient management are a welcome addition to the transition team.

Practical advice has been given throughout the last two chapters, but a summary of helpful hints in managing the CYP are also included below:

Toolkit for CYP Management

- Longer appointment times—this is time invested.
- Once daily meds where possible.
- See young person alone in the first instance—parents can come in later.
- Encourage them to tell you about themselves using open questions:
  - How is school?
  - What subjects are you doing?
  - What are your plans for afterwards?
  - What did you do at the weekend?
  - What do you like to do outside of school?
- Frame questions in a non-judgemental way: 'How many times a week would you forget to take your medicine?'
- Ask about lifestyle
- Remember they are not adults—communication and guidance may be necessary between clinic appointments.
- Set 'reminders' in their phone for medicines and appointments.
- Encourage communications with the IBD Nurse service directly from the CYP, not the parent.
- Collaboration not confrontation.

26.8 Conclusion

This chapter has been designed to illustrate the reasons for transition and how the CYP group benefit from this process. The 'Ready, Steady, Go' model has been highlighted as one example of this. Adult and paediatric teams should work together to provide a flexible approach which supports the young person as they move into the adult care setting. Young people require an age-specific approach from healthcare professionals which takes into account both their physical and emotional health.

26.9 Resources

Ready Steady Go Transition Programme (2017) https://www.nice.org.uk/sharedlearning/implementing-transition-care-locally-and-nationally-using-the-ready-steady-go-programme. Accessed 13th Aug 2017

ECCO website: https://www.ecco-ibd.eu/

Crohn's and Colitis UK: https://www.crohnsandcolitis.org.uk/

ESPGHAN website: http://www.espghan.org/

RCN Nurse network: https://www.rcn.org.uk/

RCN IBD Nurse Network: https://www.facebook.com/groups/RCNIBDNetwork/

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Elderly

27

Lisa Younge and Nienke Ipenburg

Abstract

The combination of an ageing population and now recognised second peak of onset of IBD in individuals aged 60 and over means the management of IBD in the older person is becoming ever more important.

Comorbidity and polypharmacy are more likely in this age group which may impact upon management decisions, particularly in regard to the use of immunosuppressant, steroid and biological therapies.

This chapter considers specific considerations for nurses and other healthcare professionals managing the older person with IBD, highlighting appropriate assessment and management skills nurses can develop to play a meaningful role in the management of IBD in the elderly person.

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27.1 Introduction

Until relatively recently, little data existed about IBD in the older person. Possible explanations for this include higher rates of exclusion from clinical trials, primarily due to concerns about ageing itself increasing the risk of (possibly severe) adverse events, and historically less endoscopic procedures performed within this population. Although the peak incidence of IBD is between ages 20–39, a second peak is recognised between ages 50–70 years of age (Charpentier et al. 2014). It is, however, estimated that approximately 25–35% of people living with IBD fall into the 'elderly' bracket, with 15% of those being diagnosed 'de novo' with the conditions in later life (Jeuring et al. 2016; Nguyen et al. 2015) Incidence rates of UC tend to be greater than for CD, although trends appear to suggest incidence will continue to rise in both disease groups (Charpentier et al. 2014).

The older person with IBD can therefore be stratified into one of two subgroups, late-onset and ageing individual.

27.1.1 Elderly-Onset IBD

A term used to describe first presentation/diagnosis of IBD in an individual aged 60 years and over.

A. Sturm, L. White (eds.), *Inflammatory Bowel Disease Nursing Manual*,
https://doi.org/10.1007/978-3-319-75022-4_27

27.1.2 Elderly IBD Patient

An individual with an established IBD diagnosis aged 60 years or over. Ageing with a known diagnosis of IBD may increase risk of complications and hospitalization, including prolonged hospital stays post operatively, and higher incidences of morbidity and mortality than younger patients (Nimmons and Limdi 2016).

27.2 Assessment and Diagnostic Considerations

Phenotype and presentation characteristics of late-onset IBD are summarised in Table 27.1. In addition, differential diagnosis in this patient population tends to be diverse (see Table 27.2), making robust history taking and examination essential both at the time of diagnosis and during any subsequent disease flare.

Due to the increasing number of differential diagnosis, misdiagnosis of IBD has been reported in up to 60% of older patients presenting with IBD compared with rates of 15% in younger populations (Sturm et al. 2017) with some cases taking up to 6 years to determine a positive diagnosis.

Elderly patients with IBD from either subgroup may present with atypical symptoms; less abdominal pain and systemic symptoms tend to be reported, and rectal bleeding is reported more

Table 27.1 Phenotypic characteristics of inflammatory bowel disease in elderly-onset inflammatory bowel disease

	Crohn's disease	Ulcerative colitis
Location	Colonic or ileo-colonic	Left-sided or extensive disease more common than isolated proctitis
Symptoms	Less bleeding and abdominal pain than younger patients	Less diarrhoea, abdominal pain and weight loss than younger patients
Disease behaviour	Inflammatory; less progression to penetrating and structuring disease	More likely to remain stable
First episode	More severe than in younger patients	More severe than in younger patients
Extra-intestinal manifestations	Less common than in younger patients	Less common than in younger patients
Family history	Less common	Less common
Cancer risk	Higher risk of non-Hodgkin lymphoma with thiopurines and of non-melanoma skin cancer with anti-TNF therapy	Higher risk of non-Hodgkin lymphoma with thiopurines and of non-melanoma skin cancer with anti-TNF therapy

Nimmons, D. World J Gastrointest Pharmacol Ther. 2016 Feb 6; 7(1): 51–65

Table 27.2 Differential diagnosis of IBD at elderly age

	Symptoms	Possible discrimination with IBD
Infectious gastroenteritis	Acute onset of diarrhoea	Recent antibiotic use. Stool sample for pathogenic organisms, including *C. difficile*
Ischaemic disease	Bloody diarrhoea Acute abdominal pain, associated with meal intake	Thorough cardiovascular history taking [including congestive heart failure, cardiac arrhythmias, atherosclerotic disease, embolic disease, vasculitis and diabetes], different localization pattern
Diverticular disease [diverticulitis]	Abdominal pain Diarrhoea	History of diverticular disease. Local inflammation around diverticular part of the colon during endoscopy
Microscopic colitis	Non-bloody diarrhoea Predominantly in females	No anatomical abnormalities visible at endoscopy. Histologically different from IBD
NSAID-induced enteritis	Diarrhoea Abdominal pain	History of NSAID use
Radiation colitis	Bloody diarrhoea Abdominal pain	History of abdominal or pelvic radiation Histologically different from IBD
Rectal ulcer syndrome	Bloody diarrhoea	History of constipation Histologically different from IBD

Sturm A et al. Journal of Crohn's and Colitis, 2017;263–273 2017

frequently both in UC and CD, due to an increased prevalence of colonic involvement in elderly CD patients (Nimmons and Limdi 2016).

Although disease extent tends to be more limited in elderly IBD (Jeuring et al. 2016), the assumption that the disease itself runs a milder course is not necessarily the case. Hospitalisation and surgery rates, particularly at diagnosis, have been shown to be greater amongst later-onset patients (Jeuring et al. 2016; Nguyen et al. 2015). In addition specific data relating to the disease course itself and subsequent flares/severity of flares are lacking (Sturm et al. 2017). Comorbidity and the ageing process in both elderly-onset and elderly IBD patients can further complicate the disease process and its management.

27.3 Management

27.3.1 Medical Management

In general, the principles of medical management for elderly individuals with IBD are as for any adult patient; to induce and maintain remission of symptoms, promote quality of life and prevent complications of disease.

However, advancing age can bring specific challenges:

- Frailty—Frailty can be described as a loss of reserve capacity with negative outcomes. Frailty among elderly people has been recognised as a significant risk factor for falls, disability, hospitalisation and death (Beard and Cassels 2016).
- Comorbidity—The incidence of chronic disease increases with age (Beard and Cassels 2016). Conditions may impact on each other and this needs to be taken into consideration when making prescribing or management decisions. The ageing process itself can also result in deterioration in liver, renal and cardiac function even in the absence of ill health, which will have an impact on metabolism and tolerability of therapies and may increase the potential for significant side effects. In addition, a decreased anal sphincter function might contribute to diarrhoea and incontinence.
- Polypharmacy—An elderly person with at least two chronic diseases will typically exceed the recognised threshold for polypharmacy, i.e. >5 medications. Figures as high as seven have been quoted in the elderly IBD population (Cross et al. 2005). Medications including warfarin, aspirin, NSAIDs, ACE inhibitors, statins and allopurinol are commonly prescribed in older individuals and may have significant interactions with specific IBD medications. Consequences associated with polypharmacy include increased risk of adverse drug events and drug interactions, higher levels of non-adherence and greater health-related costs for the patient. *Ensuring a thorough medication history prior to introducing new medication is essential to minimise these risks.*
- Cognitive function—Age-related deterioration in both hearing and vision, as well as a change in mental state, can impact on understanding and adherence with management plans. After the age of 65, cognitive decline can be common, with resulting levels of non-adherence. Prevalence of depression in elderly patients with IBD has also been quoted as high as 23% (Panara et al. 2014; Graham et al. 1997), which may impact on concordance and ability to manage disease and treatments.
- Financial and social considerations—Older people may have more financial constraints and age-related functional capacity that limit management options. Understanding an individuals' social history and support network can identify issues which may benefit from intervention, including referral to external agencies such as social care and home support as necessary.

In addition to the above, there are a number of drug-specific considerations important to be aware of in this patient population (Fig. 27.1).

- *5-Aminosalicylates (5-ASA)*—Generally well tolerated and often prescribed for colonic CD in the elderly as well as in UC, possibly reflecting clinical reservations about prescribing immunosuppressive therapy in this population (Gower-Rousseau et al. 2013).

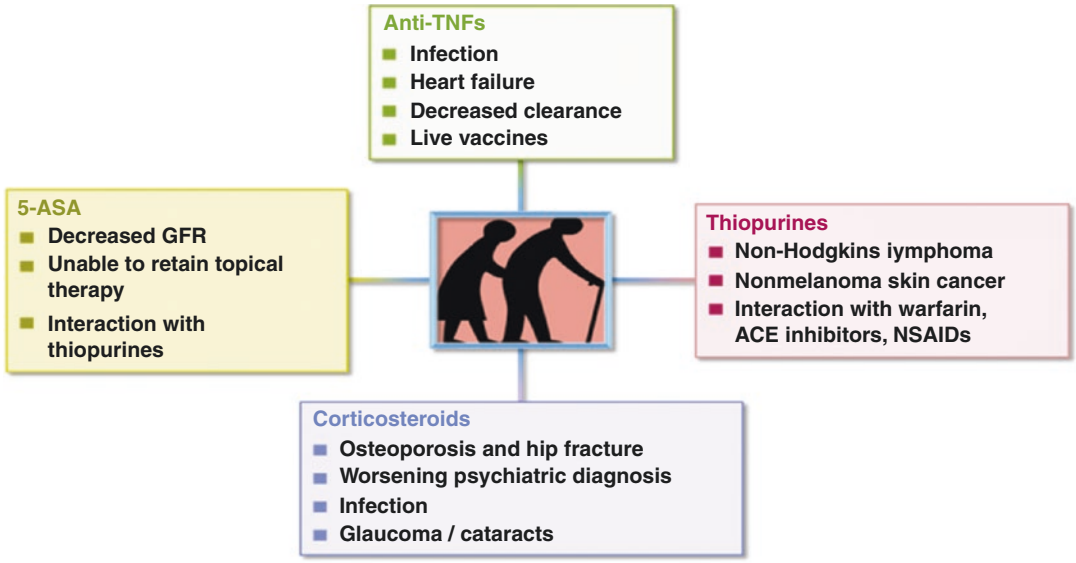

Fig. 27.1 Medical therapy Considerations in the elderly

There is a recognised enhanced effect interaction with warfarin, and caution should be exercised in patients with known renal disease.

If considering the use of topical 5-ASA, consideration should be given to a patients dexterity (and therefore ability to administer and tolerate/manage the therapy) as well as the competence of their anal sphincter, as this is known to reduce with age (Rao 2004). This requires discussion with the patient and ensuring a clear understanding of what is being asked of them, tailoring therapy as required for the best outcome.

- *Corticosteroids*—Side effects including altered mental state, fluid retention, hypertension and glaucoma are more pronounced in the elderly (Nimmons and Limdi 2016).

Osteoporosis is also a significant concern. Ageing itself is a risk factor for osteoporosis, combined with the recognised risk of corticosteroid therapy on bone density.

Corticosteroids enhance efficacy of warfarin, as well as interacting with phenytoin, phenobarbital, ephedrine and rifampin, reducing their efficacy.

Candidiasis also appears to be more of an issue in elderly patients treated with corticosteroids (Sturm et al. 2017)

Topical administrations require the same consideration as discussed previously.

- *Immunosuppressant therapy*—Little data is available in the literature regarding the safety and efficacy of immunosuppressive therapy in the elderly, and the data that does exist is contradictory, due primarily to the exclusion of elderly patients from clinical trials (Sturm et al. 2017).

However, the risk of opportunistic infection has been shown to increase with age, as does the risk of lymphoma, particularly when used in combination with an anti-TNF therapy (Sturm et al. 2017; Siegel et al. 2009). The risk of developing skin cancer is also greater in this population (Nimmons and Limdi 2016; Sturm et al. 2017; Siegel et al. 2009)

The risk of leucopenia is increased when thiopurines are used in combination with clotrimazole or angiotensin-converting enzyme (ACE) inhibitors, commonly used in cardiac disease and hypertension.

The metabolism of *methotrexate* may be reduced in older people, possibly accounting for more pronounced issues with tolerability observed in this population.

Ciclosporine is metabolised by the liver, and age may have an impact on this resulting in higher incidences of side effects, although data is lacking.

- *Biological therapy*—Conflicting data exists concerning both the effectiveness (particularly short term) and incidence of adverse events in older patients treated with *anti-TNFa therapies* such as adalimumab and infliximab.

Serious adverse events in patients aged 65 and over have been reported in a number of case series, and current consensus is that elderly patients treated with anti-TNFa have an increased risk of severe infections (Sturm et al. 2017) Comorbidity, particularly cardiac and renal, is a significant concern.

As before, combination therapy with a thiopurine increases the risk of lymphoma and skin cancers.

- *Integrin receptor antagonists*, in particular vedolizumab, owing to its gut specific mode of action, may prove a safer option for older IBD patients requiring treatment with a biologic. Preliminary real-life data to support this is reassuring (Navaneethan et al. 2017); however it will remain important to monitor this group of patients to identify any potential concerns.

27.3.2 Surgical Considerations

As with medical management, the indications for surgery in the older person with IBD are as they would be for all IBD patients, while taking into account the ageing process and its effects on an individual's physical and mental fitness for surgery. Increasing age is an important independent risk factor for post-operative morbidity and mortality (Beard and Cassels 2016); however, age alone is not considered an accurate predictor of outcome (Nimmons and Limdi 2016; Sturm et al. 2017),

Long-term complications of IBD surgery including pouchitis, anastomotic stricture or deterioration in pouch function in elderly patients undergoing ileal pouch–anal anastomosis have been reported as occurring more frequently (Delaney et al. 2002), but not consistently within the literature.

Dexterity and cognitive function may significantly limit an individual's ability to manage any type of stoma, which could potentially lead to catastrophic decline in quality of life for an individual. Careful patient selection, including assessment of anal sphincter function, locomotor and cognitive function, is important and should be undertaken as early as possible if surgery is likely to be required.

Ensuring the patient themselves and any carer or relative involved is aware of the operation being proposed and its intended outcome along with risk and benefits is essential, particularly if the older patient is likely to require more in the way of support and assistance post-operatively. Pre-operative engagement with support agencies as required should be sought wherever possible.

27.4 Other Considerations

27.4.1 Infections

The elderly patient is by definition at greater risk of opportunistic infection. Corticosteroid, immunosuppressant and anti-TNF therapy use in this population can further increase this risk (Sturm et al. 2017)

- *Clostridium difficile* infection and urinary tract infections carry greater risks of morbidity and mortality in this patient population and therefore should be actively, considered, looked for and treated promptly in any patient in whom there is a suspicion, particularly those contacting services between scheduled reviews with concerning symptoms.
- Prescreening for infection in *all* patients with IBD is an essential part of management for those in whom immunosuppressant of biological

therapy is to be considered or initiated, and the elderly patient is of course no exception.
- Pneumococcal and influenza vaccinations are recommended for everyone aged 65 and over, and IBD patients should be advised to take these regardless of therapies they may be receiving.

In general, following accepted guidelines for the management of opportunist infections in IBD (such as the ECCO guidelines) is recommended.

27.4.2 Cancer Surveillance

Elderly-onset IBD has been associated with increased rate of progression to colorectal cancer (Nimmons and Limdi 2016; Sturm et al. 2017) suggesting increased surveillance intervals should be considered in this population, although no formal screening protocols exist currently.

In *elderly IBD* patients, there does not appear to be a greater risk of colorectal cancers when compared to other patient groups enrolled within standard surveillance programmes, although advanced age itself is a risk factor both for colorectal and small bowel malignancy (Sturm et al. 2017).

Colonoscopic screening, including bowel preparation and the procedure itself, is not without risk in this patient group; therefore discussion with older IBD patients should take place regularly to determine the risk/benefit ratio, particularly with advancing age and when comorbidities are identified. This is not always an easy discussion to have with patients, and should be tackled sensitively and with due consideration of how the outcome might affect the individual.

27.5 The Nurses Role

Nurses involved in the management of people with IBD can enhance care by having a greater understanding of the specific challenges associated with different patient populations. The success of transitional care with adolescent and young adult patients with IBD is a good example of how specialist IBD nurses can help to improve communication and enhance patient experiences as part of the wider MDT. The transition into older age is also one which would also benefit from a structured approach, something which could be developed within services and where possible delivered by the IBD nurse.

- Undertaking formal assessment of the health risks (or frailty) of every independent elderly patient, e.g. medication (polypharmacy), medical history, bone density, incontinence, cognitive deficit and depression, can help to plan care appropriately, something which the IBD nurse would be well placed to do as part of their role.
- Identifying individuals who may require alterations to their management in terms of care delivery or who require extra support to manage their condition is important (Velonias et al. 2017).
- Understanding an individual's social history and support network can identify issues which may benefit from intervention, including referral to external agencies such as social care and home support as necessary.
- Identifying and facilitating changes in care provision, such as the increasing involvement of relatives if a patient becomes confused or less able to communicate, should be done in a structured way, in collaboration with the patient wherever possible (Velonias et al. 2017).

As with many aspects of IBD care, one size will not fit all, but providing a flexible service which allows for specific patient considerations to be accommodated (e.g. telephone review for a stable patient with reduced mobility and multiple hospital appointments for other medical conditions) is an aspect of care delivery which one might consider.

Understanding the unique challenges in caring for older people with IBD is important not only to try and enhance care but also to ensure safety is maintained. Nurses are patient advocates and often the member of the MDT with whom patients first identify changes and concerns with, therefore well placed to ensure everyone within the MDT is kept up to date with a patient's current health needs.

27.6 Summary

This chapter has discussed the specific considerations and challenges associated with caring for and managing the older person with IBD, ranging from diagnosis to long-term care, including disease surveillance. It is hoped by having a greater understanding of the specific needs of this patient population, nurses caring for older people with IBD will find themselves able to contribute to ensuring that individualised, safe and appropriate care can be achieved which enhances both quality of life and the care experience for this patient group.

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Patient Priorities

28

Fernando Magro and Inês Pita

Abstract

Inflammatory bowel disease (IBD) is a systemic disease. Apart from the complexities of managing bowel inflammation per se, it is important to consider the patient as a whole. IBD patients tend to be young and in their working and reproductive years; although it should not be forgotten that a relevant proportion is diagnosed after 60. This chapter explores how active and inactive IBD may cause a significant physical and psychological burden and the importance that health-care professionals understand each patient's experience and expectations about their disease. This chapter focuses on pain, fatigue and urgency; some of the symptoms that most frequently concern patients on their daily basis. The text explores the possible mechanisms behind them and their differential diagnoses, such as the numerous causes of urgency and diarrhoea in the IBD patient other than active disease. The management of each symptom is also examined, including practical daily tips for altered bowel habit and non-pharmacological therapies for fatigue.

28.1 Introduction

The management of inflammatory bowel disease (IBD) has mostly focused on controlling objective intestinal complaints directly related to mucosal healing, such as stool frequency and rectal bleeding. However, patient priorities and concerns regarding disease are multisystemic and both physical and psychological.

A prospective study from Barcelona published in 2017 showed that the most important treatment objectives for IBD patients are quality of life improvement and symptom control and that only a minority report a normal colonoscopy as an important treatment goal. The most important symptoms that patients would like to have remit were abdominal pain, bowel movement urgency, rectal bleeding, diarrhoea and fatigue (Figs. 28.1 and 28.2) (Casellas et al. 2017).

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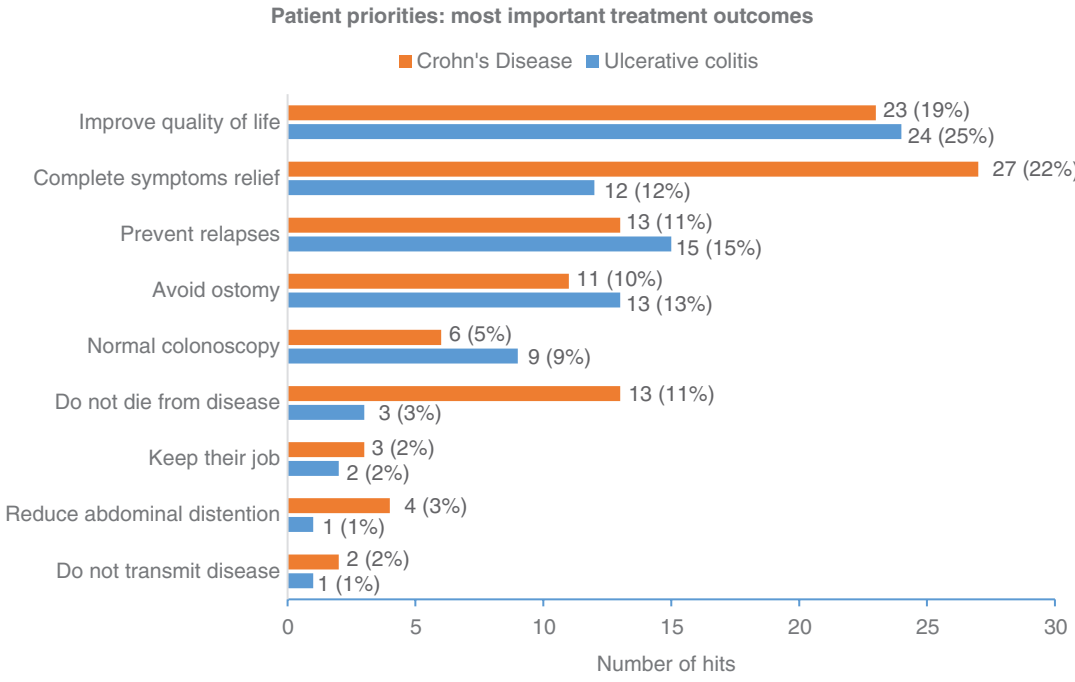

Fig. 28.1 Most important treatment outcomes according to a survey on patients with ulcerative colitis and Crohn's disease. Adapted from Casellas et al. (2017)

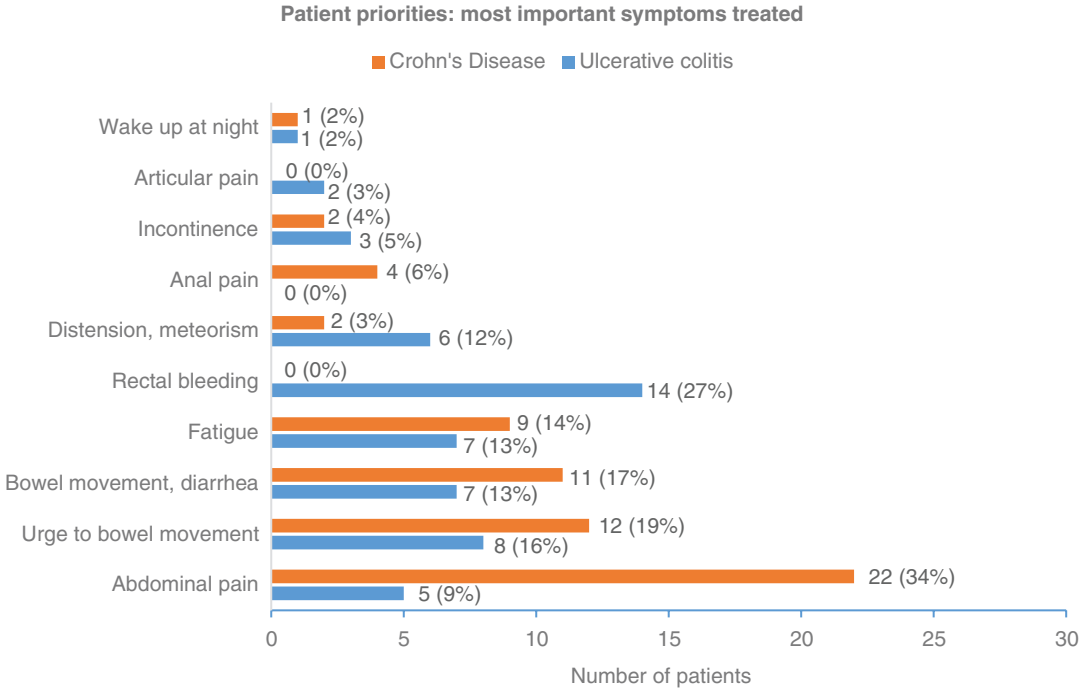

Fig. 28.2 Most important symptoms that inflammatory bowel disease treatment should control, in a survey on patients with ulcerative colitis or Crohn's disease. Adapted from Casellas et al. (2017)

Some but not all of these symptoms are incorporated in disease activity scores used in clinical practice to assess response to treatment. As our understanding of IBD pathophysiology and our pharmacological armamentarium increase, clinicians must fine-tune disease control beyond objective signs and address more elusive and subjective symptoms.

These nuances are already understood by medical professionals, including IBD nurses. A recent survey by the Nurses-European Crohn's and Colitis Organisation showed that symptom control and improving patient quality of life are pressing concerns among IBD medical professionals (Dibley et al. 2016). Additionally, patient-reported outcomes on disease activity, quality of life, fatigue, work productivity and psychosocial symptoms are increasingly being used as endpoints in clinical trials and in clinical practice (Williet et al. 2014).

28.2 Fatigue

Fatigue is a subjective and poorly defined complaint of tiredness, exhaustion and weakness, with a multitude of definitions across literature. It can be described as lack of energy to initiate activity or as impaired performance in both physical and mental tasks (Sharpe and Wilks 2002).

Chronic fatigue, usually defined as symptoms that persist for longer than 6 months, is a well-described problem in many chronic inflammatory diseases such as multiple sclerosis, rheumatoid arthritis, systemic lupus erythematosus, chronic viral and cholestatic liver disease, HIV infection and cancer (Swain 2000).

28.2.1 Physiopathology of Fatigue in Inflammatory Diseases

In many chronic inflammatory conditions, there may be a component of peripheral fatigue due to primary neuromuscular or articular disease activity. However, there appear to co-exist central causes for chronic fatigue shared by all chronic inflammatory conditions. Several mechanisms have been proposed, including an impaired stress response due to an attenuated hypothalamic–pituitary–adrenal axis; elevated circulating levels of pro-inflammatory cytokines such as IL-1β, IL-1 and interferon; and defective central serotonergic and noradrenergic neurotransmitter pathways (Swain 2000).

There are few interventional studies on inflammatory bowel disease in which fatigue is a primary outcome (Czuber-Dochan et al. 2013; Artom et al. 2016). Nevertheless, lack of energy ranks as one of the leading concerns of IBD patients (de Rooy et al. 2001). In the last few years, interest in inflammatory bowel disease fatigue has risen, as evidenced by the increasing number of papers on this field (Czuber-Dochan et al. 2013).

28.2.1.1 Physical Factors

IBD patients have higher prevalence of fatigue than healthy controls, even when in remission (Huppertz-Hauss et al. 2017; Romberg-Camps et al. 2010; Jelsness-Jorgensen et al. 2011). Chronic fatigue prevalence ranges between 44% and 86% in patients with active disease and between 22% and 41% in those in remission (Artom et al. 2016).

Fatigue level is positively correlated with disease activity in almost all studies. However, and rather incongruously, association with physical parameters of disease activity such as C-reactive protein, erythrocyte sedimentation rate, haemoglobin or ferritin deficiency is very inconsistent. It is interesting to note that in almost all studies, disease activity is measured using patient-reported clinical indices (Artom et al. 2016), suggesting that fatigue correlates more with *symptom-reporting behaviour* rather than true mucosal inflammation. It has been proposed that two distinct fatigue patient groups must exist in IBD: those with concomitant mucosal inflammation and those with fatigue symptoms in the absence of disease activity (Gracie and Ford 2017).

28.2.1.2 Psychosocial Factors

The high rates of fatigue even during IBD remission may be explained by the strong association

between fatigue levels and psychological symptoms; the same is true in other chronic inflammatory conditions. Higher fatigue levels and lower quality of life correlate with anxiety, depression and poor sleep pattern consistently across the literature; however, since most of the studies are cross-sectional, the direction of causality is unknown (Artom et al. 2016).

Recent research has also associated fatigue levels with certain personality traits, such as decreased capacity to respond to stressful events (assessed by the sense of coherence scale) (Opheim et al. 2014) or reduced ability to adapt one's behaviour to different situations (as assessed by the revised Temperament and Character Inventory) (Banovic et al. 2012).

28.2.1.3 Non-modifiable Factors

There is some evidence that fatigue levels are higher in women; in patients with shorter disease duration, higher number of previous relapses and longer length of bowel resected; and in the presence of comorbidities such as irritable bowel syndrome (Artom et al. 2016).

28.2.2 Management

It is evident that fatigue in inflammatory bowel disease is multifactorial and needs to be assessed and managed on an individual basis.

A practical guideline published in 2015 suggests screening for fatigue symptoms in all consultations (Kreijne et al. 2016). Patients with severe fatigue need a careful investigation in order to identify the most likely predisposing factors and guide treatment.

The fatigued patient should be screened for disease activity, anaemia and nutritional deficits (ferritin, copper, zinc, folate, phosphate, magnesium, vitamins B6 and B12, calcium, vitamin D) and treated accordingly. The presence of sleep disturbances, anxiety and depression should be investigated and prompt referral to a psychologist or psychiatrist when appropriate. The possibility of medication side-effects should be taken into account—corticosteroids are associated with higher fatigue levels (van Langenberg and Gibson 2014) and sleep disturbance.

There are currently no specific pharmacological treatments for IBD fatigue. Three studies report improved fatigue levels after treatment with infliximab (Minderhoud 2003; Lichtenstein et al. 2002) and adalimumab (Loftus et al. 2008); however, they were conducted on patients with active disease, and its use for fatigue per se cannot be recommended. A small noncontrolled pilot study reported fatigue improvement after thiamine supplementation, and patients taking vitamin B supplements are less likely to complain of fatigue (van Langenberg and Gibson 2014); however evidence is still scarce.

There have been a few non-pharmacological interventional studies. Garcia-Vega et al. report an improvement in fatigue after implementation of stress management techniques versus usual care, with benefits persisting after 1 year (García-Vega and Fernandez-Rodriguez 2004). Psychotherapy seems to have a short-term effect on fatigue and quality of life, as IBD patients in remission reported lower fatigue levels after solution-focused therapy sessions compared to usual care, but the difference was no longer statistically significant 9 months after enrolment (Vogelaar et al. 2014). A short consultation recommending regular physical exercise significantly reduced fatigue levels, with persistent effects after 12 weeks (McNelly et al. 2016).

28.2.3 Summary

Fatigue is prevalent in IBD and cannot always be attributed to active intestinal mucosal inflammation. Its initial assessment must begin with screening for disease activity and physical factors such as anaemia, nutritional deficits and drug side-effects.

Fatigue is strongly associated with psychological symptoms such as depression, anxiety

Table 28.1 Practical daily life tips to reduce and manage fatigue

Plan daily activities ahead
Flexible working hours
Prioritise important activities
Frequent breaks and rest
Good quality sleep
Balanced diet
Physiotherapy and regular exercise

Adapted from Fatigue and IBD Information Sheet, Crohn's and Colitis Organization UK

and sleep disorders. Although the direction of causality is unclear, psychological symptoms and sleep quality must be investigated and addressed in the fatigued patient.

There are few interventions with proven benefit in IBD fatigue, with recent studies reporting improvement with psychotherapy and stress management techniques. High fatigue levels are associated with lower activity level, and initiating regular physical exercise appears to improve symptoms of tiredness. Table 28.1 summarizes some practical tips for patients that may improve fatigue (Fatigue and IBD Information Sheet, Crohn's and Colitis Organization UK).

28.3 Pain

Pain relief is another of the primary concerns of IBD patients, especially those with Crohn's disease (CD) (Casellas et al. 2017).

Abdominal pain aetiology is multifactorial and cannot always be attributed to active disease, as 20–50% of patients in clinical or endoscopic remission complain of severe abdominal pain (Srinath et al. 2012) and abdominal pain correlates poorly with indices of disease activity (Schirbel 2010).

Pain management is complicated by the overlap of irritable bowel syndrome (IBS) symptoms in patients with IBD. The challenge in pain management lies on differential diagnosis between active inflammation, acute or chronic disease complications and functional symptoms.

28.3.1 Causes

28.3.1.1 Active Disease

IBD patients with persistent abdominal pain should be extensively investigated for signs of disease activity. Small bowel disease in CD patients may be particularly elusive and must be sought through CT or MR enterography, small bowel capsule endoscopy and/or enteroscopy. If active disease is confirmed, symptom management should rely on anti-inflammatory optimization to induce and maintain remission.

28.3.1.2 Complications

IBD patients are prone to *intestinal obstruction* from several causes: intestinal adhesions can occur after abdominal surgery or due to transmural inflammation in CD; persistent stenosing disease may culminate in intestinal strictures with a predominant fibrotic component not responsive to anti-inflammatory therapy. Low residue or liquid diet may alleviate obstructive abdominal pain, as will antispasmodics; however the latter should be used with moderation due to the risk of precipitating ileus. In the case of fibrotic strictures, endoscopic dilation or surgery can be of benefit.

CD patients are at risk for enteric stasis due to dysmotility, partial obstructions and fistulae. This predisposes them to *small intestinal bacterial overgrowth* (SIBO), which can be a cause of abdominal pain, as bacterial fermentation of enteric contents may cause bloating as well as direct mucosal irritation. The gold standard for diagnosing SIBO is culture of proximal small bowel aspirate; however, it is invasive, and hydrogen and glucose breath tests are easier to implement in clinical practice. Because both tests have low specificity, an empiric antibiotic course may be adequate if the clinical scenario is suggestive. Antibiotic regimens that have been tested in small intestinal bacterial overgrowth specifically in CD include ciprofloxacin, metronidazole and rifaximin.

28.3.1.3 Functional Symptoms

The question remains whether functional symptoms in IBD result from low-level inflammation or from postinflammatory changes in pain perception.

IBD-IBS patients have higher calprotectin levels (a marker of polymorphonuclear cell inflammation) than those without IBS symptoms and IBS controls (Keohane et al. 2010), suggesting that occult mucosal inflammation may be responsible for functional symptoms.

There is however gathering evidence for other aetiologies. Postinflammatory changes in the enteric nervous system may cause visceral pain hypersensitivity, and central autonomic and pain perception dysregulation may lead to symptoms in the absence of inflammation (Srinath et al. 2012).

As in fatigue, psychosocial factors show clear association with pain in IBD—anxiety and depression correlate strongly with pain, but once again it is difficult to extrapolate the direction of causality.

28.3.2 Management

Regardless of how one interprets seemingly functional pain in IBD patients, it is imperative to actively exclude active small bowel disease before attributing their symptoms to superimposed IBS.

There is little evidence on the treatment of functional abdominal pain in IBD, and clinical practice is often based on studies on IBS patients.

Antispasmodics are more effective than placebo for functional pain in IBS. They can be beneficial in IBD patients, but their use must be cautious due to the risk of obstruction (Ford et al. 2008).

Nonsteroid anti-inflammatory drugs (NSAIDs) are usually avoided in IBD patients due to ample evidence of their association with disease relapse. This cause-effect relationship is however questionable. There is opposing evidence in literature, and there are several confounders in most studies. Nonetheless, NSAIDs are also directly toxic to the gastrointestinal tract and are best avoided in IBD patients; paracetamol is a safer alternative (Singh et al. 2009).

Opiates are often used in hospitalized IBD patients during flares or in the post-operative period. Their chronic use in IBD is higher than in healthy matched controls and is associated with several complications, including constipation, pseudo-obstruction or toxic megacolon. Chronic opioid use is also associated with higher mortality rates even adjusting for recent hospitalizations and for immunomodulatory and biologic therapy (Bernstein 2015).

It is therefore crucial to have an integrated approach to abdominal pain in IBD, with attention to the psychosocial components of pain, in order to avoid potentially detrimental analgesic use. Figure 28.3 suggests a clinical algorithm for pain management in IBD.

28.4 Diarrhoea, Urgency and Incontinence

Diarrhoea is a frequent symptom in IBD and is often the first manifestation of disease, with 77% of ulcerative colitis (UC) patients and 82% of CD patients presenting with diarrhoea at onset (Froslie et al. 2007). The severity of diarrhoea is variable, but it is often chronic and may be associated with urgency and anal incontinence with severe psychosocial consequences. Stool frequency is the second most worrisome symptom for IBD patients, after abdominal pain (Casellas et al. 2017).

It is an important indicator when assessing disease activity; however, its aetiology might not always be active mucosal inflammation, and the differential diagnosis from other causes is important for an adequate management (Wenzl 2012).

28.4.1 Causes

Intestinal Inflammation In the inflamed bowel, reduced absorption of water and sodium is the

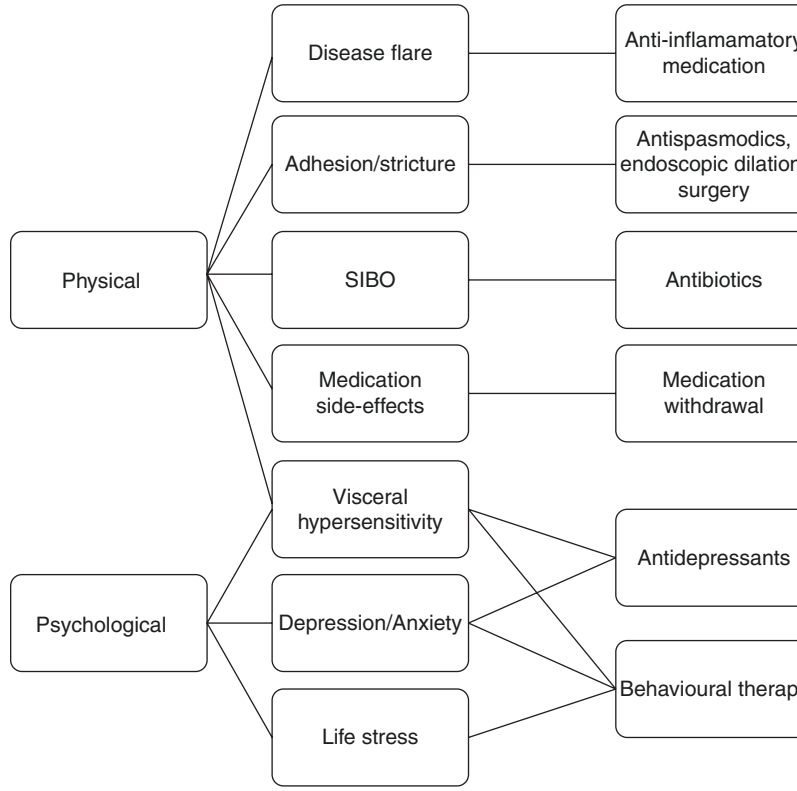

Fig. 28.3 Clinical algorithm for pain management in IBD. Adapted from Srinath et al. (2012)

main cause for looser stool consistency, due to reduced activity of sodium transport channels in colonocytes and reduced absorptive area in the case of extensive ulceration. In addition, extensive mucosal inflammation breaks the epithelial barrier permitting leaking of fluid into the lumen. The inflammatory state may also alter gut motility, and accelerated transit through the intestine further limits absorption due to reduced contact time between enteric contents and the mucosa. In CD, but not in UC, there may be a component of enhanced active secretion.

If clinical history, symptoms, blood workup and endoscopic and imaging studies are suggestive of active disease, anti-inflammatory drugs should be optimized according to guidelines.

Malabsorption Nutrient malabsorption may have an important role in CD diarrhoea. Almost all secreted *biliary acids* are reabsorbed into the enterohepatic circulation in the terminal ileum, the most commonly affected bowel segment in CD. Reduced bile salt absorption can occur if there is extensive ileal inflammation, after lengthy ileal resection or in the setting of an entero-enteric or entero-colic fistula that permits bypass of the ileum. A greater quantity of biliary acids are thus allowed to leak into the colon, leading to osmotic diarrhoea. In this scenario, a bile acid sequestrant such as cholestyramine may alleviate symptoms. Cholestyramine may be started at a low dose in fractioned doses before each meal and titrated up to a total daily dose of 24 g according to response. Improvement should be felt in a few days to 1 week.

If biliary acid loss is significant enough and hepatic synthesis cannot compensate it, *fat*

absorption may be impaired due to insufficient micelle formation, causing steatorrhea. In this scenario, bile acid sequestrants will actually worsen diarrhoea, but improvement may be achieved with a low lipid diet or by supplementation with exogenous biliary acids.

Carbohydrate malabsorption can give rise not only to osmotic diarrhoea but also to bloating and flatulence due to bacterial fermentation of nonabsorbed carbohydrates to carbon dioxide and hydrogen in the colon. Breath hydrogen testing or low stool pH can suggest this diagnosis; however generalized malabsorption may result in higher stool pH. Dietary eviction as a diagnostic and therapeutic trial may be a more practical approach.

Small Intestinal Bacterial Overgrowth As discussed previously, CD patients may be at risk of small intestinal bacterial overgrowth due to strictures and consequent stasis of bowel contents or due to abnormal connection through fistulae between the small bowel and the stomach or colon. The increased load of bacteria in the small bowel deconjugate conjugated bile acids, impairing fat absorption and causing direct toxicity to the enteric mucosa. Diagnostic and treatment attitudes were already discussed in the "Pain" subsection.

Postsurgical The most common surgery performed on CD patients is an ileocolectomy; postsurgical patients may have an increase in bowel movements due to the loss of barrier function of the ileocecal valve, with greater volumes of fluid reaching the colon and exceeding its absorptive capacity. In the case of extensive small bowel resection, the absorptive function may be severely impaired, requiring in the most extreme cases parenteral repletion of fluid, electrolytes and nutrients.

Surgical options in UC always involve colectomy. However, several reconstructions with different continence outcomes are possible (Feldman et al. 2016).

If an abdominal colectomy with *ileorectal anastomosis* is performed, the preserved rectum can compensate water and sodium absorption in the 3–6 months post-resection, resulting in a near-normal stool frequency and normal continence. Diarrhoea in these patients may be caused by active proctitis, which reduces rectal distensibility and absorptive capacity; topic anti-inflammatory drugs may improve it.

In contrast, after *proctocolectomy* (either with ileostomy or ileal pouch-anal anastomosis), stool volume will invariably be increased, and the patient will have a higher risk of electrolyte imbalance due to total loss of the colon's sodium and water absorptive function. Ileal pouch preserves anal sphincter function and continence; however, patients will have 6–8 soft stools per day. Excessive stool volumes in proctocolectomy patients may improve with stool-bulking agents such as methylcellulose or psyllium, which absorb free water and increase stool consistency. Antidiarrhoeals such as loperamide may help the post-prandial urgency that patients frequently complain of. The possibility of pouchitis must also be evaluated with endoscopy and histology; treatment includes an antibiotic (ciprofloxacin or metronidazole) or budesonide.

Infection The possibility of an enteric infection must always be considered in IBD relapses, especially considering the prevalence of immunosuppression in this population. Bacterial, mycobacterial, parasitological and virological stool studies should be obtained. In the suspicion of bacterial enteritis, empiric therapy with a fluoroquinolone may be appropriate. *Clostridium difficile* infection should be suspected in a patient with a recent or actual antibiotic course and appropriate clinical presentation (watery diarrhoea, nausea, low-grade fever, abdominal cramping and leucocytosis), and stool tests for *C. difficile* toxin should be ordered. In confirmed infection of if clinical suspicion is high, previous antibiotics should

be stopped and treatment started with oral metronidazole; recurrent or severe disease may be treated with oral vancomycin. Care should be taken to reduce interpersonal transmission by isolating the patient, using personal protective equipment and handwashing with water and soap (*C. difficile* spores are resistant to alcohol-based disinfectant solutions).

Medication Side-Effects Various medications commonly used in IBD can induce or aggravate diarrhoea through various mechanisms: aminosalicylates, NSAIDs, antibiotics, oral iron and magnesium supplements, thiopurine drugs, proton pump inhibitors and cholestyramine are just a few. If the temporal association between drug and symptoms is suggestive, discontinuation of the suspected culprit should resolve symptoms and confirm diagnosis.

Urgency and Incontinence Rectal inflammation in IBD reduces rectal distensibility and compliance, causing urgency symptoms. Extensive perianal disease or multiple perianal surgeries for fistulae or abscesses may cause internal or external sphincter lesions, leading to faecal incontinence. Endoanal ultrasonography, anal manometry and pelvic resonance imaging can support the diagnosis. Stool-bulking dietary supplements such as methylcellulose or psyllium may increase faecal consistency and improve continence; anticholinergics can alleviate urgency symptoms, but none treat the cause. Pelvic floor muscle training, biofeedback and bowel retraining may improve sphincter muscle tone and continence.

Faecal urgency and incontinence are incredibly debilitating complaints with important psychosocial consequences; an experienced nursing team can be an important tool in helping the patient deal with symptoms. Tables 28.2 and 28.3 summarize some practical daily life tips for patients dealing with frequency, urgency and incontinence.

Table 28.2 Practical tips for patients dealing with frequency, urgency and incontinence

Use continence pads or panty liners
Carry emergency kit (extra change of clothes, alcohol-free wet wipes, disposal bags)
Use neutralizer aerosol, or burn a match to eliminate odour
Plan trips with toilet stops
Avoid fibrous, spicy or greasy foods, caffeine and alcohol
Eat small frequent meals
Regular pelvic floor exercises

Adapted from Mason (2007) and Managing incontinence in IBD Information Sheet, Crohn's and Colitis Organization UK

Table 28.3 Skin care recommendations for patients with faecal incontinence

Wipe gently and only once
Wash around the anus
Dry gently and thoroughly
Avoid strong scented products
Wear cotton underwear
Avoid creams or lotions; if necessary use small amount of zinc cream
Avoid scratching

Adapted from Mason (2007) and Managing incontinence in IBD Information Sheet, Crohn's and Colitis Organization UK

28.4.2 Management

The IBD patient with new onset of diarrhoea should be thoroughly assessed. A complete history with emphasis on bowel habit changes (frequency, volume and characteristics); diet and medication alterations should be obtained. The physical examination should focus on signs of volume depletion, systemic toxicity and the abdominal assessment. A complete blood workup should be ordered, including electrolytes, vitamins and nutrients. Microbiological stool tests are relevant if there is clinical suspicion of infection. Differential diagnosis between disease reactivation and other causes of diarrhoea is paramount, and endoscopic and imaging studies may be needed to guide treatment.

Table 28.4 Most important diarrhoea aetiologies in inflammatory bowel disease, their diagnostic approach and their treatment

Aetiology	Diagnosis	Management
Active disease	Blood chemistry (ESR, CRP) Stool markers (faecal calprotectin) Endoscopy Imaging studies (entero-CT, entero-MRI)	Anti-inflammatory medication Immunosuppression Biologic therapy
Infection	History (recent antibiotic therapy, previous *Clostridium difficile* infection, epidemiological exposure) Microbiological stool tests Colonoscopy with biopsies (CMV and HSV)	Antimicrobial therapy
Malabsorption	Bile acids: tauroselcholic acid test, diagnostic trial with cholestyramine Fat: stool test Carbohydrate: breath tests, faecal pH	Bile acids: cholestyramine Fat: low-fat diet, bile acid supplement Carbohydrate: dietary exclusion
Bacterial overgrowth	Predisposing functional or anatomical abnormalities Bacterial culture of jejunal aspirate Breath tests	Antibiotics Stricture dilation Surgery
Fistula	History of halitosis/faecal vomiting Imaging studies Endoscopy	Surgery
Post-resection	Surgical history Imaging studies Endoscopy	Antidiarrhoeal Dietary measures (avoid caffeine) Stool-bulking agents
IBS	History Endoscopy, imaging studies, etc., to exclude other causes	Antispasmodics Antidiarrhoeals Tricyclic antidepressants

Adapted from Wenzl (2012)

Table 28.4 summarizes different aetiologies for diarrhoea in IBD, their diagnostic tools and their management.

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Dietary Management

29

Lisa Vokes

Abstract

All IBD patients should have access to dietitians for nutrition support and, where appropriate, for primary therapy of IBD (Donnellan et al., Ther Adv Gastroenterol 6:231–242, 2013; ibd standards: http://s3-eu-west-1.amazonaws.com/files.crohnsandcolitis.org.uk/Publications/PPR/ibd_standards_13.pdf). Dietary management of IBD remains poorly understood (Charlebois et al., Crit Rev Food Sci Nutr 56:1370–1378, 2016); most guidelines do not make recommendations for it (Halmos and Gibson, Nat Rev Gastroenterol Hepatol 12:133–146, 2015) or are insufficiently detailed (Lee et al., J Hum Nutr Diet 27:207–218, 2014).

However, there is much published about dietary management of IBD. Some dietary interventions are now well supported by the evidence, but others require more research and, as such, *cannot yet* be used as evidence-based practice. The individual with IBD may struggle with the array of information and, together with Internet contradictions and well-meaning help from suboptimally qualified advice givers, is at risk of employing dietary strategies which could be inappropriate to their clinical situation. The IBD MDT, therefore, must help by providing a clear consistent approach about dietary management of IBD.

Dietary management of IBD can be a confusing field due to how different clinical situations such as disease type, patient's age or stage in the disease, for example, may change what advice is appropriate. This chapter will discuss dietary management strategies, when to apply them but also when not to. It aims to present the available dietary information alongside the current thinking to enable the reader to discern what may or may not be appropriate for their patients. The reader will:

- Become familiar with dietary management strategies.
- Become familiar with the current evidence base for different aspects of management.
- Gain some practical tips and resources.
- Understand the role and scope of dietetic services for IBD patients.
- Appreciate that appropriate dietary management will differ from patient to patient.

It is important to appreciate that there are many dietary theories around. Some can be appropriately used, but many have been investigated and are conclusively not supported by the literature in the dietary management of IBD.

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A quick guide to investigated dietary interventions to date is summarised below. Relevant areas are then discussed in more detail throughout the chapter (see Table 29.1). A glossary of terms used appears at the end of the chapter (Table 29.5).

Table 29.1 Introductory table

	Crohn's disease		Ulcerative colitis	
Diet issue	Active	Remission	Active	Remission
Pancreatic insufficiency	Occurs in up to 22% of IBD patients (Halmos and Gibson 2015): treat by matching fat intake to pancreatic enzyme replacement therapy not by dietary restriction (Halmos and Gibson 2015)			
Probiotics	No evidence (Lee et al. 2014; Donnellan et al. 2013; Mowat et al. 2011; Durchschein et al. 2016; Yamamoto et al. 2017)		Nil studies to show positive effects 'unambiguously' (Owczarek et al. 2016) and benefits are unproven (ref = up to date); no probiotic is valid in clinical use (ref = up to date)—see Chap. 15	
			Role in pouchitis (Yamamoto et al. 2017)—see Chap. 31. Probiotics may have an adjunctive role (ref = up to date)	*
Enteral nutrition	Exclusive enteral nutrition can induce remission[a]	Some provision of enteral nutrition can maintain remission[a]	No role in UC therapy (Mowat et al. 2011; Owczarek et al. 2016; Shah et al. 2015)	
	Adjunctive role in malnutrition[a]			
Low FODMAP	Role in improvement of functional symptoms[a]			
Gluten	Possible assistance with symptoms based on patients' reports but more studies needed (Donnellan et al. 2013)			
Palaeolithic diet	No studies of efficacy (Donnellan et al. 2013)			
Semi-vegetarian diet		Suggestion of benefit to prevent relapse (Halmos and Gibson 2015)/ maintain remission (Owczarek et al. 2016). Promising in quiescent disease but more studies needed (Shah et al. 2015)		
Fibre	Weak evidence that fibre reduces disease activity and risk of relapse (Halmos and Gibson 2015); studies needed to establish if there is a role in therapy of IBD (Pituch-Zdanowska et al. 2015)			
	Lower intake is advised in flare of symptoms and stenosis[a]	No effect on maintenance of steroid induced remission at 2 years (Halmos and Gibson 2015)	High fibre in rectal UC to prevent constipation (Owczarek et al. 2016), otherwise reduced in flare of symptoms[a]	
Cow's milk protein			Restriction not recommended (Halmos and Gibson 2015). No difference of restriction seen in paediatric patients (Penagini et al. 2016)	
Omega 3 fatty acids	No efficacy demonstrated (Halmos and Gibson 2015; Shah et al. 2015); further studies needed (Owczarek et al. 2016; Barbalhoa et al. 2016)			
		Do not maintain remission (Yamamoto et al. 2017)		

Table 29.1 (continued)

	Crohn's disease		Ulcerative colitis	
Diet issue	Active	Remission	Active	Remission
Excluded cinnamon, benzoates and phenolics	'Show promise' in orofacial granulomatosis (Halmos and Gibson 2015)			
Elimination diet based on IgG testing	One study to show reduced stool frequency in active Crohn's (Charlebois et al. 2016)			
Glutamine	Studies needed to investigate efficacy in inducing remission (Yamamoto et al. 2017)			
Synbiotics	Too few studies (Yamamoto et al. 2017)			
Prebiotics	Studies show conflicting results so more research needed (Yamamoto et al. 2017)			
Specific carbohydrate diet (SCD)	May improve clinical symptoms in paediatric patients (Yamamoto et al. 2017); gaining evidence (Penagini et al. 2016). Further studies needed (Yamamoto et al. 2017; Owczarek et al. 2016) to show SCD is effective and safe, especially in paediatrics (Owczarek et al. 2016). NB children on SCD had lower BMI and weight than controls (Penagini et al. 2016). Few studies to evaluate; no published control trials or studies on mechanism of effect (Shah et al. 2015)			
Germinated barley fibre			Improved disease activity (Pituch-Zdanowska et al. 2015). May have a role in therapy but more studies are needed (Owczarek et al. 2016)	Prolonged remission and less steroids used, decreased CRP, decreased clinical signs (Pituch-Zdanowska et al. 2015). No side effects (Pituch-Zdanowska et al. 2015)
Oligofructose inulin (NB both are excluded by low-FODMAP diet (Gibson 2017; Staudacher et al. 2014))			Anti-inflammatory effect has been demonstrated in pts with mild to moderate disease (Pituch-Zdanowska et al. 2015)	
Lactose	40–70% of patients thought to be intolerant (Shah et al. 2015) but could be due to the IBD itself in flare rather than lactase deficiency (Shah et al. 2015) or maybe the fat content of dairy rather than the lactose (Shah et al. 2015).			
	Secondary lactose intolerance may occur in active colitis (Mowat et al. 2011); guidelines recommend a dairy-free diet (Mowat et al. 2011) but suggest a lactose (not 'dairy', for calcium intake (Owczarek et al. 2016))-free diet will be more appropriate. No studies have evaluated the effect of lactose on IBD activity (Shah et al. 2015)			
Parenteral nutrition	No role in primary therapy role in nutrition support of malnutrition[a]			

[a]Further discussion in chapter below

[*]= may help to maintain remission (ref = up to date)

29.1 Nutritional Screening

British Society of Gastroenterology (BSG) guidelines recognise that nutritional assessment is important (Mowat et al. 2011). However, full nutritional assessment for all the IBD population is impractical (Donnellan et al. 2013). Nutritional screening, including BMI, percentage weight loss and recent or anticipated poor oral intake should be done for the general Crohn's disease population. Full nutritional assessment would be more appropriate for those patients identified by screening as at risk for malnutrition (Nutrition support for adults: oral nutrition support, enteral tube feeding and parenteral nutrition Clinical guideline Published: 22 February 2006 nice.org.uk/guidance/cg32). Tools are available, such as MUST (Donnellan et al. 2013) (see resources), to allow nutritional screening by any of the MDT. Tools like this will and should come with instruction about how to interpret and act upon the result derived from the screening process and, in some cases, allow the nurse (or other colleague) to implement some appropriate nutritional plans. It is important to use an accepted resource and any local protocols to ensure care is accepted as safe and appropriate prior to specialist input from the dietitian.

Nutritional screening should be repeated weekly for inpatients but also when possible for outpatients at risk for malnutrition (Nutrition support for adults: oral nutrition support, enteral tube feeding and parenteral nutrition Clinical guideline Published: 22 February 2006 nice.org.uk/guidance/cg32). The UK IBD standards specify that a patient's weight and BMI should be assessed at each attendance and on any admission (ibd standards: http://s3-eu-west-1.amazonaws.com/files.crohnsandcolitis.org.uk/Publications/PPR/ibd_standards_13.pdf). Any previous screening results can then be used to provide a longitudinal assessment of the patient's nutritional status in terms of tracking their weight (weight history).

Nutritional screening:

- Allows identification of patients at nutritional risk.
- Should be done using an agreed (±locally adapted) tool.
- Risk is determined by assessment of BMI, percentage weight loss and reduction in oral nutrient intake (Nutrition support for adults: oral nutrition support, enteral tube feeding and parenteral nutrition Clinical guideline Published: 22 February 2006 nice.org.uk/guidance/cg32).

29.2 In Remission

There is dearth in the guidelines regarding advice for diet in IBD remission (Owczarek et al. 2016). Where available, recommendations promote a diverse balanced diet (Owczarek et al. 2016).

Research on diet is difficult which admittedly can result in poor-quality studies. Therefore there is much of interest but it should not be over-interpreted, where robust evidence is still lacking.

Similarly, dietary fibre is noted as unhelpful in Crohn's disease, though not limited while in remission (Owczarek et al. 2016; Pituch-Zdanowska et al. 2015). Small studies for UC offer a mixed opinion and, again, are not of sufficient size or quality to form definite recommendations (see Table 29.2).

Table 29.2 Literature on fibre in remission (not definite recommendations)

Author	Finding
Second European evidence-based consensus on the diagnosis and management of ulcerative colitis Part 2: Current management 2012	Low-fibre intake during UC remission is associated with a higher risk of relapse
Fernández-Bañares et al. (1999) Hallert et al. (1991) Owczarek et al. (2016)	Two trials with psyllium husk: Higher fibre intake in remission of UC may prevent recurrence Ameliorate UC symptoms during remission
Wedlake et al. 2014 (Owczarek et al. 2016)	Fibre may be 'mildly beneficial' in UC (Owczarek et al. 2016)
Pituch-Zdanowska et al. (2015)	In UC high fibre in remission produced a higher relapse rate (Pituch-Zdanowska et al. 2015)

Of better quality is the work related to diets targeting Fermentable Oligosaccharides, Disaccharides, Monosaccharides and Polyols (FODMAP) though this is understood to be helpful for functional GI symptoms (Lee et al. 2014; Durchschein et al. 2016; Owczarek et al. 2016; Shah et al. 2015; Charlebois et al. 2016; Gibson 2017) rather than IBD. These should only be carefully managed by specialist dietitians to avoid compromising nutritional status in the IBD patient (Gibson 2017). More trials are needed (Durchschein et al. 2016; Charlebois et al. 2016).

In CD, EN for adults remains controversial. A meta-analysis and review cite studies on both sides of the argument but ultimately conclude there is insufficient evidence at present to be sure that there is a role for inducing or maintaining remission (Shah et al. 2015; Tsertsvadze et al. 2015)—see more detail in 'Enteral Nutrition'.

In regard to a patients trying other diets (see Table 29.1), always involve the dietitian to prevent the patient from unwarranted dietary restriction (Subramanian and Triadafilopoulos 2016). In all IBD patients, continue to monitor micronutrient status (Subramanian and Triadafilopoulos 2016) (see Sect. 29.6.1).

Given the current evidence, the most important message for patients with IBD in remission is:

- Normal balanced healthy diet

29.3 In Active Disease

Traditionally patients with active IBD are advised to reduce fibre intake (Shah et al. 2015; Owczarek et al. 2016). This is with the rationale that the reduced fibre intake will try to decrease stool antigen and frequency in inflamed areas of gut (shah et al. 2015). It is important to recognise that there is not good evidence for this -it is cited within some recommendations likely on the basis of it being considered logical that an increase in fibre would increase stool bulk and thereby increase amount of stool and thereby symptoms. This does not, of course, indicate an effect on the inflammatory process (Owczarek et al. 2016; Shah et al. 2015).

Additional literature specific to disease type is:

Crohn's Disease

Enteral nutrition is considered a potential primary therapy to induce remission during active disease. This remains controversial and is discussed further under the subheading 'Enteral Nutrition' for adults and 'As Therapy' for paediatric patients.

Ulcerative Colitis

A high-fibre diet may be suitable for patients who have active ulcerative colitis in the rectum, primarily in order to prevent constipation (Owczarek et al. 2016). Again, the quality of the study mentioned in this review needs to be taken into account.

Probiotics only have a clear role in the context of pouchitis (Yamamoto et al. 2017) (see Chap. 31).

In summary, the possible dietary interventions relevant during active IBD might be:

- Low fibre in exacerbated IBD
- Enteral nutrition in treatment of CD (more accepted in paediatric populations)
- High fibre in rectal UC
- Probiotics for pouchitis

29.4 Enteral Nutrition

Enteral nutrition (EN) has three ways it can be considered within the management of IBD.

1. For any IBD patients who are malnourished and cannot support their nutritional intake orally (see below under 'malnutrition') (Durchschein et al. 2016) and therefore may be used in conjunction with other primary therapy for IBD (Lee et al. 2014).
2. For children with active Crohn's, it may be used as primary therapy to induce remission (Donnellan et al. 2013; Durchschein et al. 2016; Owczarek et al. 2016; Shah et al. 2015):

in paediatric patients, exclusive enteral nutrition is the first-line treatment of Crohn's disease (see 'As Therapy' subheading) (Donnellan et al. 2013; Durchschein et al. 2016; Shah et al. 2015). These studies also note its use in adults; however, a Cochrane review concluded steroids are superior for inducing remission (Lee et al. 2014; Yamamoto et al. 2017; Owczarek et al. 2016; Tsertsvadze et al. 2015; Nguyen et al. 2015; Wędrychowicz et al. 2016), and no guidelines currently recommend it. Those advocating EN in adults argue it as a safer option (Wędrychowicz et al. 2016) and that it is poor palatability and lack of adherence that are barriers to success rates in the evidence gathered to date (Yamamoto et al. 2017). The mechanism of possible benefit is unclear (Shah et al. 2015; Tsertsvadze et al. 2015).

3. There is increasing evidence from reviews and meta-analysis (Donnellan et al. 2013; Tsertsvadze et al. 2015; Nakahigashi et al. 2016) that EN can be used to maintain remission and reduce recurrence (Donnellan et al. 2013; Shah et al. 2015; Nakahigashi et al. 2016). There are contradictions between older and more recent reviews (Mowat et al. 2011; Donnellan et al. 2013; Tsertsvadze et al. 2015; Nakahigashi et al. 2016, respectively), and it is acknowledged that there are limitations with small studies and within the process of literature reviewing this topic overall (Tsertsvadze et al. 2015; Nakahigashi et al. 2016). Results should be interpreted with caution but do suggest that EN is more effective at maintaining remission in the short term than unrestricted diet (Tsertsvadze et al. 2015). Some of these studies are detailed below:
   (a) In a study by Verma et al. 2001 (cited in Donnellan et al. 2013), 33 steroid-dependent CD patients (with two failed steroid weaning attempts) were given EN as 30–50% of their nutritional requirements. Twenty-seven patients tolerated the feeds. Fourteen of these successfully stopped steroids. This group of 14 were then split into two: 7 continued with the supplements and 7 did not. Six of the seven on supplements were still at remission at 24 months. The other seven returned to unrestricted diet, and all relapsed within 4 months (Donnellan et al. 2013; Verma et al. 2001).
   (b) Continuation of EN to meet 50% nutritional requirements after surgery may also be of value in delaying (Day and Lopez 2015) or preventing (Nakahigashi et al. 2016) recurrence in surgically achieved remission in adults with CD (Donnellan et al. 2013; Day and Lopez 2015) but is not recommended by NICE (Tsertsvadze et al. 2015).
   (c) Fifty percent nutritional requirements via EN as an adjunct to maintenance infliximab treatment was trialled but did not significantly increase maintenance of remission rate compared to infliximab alone (Donnellan et al. 2013; Nakahigashi et al. 2016). However, this is attributed to the RCT design used (Nakahigashi et al. 2016). In a meta-analysis of enteral nutrition as an adjunct to maintenance infliximab, the combination of enteral nutrition (600–1500 kcal per day and infliximab) produced a twofold increase in the odds of clinical remission than infliximab alone (Nguyen et al. 2015). It is worth noting that all the studies pooled in this analysis were done in Japan (Nguyen et al. 2015).
   (d) In a study of patients with quiescent CD, nocturnal elemental EN monotherapy maintained remission better than nothing (Shah et al. 2015), and a recent meta-analysis supports that elemental nutrition is more effective at maintaining remission than no treatment (Tsertsvadze et al. 2015) but that it is less well adhered to than polymeric nutrition (Tsertsvadze et al. 2015).

The mechanism by which EN might maintain remission is unclear (Shah et al. 2015; Tsertsvadze et al. 2015; Nakahigashi et al. 2016). Compliance with partial EN is an issue (Tsertsvadze et al. 2015; Nakahigashi et al. 2016), and more research is required (Yamamoto et al. 2017; Tsertsvadze et al. 2015; Nakahigashi et al. 2016; El-Matary et al. 2017).

EN cannot be used for treatment of UC (Donnellan et al. 2013; Mowat et al. 2011; Owczarek et al. 2016; Shah et al. 2015).

Enteral nutrition may:

- Be used for improving patients nutritional status-adjunctive treatment for all IBD patients
- Have a role as part of maintenance therapy for Crohn's disease though evidence is currently contradictory
- Exclusively be used as primary therapy in active Crohn's disease to induce remission in children
- Exclusively be used for adults though more evidence is needed

Practical points if using exclusive enteral nutrition

Polymeric or elemental formulas (see glossary) do not have any benefit over each other clinically (Lee et al. 2014; Donnellan et al. 2013; Mowat et al. 2011; Owczarek et al. 2016; Shah et al. 2015; Nguyen et al. 2015; Kornbluth et al. 2010). They can be given orally or via feeding tube (Lee et al. 2014; Tsertsvadze et al. 2015; Wędrychowicz et al. 2016), although, if orally administered, enteral nutrition may be better tolerated as polymeric formula, due to taste (Donnellan et al. 2013). Also, the fat (Donnellan et al. 2013; Durchschein et al. 2016; Shah et al. 2015) or protein (Durchschein et al. 2016) content of the formula used does not appear to change effectiveness of exclusive enteral nutrition (EEN). While having EEN, only water is permitted or, to aid compliance in some cases, weak black tea or coffee (Lee et al. 2014) and small amounts of sugar-free chewing gum in children (Day and Lopez 2015) (bearing in mind that sugar-free gum is often a FODMAP source (Staudacher et al. 2014)). To induce remission, EEN is introduced and increased gradually to the patient's estimated nutritional needs (Lee et al. 2014). The EEN is required for between 10 days and 6 weeks to realise any beneficial effect (Lee et al. 2014). Limited weak evidence using elemental formula via NGT shows induction of remission at 10 days (Lee et al. 2014).

EEN is not the end of the dietary intervention. Food is reintroduced but research and guidance about this process is limited (Lee et al. 2014). What evidence there is suggests that after EEN, an elimination diet is better than general dietary intake (Lee et al. 2014; Donnellan et al. 2013) or even steroids to maintain remission at 2 years (Lee et al. 2014). It is also better than an unrefined carbohydrate high-fibre diet for maintaining remission at 6 months (Lee et al. 2014). A low fat/fibre limited exclusion (LOFFLEX) diet could also be considered as it has similar efficacy to an elimination diet (Lee et al. 2014; Donnellan et al. 2013).

An elimination diet after EEN means all foods are introduced one by one daily (Donnellan et al. 2013). A LOFFLEX reintroduction allows low fat and limited fibre initially, followed by single reintroductions of a shorter list of foods than the elimination list of foods (Donnellan et al. 2013) (http://crohns.org.uk/crohns_disease/nutritional_therapy/the-lofflex-diet). LOFFLEX is better tolerated than single food reintroduction (Donnellan et al. 2013) and, when compared to an elimination diet, is preferred by patients and thereby leads to better adherence (Lee et al. 2014). There is limited weak evidence that an unrefined carbohydrate, high-fibre diet is not effective at maintaining remission (Lee et al. 2014). Whatever the approach, the patient should be supported while returning to their normal diet using oral nutrition and micronutrient supplementation as appropriate (keeping in mind other factors that may affect symptoms such as concomitant medication) (Lee et al. 2014).

In summary:

- Any type of feed formulation can be used for exclusive enteral nutrition, given orally or via a feeding tube.
- Only water and, in exceptional circumstance, weak black tea or coffee are allowed alongside EEN.
- EEN is usually given for 10 days to 6 weeks.
- Foods are reintroduced after EEN, and maintenance of remission is better if reintroduction is via an elimination or LOFFLEX diet vs restarting normal diet.

29.5 As Therapy in Paediatrics

Unlike in the adult arena, the research on the use of EEN in paediatric cohorts is less contested. It can be used as first-line primary therapy for Crohn's disease in paediatric patients and is well supported by the literature (Donnellan et al. 2013; Shah et al. 2015; Wędrychowicz et al. 2016; Day and Lopez 2015), inducing remission in 60–85% of patients (Mowat et al. 2011; Day and Lopez 2015) and with an equivalent response to corticosteroids (Day and Lopez 2015). However, clinical practice varies worldwide with EEN being used by only 5% of practitioners in the USA compared to 96% of units in Sweden (Day and Lopez 2015). Effectiveness cannot be contributed to the location of disease activity (Day and Lopez 2015). EEN as therapy is thought to affect the inflammation rather than be a result of improved nutrition status per se (Wędrychowicz et al. 2016). In paediatric patients, mucosal healing has been shown by Borrelli et al. (2006) (Lee et al. 2014; Donnellan et al. 2013; Owczarek et al. 2016; Nguyen et al. 2015; Day and Lopez 2015) but not confirmed by another study (Donnellan et al. 2013), and the mechanism is unclear (Lee et al. 2014; Nguyen et al. 2015). This mucosal healing is better than that seen with steroid treatment (Day and Lopez 2015), and transmural resolution of inflammation has also been demonstrated by Grover et al. (2014) (Day and Lopez 2015). It may take 8 weeks of EEN to achieve mucosal healing in paediatric patients (Lee et al. 2014).

Practically, using EEN in paediatric patients is much as with adults (as described above), regarding the type of formula used (Wędrychowicz et al. 2016) (polymeric or elemental (Day and Lopez 2015)), gradual introduction to target regimen (Day and Lopez 2015) and oral or artificial feeding tube administration route (Tsertsvadze et al. 2015; Wędrychowicz et al. 2016). In children, inclusion of TGF β (the active ingredient in Modulen) has produced better results than without (Wędrychowicz et al. 2016). Only water and a small amount of sugar-free chewing gum are allowed alongside the EEN for the duration of the treatment, which is typically 8 weeks (Day and Lopez 2015). Bear in mind that sugar-free gum is often a FODMAP source (Staudacher et al. 2014). At the end of 8 weeks, one meal per day is introduced every 3 days while tapering the enteral nutrition administration (Day and Lopez 2015).

- EEN is an evidence-based first-line primary therapy for inducing remission in paediatric Crohn's disease patients, but implementation rates vary worldwide.
- It has been shown to achieve mucosal healing better than steroids.
- Patients can have water or chewing gum only in addition to EEN which lasts for 8 weeks.
- EEN is introduced and weaned gradually.
- Any formula is suitable and is usually given orally in preference to administration via a feeding tube; however, a feeding tube can be used if necessary.

As with adults, EN is also gaining evidence base as method of maintaining of remission (Penagini et al. 2016).

29.6 Treatment of Malnutrition

IBD malnutrition results from (Wędrychowicz et al. (2016)):

- Reduced/poor intake (Donnellan et al. 2013; Wędrychowicz et al. 2016; Nakahigashi et al. 2016; El-Matary et al. 2017; Schwartz 2016) including deficiency due to (certain) food avoidance (Schwartz 2016) and due to loss of appetite and reduced mood (Donnellan et al. 2013)
- Increased energy expenditure of disease process (Donnellan et al. 2013; Wędrychowicz et al. 2016; Nakahigashi et al. 2016) and nutrient losses (Wędrychowicz et al. 2016) including diarrhoea (Wędrychowicz et al. 2016; Nakahigashi et al. 2016)
- Pharmacological: drug nutrient interactions (Donnellan et al. 2013; Nakahigashi et al. 2016; El-Matary et al. 2017) or drug side effects (Wędrychowicz et al. 2016)
- Malabsorption (Nakahigashi et al. 2016; El-Matary et al. 2017): due to intestinal

inflammation (Nakahigashi et al. 2016; El-Matary et al. 2017) or consequences of disease, e.g. bacterial secondary lactose intolerance or reduced absorptive area following surgery (Donnellan et al. 2013; Wędrychowicz et al. 2016)
- Increased requirements (El-Matary et al. 2017)

Twenty to eighty-five percent of IBD patients are malnourished (Lee et al. 2014; Donnellan et al. 2013; Durchschein et al. 2016; Wędrychowicz et al. 2016; Schwartz 2016) which occurs more in CD than UC (Wędrychowicz et al. 2016) with bowel surgery and fistulating disease, increasing the risk of malnutrition for IBD patients (Donnellan et al. 2013). Protein energy malnutrition are characterised by weight loss (Wędrychowicz et al. 2016). Malnutrition is associated with risk of mortality and increased length of hospital stay (Donnellan et al. 2013).

Where oral autonomous nourishment (eating) has failed, nutrition support should be provided (Dignass et al. 2012) using the oral route in the first instance (ESPEN suggests 600 kcal per day via oral nutrition supplements [drinks] (Donnellan et al. 2013)) or an artificial enteral route if this is not achievable (Donnellan et al. 2013). Parenteral (intravenous) nutrition should be reserved for times only when using the gastrointestinal tract is not an option (Donnellan et al. 2013; Durchschein et al. 2016; Shah et al. 2015; Wędrychowicz et al. 2016; Schwartz 2016) (Nutrition support for adults: oral nutrition support, enteral tube feeding and parenteral nutrition Clinical guideline Published: 22 February 2006 nice.org.uk/guidance/cg32). In this nutritionally supportive way, enteral nutrition is an adjunct to IBD therapy rather than a primary therapy.

If nutrition via the gastrointestinal tract is not possible, parenteral nutrition (PN) support is warranted (Donnellan et al. 2013; Durchschein et al. 2016; Shah et al. 2015; Wędrychowicz et al. 2016) but only as nutrition support, not as a primary treatment of IBD (Donnellan et al. 2013; Mowat et al. 2011; Shah et al. 2015; Wędrychowicz et al. 2016; Kornbluth et al. 2010). This can be either required short term perioperatively (Donnellan et al. 2013; Wędrychowicz et al. 2016; Schwartz 2016) or longer term in the case of intestinal failure (Donnellan et al. 2013; Wędrychowicz et al. 2016). PN is stopped as soon as adequate oral or enteral nourishment is achieved (Nutrition support for adults: oral nutrition support, enteral tube feeding and parenteral nutrition Clinical guideline Published: 22 February 2006 nice.org.uk/guidance/cg32) though in some cases lifelong PN is unavoidable (Wędrychowicz et al. 2016). It can be administered to inpatients by appropriately trained MDT colleagues (http://www.ncepod.org.uk/2010pn.html) via dedicated peripheral, short-term access or central access (Nutrition support for adults: oral nutrition support, enteral tube feeding and parenteral nutrition Clinical guideline Published: 22 February 2006 nice.org.uk/guidance/cg32). The IBD patient can also have PN at home (HPN) after they have left the hospital which requires set-up prior to them being discharged home (Donnellan et al. 2013). Patients receiving HPN should be supported by an appropriately experienced and resourced HPN team (Nutrition support for adults: oral nutrition support, enteral tube feeding and parenteral nutrition Clinical guideline Published: 22 February 2006 nice.org.uk/guidance/cg32) as training, an individualised management plan and arrangements for equipment and ancillaries will be required (Nutrition support for adults: oral nutrition support, enteral tube feeding and parenteral nutrition Clinical guideline Published: 22 February 2006 nice.org.uk/guidance/cg32). Enteral nutrition, where possible, is always preferred (Wędrychowicz et al. 2016; Schwartz 2016) due to complications of PN (Wędrychowicz et al. 2016):

- Metabolic disturbances
- Line infection
- Venous thrombosis
- Liver failure
- Cholestasis

(Please also see chapter on short bowel syndrome.)

In reality, patients may be nutritionally supported by more than one route at the same time (Donnellan et al. 2013). If there is a specific

micronutrient deficiency, supplementation will be arranged with the MDT to correct this (see 'Micronutrients').

- Protein energy malnutrition is treated with nutrition support.
- Nutrition support can be oral, enteral or parenterally administered.

29.7 Micronutrients

It is possible for any patient with IBD to be deficient in a specific nutrient. Where a single or particular nutrient is deficient, replacement is not always achievable via diet alone. For example, with oral iron supplementation, the gastrointestinal tract is not able to absorb more than 10–20 mg per day (Donnellan et al. 2013). Therefore corrective iron doses need to be given via another route. Another challenge with dietary replacement is that concentrating on a single nutrient in sufficient amounts required would disproportionately change another aspect of oral intake—which may not be desirable or achievable. The more common deficiencies found in the literature are listed below:

- Vitamin D: deficiency results in osteomalacia in adults (Donnellan et al. 2013), called rickets in children. Fifty-seven percent of Crohn's disease patients are deficient (Sadeghian et al. 2016), and there is an inverse relationship between it and disease activity (Wędrychowicz et al. 2016; Sadeghian et al. 2016).
- Iron: the most common deficiency (Donnellan et al. 2013) with reported 20–88% patients being deficient (Owczarek et al. 2016; Wędrychowicz et al. 2016). There is 13.6–90% prevalence of anaemia reported in the literature (Donnellan et al. 2013; Wędrychowicz et al. 2016; Weisshof and Chermesh 2015), and iron deficiency is the leading cause of anaemia in IBD patients (Weisshof and Chermesh 2015).
- Vitamin B12: 6–22% patients are deficient (Donnellan et al. 2013; Wędrychowicz et al. 2016; Weisshof and Chermesh 2015). Deficiency results when >20 cm (Wędrychowicz et al. 2016)–30 cm ileum is resected (Weisshof and Chermesh 2015), and replacement (intramuscularly (Halmos and Gibson 2015)) should be considered for any patient with more than 20 cm ileum resected (Weisshof and Chermesh 2015).
- Folate: 4.3–28% of patients are affected (Donnellan et al. 2013). Patients on sulfasalazine (Donnellan et al. 2013; Weisshof and Chermesh 2015) and methotrexate (Weisshof and Chermesh 2015) are more at risk of deficiency.
- Zinc: 40% of paediatric IBD (Wędrychowicz et al. 2016) and 15% of all IBD patients (Weisshof and Chermesh 2015) are deficient.
- Vitamin B6: 30% deficiency in adult IBD patients (Wędrychowicz et al. 2016).
- Vitamin A (Wędrychowicz et al. 2016): night blindness (Donnellan et al. 2013) and patients also with PSC are especially at risk (Donnellan et al. 2013). Sixteen percent of paediatric IBD patients are deficient (Wędrychowicz et al. 2016).
- Vitamin K: bioavailability affected in IBD (Wędrychowicz et al. 2016) and deficiency is also due to malabsorption (Weisshof and Chermesh 2015). In paediatric patients, rates of 54% deficiency in CD and 43.7% in UC have been reported (Wędrychowicz et al. 2016).
- Vitamin C (Donnellan et al. 2013).
- Magnesium (Owczarek et al. 2016): especially in severe UC (Kornbluth et al. 2010).
- Selenium: lower in UC patients than controls (Wędrychowicz et al. 2016), effect of supplementation not studied (Weisshof and Chermesh 2015).
- Thiamine/vitamin B1 (Subramanian and Triadafilopoulos 2016).
- Niacin/vitamin B3 (Subramanian and Triadafilopoulos 2016).

- Calcium: osteopenia in 23–77% (Donnellan et al. 2013; Kornbluth et al. 2010) and osteoporosis in 12–30.6% of patients (Donnellan et al. 2013; Kornbluth et al. 2010).
- Potassium: in severe UC (Kornbluth et al. 2010).

In summary, micronutrient deficiencies are common and not usually replaced via diet alone. Utilise MDT expertise to advise on appropriate therapeutic supplementation.

29.8 Diet and Stenosis

For stenosis, a low-fibre diet is often advised despite no evidence base (Halmos and Gibson 2015; Lee et al. 2014). The most recent reviews of fibre intake in IBD offer opinion in a variety of settings and include discussion around the effect fibre has on the microbiota and production of butyrate (Shah et al. 2015; Pituch-Zdanowska et al. 2015; Wong et al. 2016). In the case of stenosis, however, there is no actual evidence supporting specific fibre intake (Pituch-Zdanowska et al. 2015; Penagini et al. 2016). The literature acknowledges this lack and the difficulties inherent to establishing a literature base and thereby still advises a low-fibre diet (Lee et al. 2014; Shah et al. 2015; Pituch-Zdanowska et al. 2015; Kim and Koh 2015). Cited by Pituch-Zdanowska et al. (Pituch-Zdanowska et al. 2015), guidelines from AND, AGA and WGO concur having a low fibre in the context of stricturing disease though ultimately this advice is based on expert opinion. See Table 29.3 for foods which are high in fibre and thus to avoid in stricturing disease:

Table 29.3 High-fibre foods to exclude in structuring disease (Lee et al. 2014)

Fibrous parts of fruits and vegetables (skins, seeds, woody stalks, etc.)
Wholegrains
Nuts and seeds
Gristle, skin or edible bones on meat or fish

To counter any nutritional deficit from the restriction of these foods, nutritional supplementation may be required (Lee et al. 2014). The extent of restriction of fibre will be guided by the MDT, and the patient should be assessed and reviewed by the dietitian (Lee et al. 2014).

- The literature supports a low-fibre diet in stenosis.
- Micronutrient supplementation may be required.

29.9 Diet and Stoma

Outdated practice after stoma formation is to delay oral intake until 24–96 h postoperatively and then start with sips of water and progress via fluids, soft foods and eventually to full diet (Cronin 2012). Many centres now adopt enhanced recovery programs and following stoma surgery patients recommence oral intake a few hours postoperatively. This can be supplemented by sip feeds depending on the local enhanced recovery program (https://www.uptodate.com/contents/enhanced-recovery-after-colorectal-surgery). A colostomy patient should be able to tolerate a well-balanced diet longer term (Cronin 2012; Burch 2013).

There is uncertainty regarding the oral intake for patients with an ileostomy (Cronin 2012). Generally, and in the long term, ileostomy patients should only avoid certain foods if problems arise after eating them; this tolerance is individual to each patient (Cronin 2012; Burch 2013). All ostomists, especially urostomists (Cronin 2012; Burch 2013), should be counselled regarding adequate hydration, as fluid and electrolyte losses will be altered (Cronin 2012), increasing risks of dehydration. The MDT may identify that the patient requires rehydration solution (see Chap. 18 for more information). Some ileostomists may reduce or avoid high-fibre foods (Cronin 2012).

Table 29.4 cites foods and the potential effects they may have for the ostomist; not all people

Table 29.4 Particular foods and potential arising issues (Gibson 2017; Staudacher et al. 2014; Cronin 2012)

Dietary component	Stoma effect
Indigestible fruit and vegetable skins	Could cause a blockage
For the first 3 months, nuts, seeds and dried fruit as well as foods high in indigestible cellulose should be avoided	Can cause a blockage
Limit chewing gum, fizzy drinks and beans and peas	To reduce gas from a stoma
Carbohydrates, root vegetables and gelatine-containing confectionary	Thicken stoma output
Low-FODMAP diet	To reduce water content and weight of output in ileostomists NB care necessary due to potential of nutritional compromise from restrictions

will experience the same effects, so this information is meant to highlight potential effects rather than to be followed by all patients rigidly.

As long as an adequate length of small bowel remains, the patient can expect to be nutritionally autonomous (i.e. absorb enough from food), even if the lack of a colon causes watery output. Therefore nutritional issues are the same for stoma patients as those without, though anatomical changes from the surgery may have an impact. For example, malnutrition (especially of vitamin B12) is more likely to be a problem if there is an ileostomy before the terminal ileum. Of course, in the case of a stoma giving rise to a short bowel, and therefore intestinal failure, the patient will need to have detailed and specialist dietary management (see Chap. 17 'Short Bowel Syndrome').

Table 29.5 Glossary of definitions

Micronutrients	Trace minerals and vitamins required in minute quantities (Donnellan et al. 2013)
Elemental feed/ formula	A liquid monomeric amino acid-based formula, which contains individual amino acids and glucose polymers and is low in fat, with only 2–3% of calories derived from long-chain triglycerides, and does not contain antigen (Tsertsvadze et al. 2015) thus requiring no digestion (Shah et al. 2015), originally designed by NASA (Donnellan et al. 2013)
Semi-elemental feed/formula	'A liquid oligopeptide formula that contains peptides of various chain lengths, simple sugars, glucose polymers or starch and fat, mainly as medium-chain triglycerides' (Tsertsvadze et al. 2015)
Polymeric feed/ formula	A liquid whole protein-based formula that contains intact proteins, complex carbohydrates and long-chain triglycerides (Tsertsvadze et al. 2015) thus requiring gastric, intestinal and pancreatic enzymes to be digested (Shah et al. 2015)
Elimination diet	Induce remission with elemental feeds and then reintroduction of single foods to identify dietary symptom triggers (Donnellan et al. 2013)
LOFFLEX	LOw Fat/ Fibre Limited EXclusion diet-a dietary process for food re-introduction after EEN (Donnellan et al. 2013 and http://crohns.org.uk/crohns_disease/nutritional_therapy/the-lofflex-diet)
Fibre	Intact plant-based carbohydrate that is indigestible by humans (Shah et al. 2015) Soluble (Shah et al. 2015): • Guar gum • Inulin • Fructo-oligosaccharides/fructans • Galacto-oligosaccharides/galactans Insoluble (Shah et al. 2015): • Cellulose • Lignin
Residue	Any food that is not digestible or contributes to stool output, usually from plants based foods and may include some dairy and meat products (Shah et al. 2015)
Enteral nutrition	Nutrition delivered through a nasogastric or nasoenteral tube, gastrostomy or percutaneous endoscopic gastrostomy tube, jejunostomy or percutaneous endoscopic jejunostomy tube. Formula/feed used can be elemental, semi-elemental, polymeric or specialised (Tsertsvadze et al. 2015)
Parenteral nutrition	Intravenous feeding via the bloodstream (Tsertsvadze et al. 2015)
FODMAP	Fermentable Oligosaccharides, Disaccharides, Monosaccharides and Polyols

29.10 Conclusion

Dietary therapy is a popular option with patients and clinicians alike, but there are many options that must be navigated by being informed of the evidence base. Some strategies will seek to modify the disease course, while others aim more to improve symptoms or necessarily help with malnutrition arising from an IBD-related mechanism. Appropriate application of the dietary managements described above, use screening, assessment and subsequent dietary care planning, along with the support of the whole IBD MDT, are essential.

It must also be emphasised that dietary therapy in IBD must be individualised given the many variables; phenotype, localisation, grade of inflammation, previous surgery and different operative status, individual microflora, concomitant medical therapy, age and gender, status of malnutrition and many possible unknown factors determine the individual nutritional need and response to dietary interventions. It is not possible to detail and predict the effect of all of these factors, and therefore the IBD MDT must ensure open and continuous communication with each other to present a consistent, individualised message for each person with IBD.

Resources

Diet in IBD

Canada: http://www.crohnsandcolitis.ca/Crohns_and_Colitis/documents/CCF_59189_FOODFORTHOUGHTEN_1.PDF

USA: http://www.aga-resources.com/crohns/guide/pubData/mobile/index.htm#/24/

UK: http://s3-eu-west-1.amazonaws.com/files.crohnsandcolitis.org.uk/Publications/food-and-IBD.pdf

*Screening*http://www.bapen.org.uk/screening-and-must/must/introducing-must

Remission

Diet and nutritional factors in inflammatory bowel diseases Danuta Owczarek, Tomasz Rodacki, Renata Domagała-Rodacka, Dorota Cibor, Tomasz Mach World J Gastroenterol 2016 January 21; 22(3): 895–905

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Enteral nutrition for maintaining remission in patients with quiescent Crohn's disease: current status and future perspectives Maki Nakahigashi & Takayuki Yamamoto & Rodolfo Sacco & Hiroyuki Hanai & Fumio Kobayashi Int J Colorectal Dis (2016) 31:1–7 DOI 10.1007/s00384-015-2348-x

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As Therapy

Exclusive enteral nutrition in children with Crohn's disease Andrew S Day, Robert N Lopez World J Gastroenterol 2015 June 14; 21(22): 6809–6816

Malnutrition

Advances in nutritional therapy in inflammatory bowel diseases: Review 2016 Inflammatory Bowel Disease: Global view Andrzej Wędrychowicz, Andrzej Zając, Przemysław TomasikWorld J Gastroenterol 2016 January 21; 22(3): 1045–1066

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Micronutrients

Curr Opin Clin Nutr Metab Care 2015, 18:576–581 Micronutrient deficiencies in IBD Weisshof and Chermesh

BNF

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Dietary advice for patients with a stoma E Cronin British Journal of Nursing, 2012 (Stoma Care Supplement), Vol 21, No 16

http://www.crohnsandcolitis.ca/Crohns_and_Colitis/documents/CCF_59189_BETTEREN.PDF

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Stoma

30

Daniel Rohweder

Abstract

In some cases of refractory inflammatory bowel disease (IBD), fecal diversion with ostomy is needed. It can be a temporary or definitive surgical measure. Fecal diversion surgery is associated with complications, thus professional pre- and postoperative stoma therapy and care including preoperative marking of the stoma site and structured stoma-specific follow-up by stoma therapists and physicians are crucial to optimize the outcome after ostomy surgery.

30.1 Introduction

A stoma is a surgically created opening in the abdomen to which a healthy portion of intestine is attached. In this way it diverts feces into a bag that is affixed to the skin of the opening. This generally occurs after a portion of diseased bowel has been removed. There are different types of stomas which may be created in people with inflammatory bowel disease (IBD), small and larger bowel stomas, and permanent and temporary ones. If a patient is given a permanent stoma, then it is impossible to reconnect the gastrointestinal tract. A temporary stoma is given when it is likely that a reversal will take place at a later date. In this case, the GI tract is reconnected so that the patient can resume to pass stool through the anus.

30.2 Preoperative Procedure

Once the decision has been made to create a stoma, the patient is prepared for surgery in a clinical environment. During the preoperative consultation, the patient should be visited by a stoma therapist. In general, the following aspects are covered during that visit:

- Marking of the stoma site.
- Colonic irrigation/cleansing, if necessary.
- Answer questions from patient and family.
- Discuss individual challenges:
  - Sexuality and stoma.
  - Obstacles at work.
  - Re-examine lifestyle habits.
- Involve the stoma care nurse for postoperative care.
- Other experts may be required:
  - Nutritionist, social services, etc.
- Contact to local and national patient support groups.

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https://doi.org/10.1007/978-3-319-75022-4_30

30.2.1 Marking the Stoma Site

Marking the stoma site is an important step in ensuring the functionality of the stoma and the patient's acceptance postoperatively. Preoperative marking of the stoma site is generally done by a stoma therapist in agreement with the surgeon.

Frequently, despite instrumental diagnostics, the specific type of stoma and its final position can only be determined during the operation. This poses a specific challenge because the abdominal skin of sedated patients often appears smooth and crease-free, which is not the case in everyday life when sitting or lying down. The risk that the stoma will be sutured to the skin at a site on the abdomen which may be optimal from a medical perspective but is difficult for the patient to manage when caring for their stoma is therefore high in this situation.

The following aspects should be kept in mind:

- The stoma should pass through the rectus abdominis muscle.
- The stoma should lie above or below the waist.
- The stoma should not be sited in skin folds, the navel, scars, or bony prominences.
- The stoma should be visible and accessible to the patient.
- There should be only minimal interference with clothing.
- Check position when lying down, standing, sitting, and bending.

The precise location for an ileostomy or colostomy is found by drawing an imaginary line between the navel and the iliac crest, finding the middle of that line, and marking a point approximately two finger widths below it. A transverse (loop) colostomy is normally sited two finger widths below the right or left costal arch. However, appropriate alternatives should be discussed with the physician before a decision is made in favor of a transverse colostomy. For example, women with large breasts not only have aesthetic concerns but also could have problems managing a stoma at these sites.

Marking is done with a waterproof pen such as sterile surgical skin markers. Afterward, the site can be covered with a transparent, waterproof film dressing allowing the patient to shower before the operation without affecting the ink.

30.2.2 Ostomy Bagging Systems

There are one-piece and two-piece systems, each of which can have a flat or a convex baseplate. Flat baseplates are used for prominent stomas, convex baseplates for flush, or retracted stomas. For both the one- and two-piece systems, there are several types of stoma bag, each of which comes in transparent or opaque versions:

- Ileostomy stoma bag (Velcro closure or clamp closure)
- Colostomy stoma bag (disposable, sealed at the bottom)
- Drainage stoma bag (with and without backflow valve, round outlet)

Stoma bags for ileostomies must be open ended and, therefore, drainable. Never apply a closed stoma bag when caring for an ileostomate because stool can emerge in a sudden gush and cause the stoma bag to detach. If the stool is watery, drainage stoma bags with a round outlet are suitable; if the stool is pulpy in consistency, Velcro closures and wide outlets that can be resealed are more practical.

Colostomies are generally characterized by solid to pulpy stool which is difficult to "knead out" in order to empty open-ended bags. Consequently, these stoma bags are always the closed, disposable type and are changed as soon as they are at least half-full or at most three-quarters full.

30.3 Postoperative Care Plan

- Initial care of the stoma after surgery.
- Monitor consistency of the feces to check for extensive fluid and electrolyte loss.
- Ensure that the stoma wound is healing without complications.
- Instruct the patient or their family members.

30.3.1 Stoma Care

With one-piece systems, the stoma bag is changed usually once daily. The best time to do this is in the morning after getting up. With two-piece systems, the baseplate is changed every 2–3 days and the stoma bag from once a day (ileostomates) to up to three times a day (colostomates).

Changing of the stoma bag is best done standing in front of the sink to prevent leakage onto clothing. If the patient is not able to stand safely, the stoma bag can be changed in the sitting position. The lying position should only be used when a second person is changing the stoma bag.

When changing the stoma bag in a standing position, it has proven useful to tuck a small bin liner into the trousers across the abdomen, fix it with a clothes peg on the right and left, and place the bin liner in the sink. The stoma bag is then hung into the bin liner.

If the skin is very sensitive, any appropriate adhesive remover can be used to remove the old stoma bag. This is sprayed or trickled sparingly directly onto the adhesive border. When pulling off the baseplate, always pull the skin taut with one finger.

Procedure when changing a two-piece stoma bag system:

- Have all required materials prepared and close at hand.
- Peel off the old baseplate using the abovementioned technique.
- Thoroughly clean the skin around the stoma with a damp compress:
  - Colostomy/ileostomy: from the outside inward.
  - Do not use any creams, lotions, or soaps.
  - Do not use baby wipes or wet wipes.
- Dry with a dry, non-woven compress.
- If necessary, shave the skin (moving the razor away from the stoma).
- Place a dry, non-woven compress on top.
- Cut the new baseplate to fit the stoma precisely, even if the skin underneath is red.
- When applicable, close the bottom of the stoma bag first.
- Peel off the protective film.
- Remove the dry compress and check that there has been no further flow of stool.
- Hold the skin taut with one hand.
- Put the baseplate in place with the other hand.
- Let go of the skin.
- Put the stoma bag in place.
- Keep hand pressed down for 2 min.
- Put a knot in the bin liner and dispose of it in the household waste.
- Wash hands with soap.

The procedure for changing a one-piece system is the same except that after peeling off the protective film, the baseplate is folded in the middle and then, while still folded, placed against the underside of the stoma and folded back in an upward direction. Again, the skin must be pulled taut beforehand.

Ostomy patients generally receive a fixed monthly payment from their health insurance fund (this might vary from country to country) to pay for enough supplies to maintain the above-described management schedule. If more supplies are needed, e.g., due to drug-related bouts of diarrhea or unfavorable siting of the stoma, the medical insurer will require a statement of the medical reasons for the increased requirement from a physician.

30.3.2 Skin Care

Damage to the skin through poor skin care, the wrong choice of ostomy bagging system, or unfavorable position of the stoma (e.g., in skin folds) is commonly encountered in clinical practice. It is both necessary to protect the skin in these situations as well as allow the injured skin to heal. Certain aids are available to protect against leaks and subsequent skin breakdown. Modern ostomy baseplates, for example, are essentially composed of gelatine, pectin, and cellulose. Together these materials produce a gel-forming adhesive layer that swells upon contact with moisture and promotes wound healing similar to wound dressings such as hydrocolloid dressings.

The following additional materials attempt to aid the stool in passing directly into the stoma

bag without contact to the skin while absorbing the residual moisture of any damaged skin:

- Moldable strips for filling in deep folds and wrinkles
- Skin barrier rings for retracted stomas to increase convexity
- Alcohol-free stoma paste for uneven skin or retracted stoma where the stoma retracts below the skin level
- Stomahesive powder for weeping skin areas and small wounds
- Hydrocolloid skin barrier strips to enlarge the adhesive surface
- Skin barrier films (sprays, "lollipops," barrier creams, barrier wipes)
- Ostomy belt to apply more pressure to the baseplate; for severely retracted stomas, bathing/swimming

Moldable strips, rings, alcohol-free stoma paste, Stomahesive powder, and skin barriers can be applied directly to injured skin. If there is no alcohol-free paste available, glycerol 85% and Stomahesive powder can be mixed together to form a paste. Stomahesive powder turns to gel on contact with wound exudate forming a hydrocolloid mass and thereby binding moisture. A baseplate can be glued to a thin layer of the fanned powder where any resulting moisture causes the powder to swell and turn to gel, thus creating a leak-tight layer between the skin and the baseplate.

Early complications (and possible causes):

- Parastomal abscess (bacteria in the wound area)
- Wound dehiscence (wrong suture, too much tension on the stoma, infection)
- Stomal tear (infection, too much pressure on or below the stoma, bridge too tight)
- Stomal necrosis (hypoperfusion)
- Toxic contact dermatitis (often caused by the presence of waste material underneath the baseplate, alcohol abuse)
- Fungal infection (poor skin care, infrequent changing of the baseplate)
- Parastomal fistulae (e.g., in Crohn's disease patients)
- Ulceration (Crohn's disease, pressure ulcers, pyoderma gangrenosum, etc.)
- Stomal edema (opening too narrow, systemic disease)

Late complications (and possible causes):

- Stomal prolapse (e.g., lifting heavy weights)
- Parastomal hernia (lifting heavy weights, weakness of the connective tissue, widening of the muscle fascia)
- Pseudoepitheliomatous hyperplasia

30.4 Treatment of Complications

30.4.1 Toxic Contact Dermatitis

This results from exposure to aggressive digestive juices found in high ileostomies (in the duodenum and jejunum). It is less common in colostomies because the composition of the stool is different and its consistency is pulpy to dry.

The skin around the stoma tends to appear very red or macerated (Fig. 30.1). Treatment generally consists of directing the flow of stool into the stoma bag and away from the skin. In practice, the following procedure has proved effective:

- Dry the skin as much as possible (fan or pat the area with a dry compress).
- Apply Stomahesive powder to skin erosions and fan with a compress.

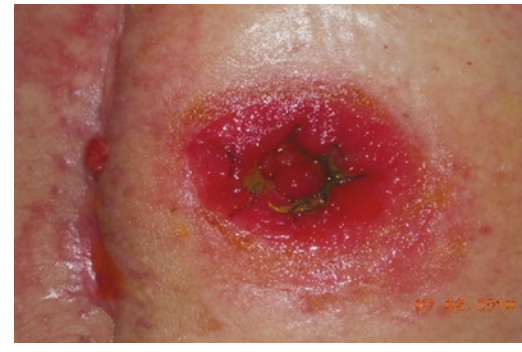

Fig. 30.1 Toxic contact dermatitis

– Fill in skin folds and creases with a suitable filler (e.g., moldable strips/rings).
– Additionally seal any remaining creases with alcohol-free stoma paste.
– If necessary, cover large areas of skin with hydrocolloid skin barrier strips.
– Cut the baseplate to fit snugly around the stoma.
– Where applicable, put the ostomy belt in place.

In the past, such skin irritations were dried using a dye (e.g., merbromin) or silver nitrate. Hydroactive materials, which are much better tolerated by patients, have now become the preferred treatments of choice.

30.4.2 Wound Dehiscence

This arises in the first few days after surgery. A furrow forms between the intestinal mucosa and the skin (Fig. 30.2). The stoma rarely separates completely because it is additionally fixed to the abdominal muscle.

When caring for the stoma, ensure that the size of the hole in the baseplate fits precisely around the wound so that intact skin is completely covered by the baseplate.

Smaller wound dehiscence can be filled with Stomahesive powder. Tamponade with, e.g., alginates may be done, but these often fall out of the wound and end up in the stoma bag, so this method is not recommended. Generally speaking, stool will not harm a superficial wound as long as it can pass freely into the stoma bag and is not able to form deeper wound pockets. Re-suturing of the stoma should be avoided because this often only leads to new wound dehiscence; it is better to rely on conventional wound healing.

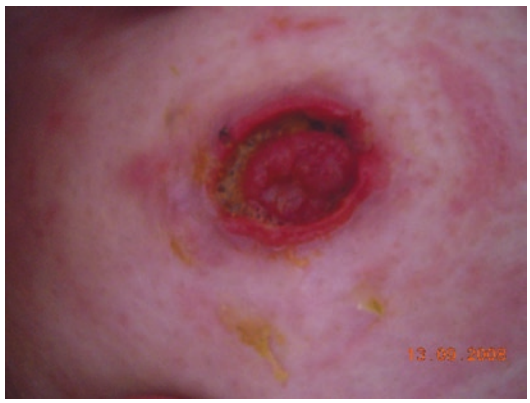

Fig. 30.2 Wound dehiscence

30.4.3 Pseudoepitheliomatous Hyperplasia (PEH)

PEH is a hyperplasia of the epidermis which can protrude through the epidermis of the stoma. It might be misdiagnosed as squamous cell cancer.

This is characterized by swelling of the skin, hypergranulation, and, in extreme cases, the presence of warts (Fig. 30.3). Because the skin's protective acid mantle is constantly being damaged, bacterial infections are common.

Treatment consists of selecting an appliance that separates the skin from the stoma effectively so that the skin beneath the baseplate can heal and dry. An ostomy belt, which puts pressure on the damaged tissue and thereby smooths the surface of the skin, can be used as a supporting measure. Initially, the level of pressure exerted should

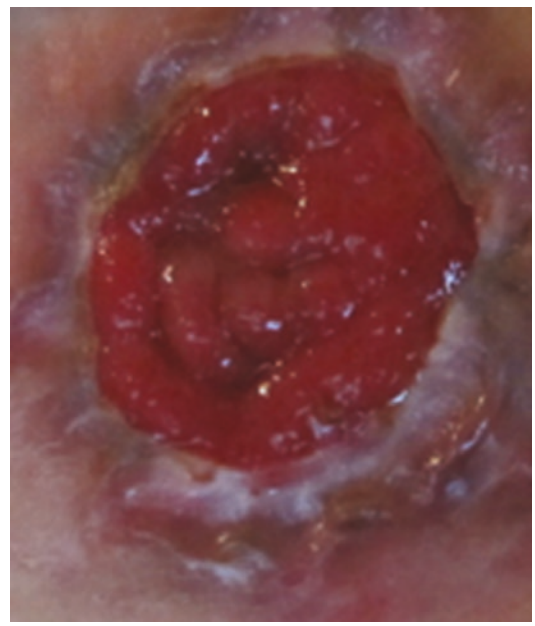

Fig. 30.3 Pseudoepitheliomatous hyperplasia

not be too high in order to prevent ulceration; the exact degree of pressure should be tried out with each patient individually.

30.4.4 Skin Mycoses

Classic fungal infections can be expected to occur frequently at the stoma site in cases of poor care or too lengthy exchange intervals; long-term high-dose antibiotic treatments also encourage fungal infection. They can be recognized by itching and scale-rimmed satellite lesions that spread in a mostly asymmetrical dotted fashion underneath the baseplate (Fig. 30.4).

Should a fungal infection be determined by a swab test, it is important that topical drug therapies always be applied in the form of a tincture and not as a cream or paste to prevent problems with the stoma appliance adhering to the skin. In cases of *Candida albicans* infection, local treatment with an antimycotic tincture is suitable. The stoma care routine should be performed once a day until the fungal infection has resolved.

30.4.5 Parastomal Fistulae

Fistulae can arise as a result of inflammation, tumors, Crohn's disease at the stoma site, and intestinal injury, or as a consequence of frequent bowel surgeries. External fistulae (between the intestine and the skin) are of relevance for the care of stoma patients. While fistulae of the large intestine often close spontaneously without surgical intervention, fistulae of the small intestine sometimes persist for long periods and expel large amounts of waste matter or small intestine secretions (Fig. 30.5).

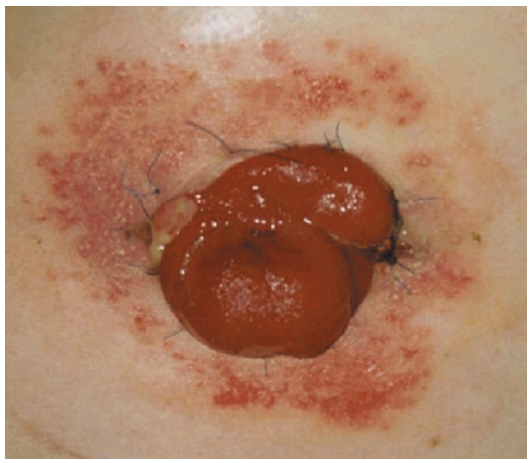

Fig. 30.4 Skin mycoses

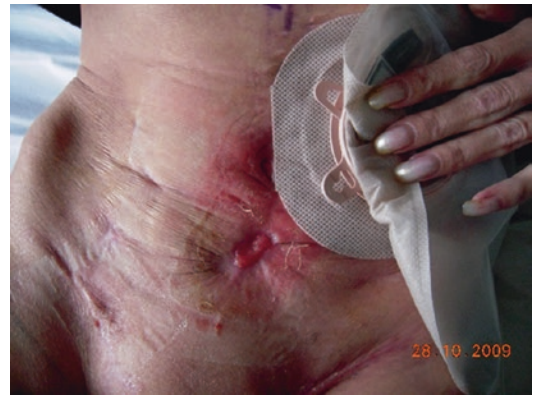

Fig. 30.5 Parastomal fistula

For the management of the stoma, it is important to cut the baseplate in such a way that the fistula(e) can empty into the ostomy stoma bag as well. Fistulae should not be taped over or "blocked" because they would find other drainage pathways which could result in the formation of burrow-like structures under the skin. In the case of high-output fistulae (>500 ml per day), parenteral fluid substitution should also be considered.

30.4.6 Parastomal Ulcerations

Ulcerations can arise as a result of too much pressure from the overlying ostomy baseplate, systemic causes such as Crohn's disease, severe bacterial infections, or autoimmunological processes like pyoderma gangrenosum (Fig. 30.6). Parastomal ulcerations differ from toxic contact dermatitis in that the skin damage goes deeper, sometimes invading the fatty tissue.

Procedure when cause is too much pressure

- Use a flat baseplate.
- Use a one-piece stoma bagging system if possible.
- If applicable, adjust/loosen the belt.

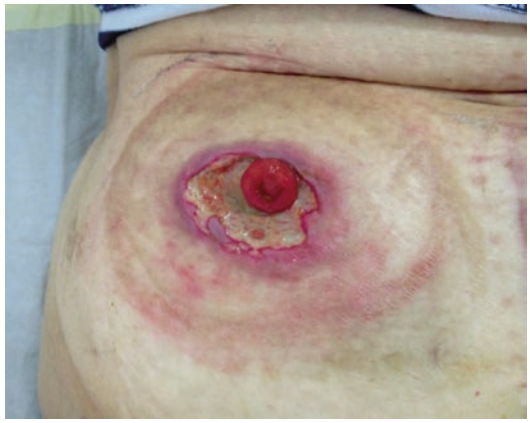

Fig. 30.6 Parastomal ulceration

Procedure when cause is systemic

- Clarify the exact cause.
- If necessary, take a sample for histological examination.
- Crohn's-related wounds are often very hard to heal; a new stoma site should be identified in addition to treatment with systemic drugs.
- The stoma appliance/stoma bagging system should fit the size of the wound without additional pressure, if necessary by enlarging the hole.

Procedure when cause is bacterial infection

- Swab wound.
- In case of accompanying systemic symptoms such as fever, elevated CRP, leukocytosis, etc., follow appropriate systemic antibiotic therapy when necessary.
- Local: disinfect the wound area with, e.g., polihexanide 0.04%/Prontosan wound irrigation solution, taking the application time into consideration.
  - Cut the baseplate to the size of the wound so that the wound exudate can flow into the ostomy stoma bag. Stool in the superficial wound does not generally lead to infection, as long as it can move into the bag freely.
  - Change the ostomy stoma bag daily.
  - Alternatively, one can attempt to cut the hole to fit the size of the stoma and cover the infected wound area with silver fiber (e.g., silver-containing hydrofiber dressings or silver-containing alginate dressings).

30.4.7 Edema of the Stoma

An increased accumulation of lymph in the intestinal mucosa leads to stomal edema. The stoma appears excessively large and swollen and is pale pink in color (Fig. 30.7).

Possible causes:

- Disruption in circulation of lymph or blood in the protruding intestinal loop.
- Liver cirrhosis, protein deficiency.
- High intra-abdominal pressure.
- Hole in the baseplate is too small.

Treatment:

- Determine the exact cause.
- Customize a flat baseplate, and change the ostomy stoma bagging system frequently (every 1–2 days).
- Acute: with a cupped hand, cover the stoma and carefully compress; this procedure can take several minutes.
- Place a cold (tap water) non-woven compress (do not use cold packs) on the stoma.

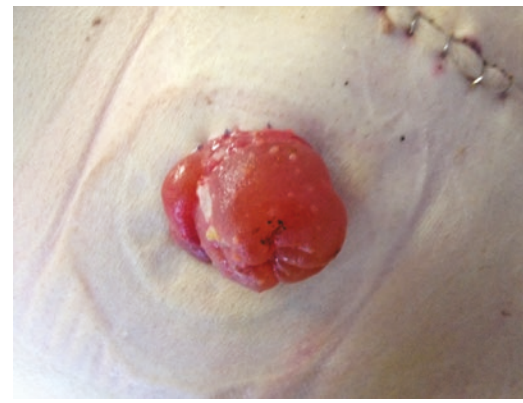

Fig. 30.7 Stomal edema

– Under no circumstances should decongestant nose drops or eye drops containing naphazoline be applied as they can cause necrosis.

30.4.8 Stomal Prolapse

A prolapse is a trunk-like protrusion of the intestine that can measure up to 15–20 cm in length (Fig. 30.8).

Possible causes:

– Significant weight gain
– Excessive strain on the abdominal muscles
– Insufficient intraoperative fixation of the intestine

Stomal prolapse needs to be treated surgically if the patient is in pain or has defecation problems that cannot be resolved by adapting the patient's stoma care. Surgical reconstruction of the stoma often leads to recurrent prolapse; therefore, a new site should be found and a new stoma created.

Generally, prolapsed stomas are treated conventionally. One option is to massage the intestine back into place (repositioning). This is, however, quite painful for the patient and is not effective long term. Another option is to prescribe a prolapse cap (abdominal support belt with a special, hard plastic cap in front of the stoma). The belt should be fitted properly by a medical supplies retailer.

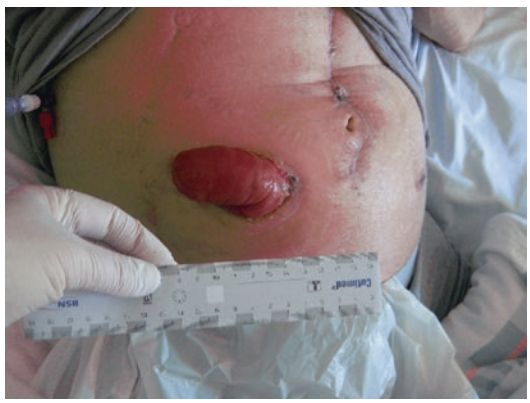

Fig. 30.8 Stoma prolapse prolapse

In case of prolapse:

– Don't perform sporting activities that put a heavy strain on the abdominal muscles.
– Don't lift more than 5–10 kg.
– Wear an adapted abdominal support belt if strenuous work is unavoidable.
– Press on the stoma with one hand when coughing or sneezing.

30.5 Lifestyle Changes

As a rule, the ostomate has a long, devastating history of countless bouts of diarrhea, chronic pain, and a severely reduced quality of life. A stoma is often a new beginning where the patient can regain control of their day to day life. However, the physical, emotional, and psychological pressures will be a major influence in the new ostomate life. By using appropriate responses, the nurse can ease the patients concerns, gain their trust, and help them begin a path of acceptance and healing.

For example, patients with a new stoma are often overly sensitive to resulting odors and subsequent facial expressions of others. The following behaviors can be used to reduce the patients' discomfort and establish a good nurse-patient relationship:

– Avoid use of endearments or nicknames to maintain patient dignity.
– Resist the urge to open a window unless at the patient's request.
– Control facial expressions.
– Eliminate the use of careless expressions that may offend the patient, particularly in reference to odors.
– If other patients in the room are bothered by odors, move the stoma care into the bathroom.

Additional methods can be used to help both the patient and their family with acceptance of the stoma:

– Be accepting if the patient refuses to initially look at the stoma.

– If close relatives are in the room, ask if they can remain during stoma care.
– Allow the patient to assume responsibility for stoma care one step at a time.
– Work at the pace of the patient; do not put them under undue pressure.

Long-term care may include issues such as stoma care at the workplace, sex and intimacy, and other lifestyle changes. As these needs differ in each patient, it is up to the stoma nurse to establish the communication necessary to address these problems with the patient as they arise.

30.6 Summary

Patients who have a stoma or must undergo ostomy surgery need comprehensive pre- and postoperative education, training, and transition care as well as lifelong supervision by specially trained personnel. For many of those patients, confronting this issue represents a critical phase in their lives which can, however, be well managed with elective preoperative education such as the correct marking of the stoma site as well as ongoing postoperative support. With the right choice of ostomy appliance, individual patient training, and early recognition and treatment of complications, patients can securely manage their stoma and raise their quality of everyday life.

Further Reading

Burch J (2017) Stoma care: an update on current guidelines for community nurses. Br J Community Nurs 22(4):162–166

https://www.ibdrelief.com/learn/treatment/surgery/stomas

Stomas and inflammatory bowel diseaseIBDrelief: https://www.ibdrelief.com/learn/treatment/surgery/stomas

National Clinical Guidelines - Association of Stoma Care Nurses UK: http://ascnuk.com/wp-content/uploads/2016/03/ASCN-Clinical-Guidelines-Final-25-April-compressed-11-10-38.pdf

Pouch Care

31

Idan Goren, Revital Barkan, and Iris Dotan

Abstract

Although the pharmaceutical armamentarium for the therapy of ulcerative colitis (UC) is growing, some patients still require surgical intervention with removal of the diseased colon and rectum. Proctocolectomy with ileal pouch-anal anastomosis, also known as pouch surgery, is the surgery of choice in the majority of these patients. Pouchitis, an inflammation of the pouch, is the most common long-term complication in patients undergoing pouch surgery. This chapter will review the indications and the surgical technique of pouch surgery, the medical management of patients with pouch, the clinical manifestations of postoperative complications, and the role of the IBD nurse in the medical team caring for patients with pouch.

31.1 Introduction

The prevalence of inflammatory bowel diseases and particularly that of UC is increasing worldwide (Kaplan and Ng 2017). Although the majority of patients can be managed conservatively, especially in the era of biologic therapy, a subset of patients with UC may require surgical intervention with total removal of the colon. This is expected in about 10% of patients within the first 5 years from UC diagnosis (Bohl and Sobba 2015), and over time approximately 25% may eventually require elective or emergent surgery (Penna et al. 1996; Blumberg and Beck 2002).

31.1.1 Indications for Surgery

Surgical treatment for patients with UC includes three main clinical settings: emergent, urgent, and elective procedures (Bohl and Sobba 2015; Fowkes et al. 2008; Cima 2010).

Emergent surgery is used in cases of life-threatening complications of UC such as massive bleeding, bowel perforation, or, in cases of toxic megacolon, a life-threatening nonobstructive colonic dilatation and systemic toxicity caused by *Clostridium difficile*. For emergent surgery, the procedure of choice is subtotal colectomy which includes removal of the colon, while leaving the rectum intact, and ileostomy.

Urgent surgery is indicated in cases of fulminant acute severe colitis that do not benefit from maximal conservative treatment. In any patient with acute severe colitis who is resistant to intravenous steroids, a surgical consultation should be initiated alongside with initiation of advanced medical therapies, such as infliximab or cyclospo-

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rine. For urgent surgery the procedure of choice is a subtotal colectomy and ileostomy with consideration of reconstruction at a later stage.

Elective removal of the colon is indicated in cases when disease is refractory to medical therapy, in steroid-dependent patients or those with severe systemic complications from medications, when a stricture or bowel obstruction develops and in cases of dysplasia or malignancy. In elective removal the procedure of choice is total proctocolectomy with reconstruction by the formation of an ileal pouch constructed from the normal small bowel, i.e., ileal pouch-anal anastomosis (IPAA).

31.1.2 The Surgical Technique of Pouch Surgery

Pouch procedure provides a major benefit as it allows preserving patient's continence and maintains the normal route of defecation, as opposed to permanent ileostomy.

The surgical technique includes either open approach or laparoscopy. The surgeon removes the colon and rectum while sparing the pelvic nerves and the anal sphincter mechanisms; next, the surgeon forms a pouch made of loops of ileum serving as stool reservoir, and finally the ileal reservoir ("the pouch") is connected to the anal canal. In cases when a single-stage procedure is done, it includes the proctocolectomy and immediate IPAA construction, without a temporary ileostomy to protect the anastomosis. However, in most cases, surgery is done in a staged fashion. A traditional two-stage procedure includes total proctocolectomy with IPAA and diverting ileostomy, followed by ileostomy closure as a second step performed after a period of recovery (Sofo et al. 2016). A modified technique for the two-staged procedure includes subtotal colectomy with end ileostomy, followed by completion proctectomy and IPAA, without diverting ileostomy (Zittan et al. 2016). A three-staged procedure includes subtotal colectomy and ileostomy, followed by IPAA and creation of loop ileostomy as a second stage and concluded by a third stage of ileostomy closure. The latter technique may be reserved for cases with more severe disease activity or in cases where the underlying disease is unclear (i.e., UC vs Crohn's disease [CD]) (Mège et al. 2016; Hare et al. 2008). In specific circumstances in selected patients (such as those with familial adenomatous polyposis), a single-stage surgery may be preferred (Joyce et al. 2010).

Of note, in selected patient populations, total abdominal colectomy with ileorectal anastomosis (TAC-IRA) was considered by some authors (Pastore et al. 1997).

31.2 Functional Outcomes of Pouch Surgery and Complications

31.2.1 Functional Outcome

Most patients undergoing pouch surgery report good functional outcomes (Tulchinsky et al. 2010). After the first year postoperatively, less than 10% report having less than four daily bowel movements, and on average most patients have five to eight bowel movements a day and one at night. About 30% have 9–12 bowel movements per day, and less than 9% report having more than 13 bowel movements per day. Full daytime continence for stool and gas is reported in 70–79% of patients over 10 years of follow-up and full overnight continence in 53–74% (de Buck van Overstraeten et al. 2014; Ramage et al. 2016; Fazio et al. 1995, 2013). Commonly reported complaints include episodic soiling especially at night, incontinence, and need for antidiarrheal medications to control bowel activity (Tonelli et al. 2016).

Pouch failure is defined as excision of the ileoanal pouch, formation of a permanent ileostomy, or pouch-related mortality (Fazio et al. 2003). Surgical complications, such as pelvic sepsis, as well as inflammatory complications and Crohn's disease of the pouch are the most common causes of pouch failure. The rate of pouch failure increases over time with 5–9% cumulative risk at 5 years and up to 18% over 20 years of follow-up (Mark-Christensen et al. 2017).

31.2.2 Postoperative Complications

Postoperative complication may be divided into early and late, although some overlap exists between the two groups especially with regard to small bowel obstruction that may occur at any time. Early postoperative complications are usually directly related to surgery and may lead to periprocedural morbidity and even mortality. These mainly include anastomotic leaks leading to pelvic sepsis, pouch bleeding, and ileus. Over time, the most frequent late complication of pouch is inflammation of the pouch, termed pouchitis (Peyrin-Biroulet et al. 2016).

31.2.3 Pouchitis

The term pouchitis represents different conditions with similar clinical presentations. The clinical presentation of patients with pouchitis includes the combination of typical symptoms, endoscopic findings, and histologic support of inflammation. The most common symptoms of pouchitis include increased frequency of bowel movements, abdominal pain, incontinence, tenesmus, and rectal bleeding. In severe cases fever, dehydration, and electrolyte imbalance may occur (Shen et al. 2001a).

31.2.3.1 Etiological Classification of Pouchitis

Idiopathic pouchitis accounts for the majority of cases with pouchitis. As in IBD, the etiology is unknown. However, similarly to IBD, interaction of environmental factors with the intestinal immune system in a genetically susceptible host is the presumed etiology for pouchitis. Intestinal microbiota plays a major role in this form of IBD (Reshef et al. 2015; Maharshak et al. 2017). This is supported by several observations: Pouchitis develops only after ileostomy closure and renewal of fecal stream to the pouch. Furthermore, manipulations of pouch flora composition such as with probiotics may prevent pouchitis (Mimura et al. 2004). Finally, pouchitis is considered the most antibiotic-responsive IBD (Gionchetti et al. 2012). When stratifying patients to those with high or low risk for idiopathic pouchitis, it is evident that patients with UC as their background disease have higher risk for pouchitis compared to patients with pouch due to familial adenomatous polyposis (Lovegrove et al. 2006). Additionally, among patients with UC at baseline, idiopathic pouchitis is more common when the indication for surgery was refractory UC as opposed to non-refractory indications, such as dysplasia (Yanai et al. 2017; Hashavia et al. 2012). These two observations suggest that immunologic processes occurring before surgery may proceed/progress after surgery and cause inflammation at the previously normal pouch. Few studies suggested genetic predisposition such as polymorphism at NOD2/CARD15 gene (Landy et al. 2012).

Secondary pouchitis is defined when a causative factor such as infection, use of nonsteroidal anti-inflammatory drugs, ischemia, or Crohn's disease can be identified.

Pouchitis may also be defined by disease behavior. This is based mainly on clinical characteristics. Thus, acute pouchitis is defined as an acute flare, responding to short (usually up to 2 weeks) of antibiotics; recurrent acute pouchitis is defined as up to four episodes of acute pouchitis per year; and chronic pouchitis is defined as at least 4 weeks or more of persistent symptoms and anti-inflammatory therapy; Crohn's-like disease of the pouch is defined as inflammation in the afferent limb, appearance of proximal small bowel strictures unrelated to the surgery, or perianal and abdominal fistulas or abscesses which are not direct complication of the IPAA procedure (Tulchinsky et al. 2008, 2010; Goldstein et al. 1997).

Pouchitis may also be defined based on response to antibiotics. The mainstay treatment of *idiopathic* pouchitis is a 2 weeks course of antibiotics, specifically ciprofloxacin and/or metronidazole (Gosselink et al. 2004). Based on patient response to antibiotics, pouchitis may be defined as antibiotic responsive, antibiotic dependent, and antibiotic resistant. The latter, may require the use of anti-inflammatory medications such as corticosteroids, immunomodulators (azathioprine, 6-mercaptopurine),

or biologic therapy such as anti-TNF (Herfarth et al. 2015). A table with therapy of pouchitis is attached (Table 31.1). Noticeably, the use of most therapies mentioned is based on anecdotal reports rather than randomized placebo-controlled studies (Singh et al. 2015).

In a subset of patients with severe cases of medically refractory chronic pouchitis or Crohn's-like disease of the pouch, diversion of fecal steam and ileostomy with or without excision of the pouch is indicated.

31.2.4 Miscellaneous Conditions

One should keep in mind that functional symptoms may mimic pouchitis. When such symptoms exist without proof for organic disease such as pouchitis, pouch stenosis or obstruction, dysplasia or neoplasia, or secondary reasons for pouchitis, the term irritable pouch syndrome (IPS) is used. Treatment may include antidiarrheal, anticholinergic, and antidepressant medications (Shen et al. 2002).

An additional condition unique to patients after pouch surgery due to UC is cuffitis. This is defined as inflammation recurring in the transitional zone or the 1–2 cm of the rectal cuff remaining after proctocolectomy and IPAA. Cuffitis represents recurrence of residual UC. Topical treatment with mesalamine suppositories or enemas is recommended in order to improve symptoms of cuffitis as well as endoscopic and histologic inflammation (Shen et al. 2004).

31.3 Fertility and Sexual Dysfunction

One of the most common concerns of patients undergoing pouch surgery is sexual function and fertility after IPAA.

Female patients with a pouch have decreased fecundity compared with women with UC under medical therapy. In older reports, this was estimated in up to fourfold risk (Counihan et al. 1994; Ørding Olsen et al. 2002). The hypothesis was that scarring of the fallopian tubes may play a role (Waljee et al. 2006).

More recent studies demonstrated that decreased fecundity could be significantly decreased by performing laparoscopic pouch surgery (Beyer-Berjot et al. 2013; Bartels et al. 2012). This should be discussed with a female patient who is a candidate for IPAA. Alternative strategies may be colectomy and ileostomy, postponing pouch surgery until after birth plans were fulfilled (Pinder et al. 2016), or performing subtotal colectomy with an ileorectal anastomosis (Pastore et al. 1997).

Pouch surgery may have significant effects on male and female sexual function and sexuality. Problems in erectile function and ejaculation were reported by several groups (Fazio et al. 1980; Dozois et al. 1993). Up to 15% reported erectile function problems. It was assumed that pelvic dissection may be the cause for such symptoms. Patient expectations and counselling should be adjusted accordingly.

As for female sexual dysfunction postsurgically, in a Scandinavian study by Tiainen et al. (Tiainen et al. 1999), women reported increase in dyspareunia after the operation, but sexual satisfaction improved. Generally, sexual satisfaction has improved after operation, mainly due to improved general health.

Mode of delivery: due to the risk of anal sphincter injury during vaginal delivery, many caregivers advise to consider a planned cesarean section to eliminate this potential concern (Remzi et al. 2005).

31.4 Role of IBD Nurse in the Management of Patients with Pouch Surgery

Patients after pouch surgery have a combination of medical, surgical, emotional, obstetric, and sexual problems. This unique patient population is thus a prototype of patients requiring multidisciplinary team (MDT) approach (Tulchinsky et al. 2008, 2010).

Table 31.1 Medical therapy for antibiotic responsive and antibiotic resistant pouchitis

Therapy	Suggested dose	Ref	Comments
Ciprofloxacin	1000 mg daily in divided doses for 2 weeks	Shen et al. (2001b)	For acute and recurrent acute pouchitis use as monotherapy. Based on a single study on 18 patients, ciprofloxacin may be more effective than metronidazole for the treatment of acute pouchitis In chronic pouchitis use combination of ciprofloxacin and metronidazole for 4 weeks
Metronidazole	1000 mg daily in divided doses for 2 weeks	Shen et al. (2001b)	For acute and recurrent acute pouchitis use as monotherapy. Based on a single study on 18 patients ciprofloxacin may be more effective than metronidazole for the treatment of acute pouchitis. In chronic pouchitis use combination of ciprofloxacin and metronidazole for 4 weeks Dose and duration of therapy may be limited by intolerance
Tinidazole	1000 mg in divided doses for 2 weeks	Shen et al. (2007) and Ha et al. (2010)	Extrapolated from the effect of metronidazole. Assessed only in combination with ciprofloxacin on 16 patients with chronic pouchitis. One study found tinidazole effective for pouchitis prophylaxis when given for 1 year post IPAA
Rifaximin	400 mg three times daily for 4 weeks	Isaacs et al. (2007)	Based on a single study on 18 patients, no differences were found between rifaximin and placebo in terms of clinical remission, clinical improvement, or adverse events
Mesalamine	Rectal suppositories, 1000 mg three times per day for 8 weeks	Belluzzi et al. (2010)	For acute pouchitis. Remission achieved in 63% of patients and 73% improved clinically
Budesonide	Enema, 2 mg/100 mL at bedtime for 6 weeks	Sambuelli et al. (2002)	Similar efficacy but better tolerability than oral metronidazole in the treatment of active pouchitis
Beclomethasone	Oral beclomethasone dipropionate 10 mg/day for 8 weeks	Gionchetti et al. (2014)	Series of ten patients with antibiotic refractory pouchitis with 80% response rate
Infliximab/ AZA/6-MP	Infliximab 5 mg/kg with induction and maintenance as in other IBDs. AZA/6-MP at daily starting dose of 1–1.5 mg/kg and increased to a maximum dose of 2–2.5 mg/kg	Haveran et al. (2011) and Barreiro-de Acosta et al. (2012)	Retrospective analysis of 22 patients with Crohn's-like disease of the pouch suggests that fistulizing disease may be treated with infliximab, and stricturing disease as well as antibiotic-resistant pouchitis may be effectively treated with azathioprine/6-mercaptopurine only (Haveran et al. 2011). In retrospective analysis of 33 patients with chronic pouchitis on infliximab at weeks 26 and 52, 33% and 27% achieved complete response, and 33% and 18% showed partial clinical response, respectively
Adalimumab	Given at induction and maintenance protocol as in other IBDs	Li et al. (2012)	Out of 48 patients with Crohn's-like disease of the pouch, 50% and 33% achieved complete response at median of 8 and 24 weeks, respectively
Tacrolimus	Tacrolimus enema of 4–5 mg/100 mL daily for 8 weeks	Uchino et al. (2013)	Ten patients with antibiotic refractory chronic pouchitis were enrolled. Of which, 90% improved symptomatically and 30% achieved remission as well
Alicaforsen	Alicaforsen enema 60-mL, 240 mg/60 mL daily for 6 weeks	Miner et al. (2004)	Out of 12 patients with antibiotic refractory chronic pouchitis, 58% achieved remission by week 6

(continued)

Table 31.1 (continued)

Therapy	Suggested dose	Ref	Comments
FMT	Fresh or frozen samples, three studies used single FMT and one repeated doses. In two studies the route was via pouchoscopy, one via nasogastric tube, and one via endoscopy to the jejunum	Paramsothy et al. (2017)	In four studies on patients with pouchitis, overall 21.5% (5/23) of pouchitis patients achieved clinical remission
IVIG	At least 1 dose of IVIG (0.4 g/kg)	Horton et al. (2017)	Overall 16 patients with refractory chronic pouchitis achieved decrease in PDAI after IVIG infusion but no data regarding remission rates
Exclusive elemental diet	Four weeks	McLaughlin et al. (2013)	Symptoms improved in some patients with chronic antibiotic refractory pouchitis but was not effective strategy for inducing remission

AZA azathioprine, *6-MP* 6-mercaptopurine, *FMT* fecal microbiota transplantation, *IVIG* intravenous immunoglobulins, *PDAI* pouchitis disease activity index

A major role in the multidisciplinary team is reserved for the IBD nurse.

A. Before surgery—IBD nurse as part of the MDT takes part in the follow-up of patients with UC. Given that surgical intervention in UC is a major milestone that requires mutual decision-making by patients, families, and caregivers, the IBD nurse is a key player in assuring efficient communication. At this critical point, the IBD nurse may provide medical guidance and information regarding the procedure, as well as emotional support. When possible, introducing patients to patients with a similar background who already underwent surgery is advised.
B. In the immediate postoperative period and before hospital discharge, the IBD nurse should provide support, as well as coordination of consultations with other members of the MDT such as with a nutritionist and a stoma-specialized nurse.
C. In the first postoperative year, patients require closer attention as they are learning how to live with their new pouch and getting used to the change in number of bowel movements, with difficulties emptying their pouch and with the impact IPAA may have on quality of life. IBD nurses are commonly responsible for medical help lines and online-based communication with patients and therefore should be familiar with the common early and late postoperative complications, being able to identify, treat, and refer patients accordingly.
D. In the regular follow-up of pouch patients, IBD nurse with knowledge in pouch care can provide information, education, encouragement, and counselling for patients and their families in a diverse range of subjects.
E. In centers where specialized pouch care clinics are available, the IBD nurse is a long-term point of contact and a key player among the MDT. Nurses actively participate in patient follow-up and may refer patients to other members of the MDT to provide medical care and psychological and social support when needed (see Chap. 50).
F. In countries where nurse practitioners are employed, IBD nurses with extended autonomy can independently provide care for patients with pouch, such as the experience of nurse-led pouch clinic in Oxford (Perrin 2005). Such nurse-led clinics include clinical follow-up visits, physical and laboratory investigations, medication prescription, and monitoring of effects and adverse effects.

31.5 Summary and Conclusions

IPAA, known as pouch surgery, is the surgical procedure of choice in patients with UC. While usually associated with good short- and long-term consequences, this surgery may have specific outcomes requiring multidisciplinary expertise and care. IBD nurses participate in the care of patients with UC before and after pouch surgery and therefore should be able to provide patients with information, support, and care. Long-term and regular follow-up after pouch surgery is essential for the management and prevention of both medical and surgical complications. MDT approach provided by IBD nurses, stoma nurses, gastroenterologists, colorectal surgeons, nutritionists, and social workers as well as psychological support could improve both clinical outcomes and patients' satisfaction.

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Adherence

32

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Abstract

Inflammatory bowel disease (IBD) is an unpredictable, complex and chronic condition with symptoms that are unpleasant, embarrassing and painful. The global incidence is rising though the majority of patients will remain capable of leading a reasonably normal life (Haynes 1979). Individuals with IBD will often require intensive on-going input from health professionals. The chronic nature and increasing incidence of IBD demand health care innovations to guarantee future high-quality care. This chapter considers specific considerations for nurses and other health care professionals managing adherence in IBD to improve the quality of care. Understanding the patient perspective and being willing to listen to them might be the keys to change.

32.1 Introduction

Many patients, especially those with chronic illnesses, experience difficulty with taking their medication as prescribed. As such, poor medication intake behavior can be considered an important health problem. This is especially true for patients with a long-term illness because successful medication intake is crucial for the effectiveness of a therapy. The patients' willingness to start and continue to take prescribed medication is influenced by the way in which they judge their personal need for the treatment relative to potential adverse consequences of taking it. Poor medication intake behavior can be either unintentional or intentional, given that patients need to adhere over a long period of time. This makes the average successful medication intake rates for long-term treatment low. This can lead to increased use of healthcare services, reduction in patients' quality of life, and increased healthcare costs overall. Tight control of disease activity, medication side effects, and adherence are crucial to prevent disease complications and improve quality of life in patients with IBD (Horne et al. 2009).

▶ Nurse: "How often are you taking your medication?" Patient: "Not at all anymore, I stopped taking them, I don't like them and I would not recommend them to anyone" (male, 45 years old, Crohn's disease) etc.

32.2 Definition of Adherence

▶ The extent to which a person's behavior (in terms of taking medications, following diets, or executing lifestyle changes) coincides with medical or health advice (Johnson et al. 2007).

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The term "adherence" is now more commonly used than terms such as "compliance" as it connotes a more positive interpretation of patient behavior. It also reflects the ideal collaboration between patients and providers in treatment planning and implies a continuum of behavior related to treatment completion. Unfortunately, 20–40% of the IBD patients are noncompliant (Linn et al. 2012). Reasons for this may be a treatment that is too complex to understand or fear of side effects from immunosuppressive therapy and biologics. For example, nonadherence to anti-TNF agents is strongly associated with loss of response to anti-TNF agents and illness perceptions. The latter may provide an important target for interventions aimed at improving adherence and health outcomes (van der Have et al. 2016).

32.2.1 Risk Factors in Nonadherence

Treatment beliefs and illness perceptions are modifiable factors that have been consistently associated with nonadherence to medication across a range of chronic illnesses including IBD. Treatment beliefs are patients' beliefs about the necessity of their medication for controlling their illness and their concerns about potential side effects (Haynes et al. 2002). Illness perceptions constitute patients' views, cognitive or emotional, about several components of the illness such as the causes, clinical course, daily consequences, curability, and emotional impact (Sewitch et al. 2003). Barriers to successful medication intake behavior can be practical (cognitive and/or behavioral) and/or perceptual (affective) and are considered important determinants of taking the medication as prescribed. Evidence suggests that patients' perceptual barriers are more predictive of intentional nonadherence types of behavior rather than that of unintentional poor medication intake behavior.

Conversely, practical barriers (e.g., time, work) have been shown to be indicative of unintentional poor medication intake behavior rather than of intentional nonadherence (Linn et al. 2012).

Demographic risk factors for nonadherence include gender, age, smoking status (current smoker, ex-smoker, non-smoker), and education level (low versus high). Low education includes no education, primary education, secondary education, and technical or professional school, whereas high education includes higher vocational education and university. Although some correlations do exist, demographic variables as well as disease and treatment factors are considered to be poor predictors of medication intake behavior in IBD patients specifically (Linn et al. 2012).

Clinical risk factors for nonadherence include age at diagnosis, disease duration, disease localization, perianal disease, concomitant medication (mesalazine, corticosteroids, immunomodulators, anti-TNF agent), and duration of the treatment (Sabaté 2003).

32.2.2 Interventions to Enhance Adherence in IBD

Existing intervention approaches to enhance adherence in IBD can be broadly grouped into four categories:

- Educational (knowledge about the disease, symptoms, medication, side effects, etc.)
- Behavioral (how the medication fits in daily routine and the convenience of the regimen, e.g., once daily dosing)
- Cognitive behavioral (a structured framework for identifying barriers to adherence)
- Multicomponent interventions (using a variety of theoretically or empirically based approaches to enhancing adherence) (van der Have et al. 2016)

Within each domain, interventions vary with respect to the extent of technology used in the delivery of the intervention, whether the intervention is delivered individually or in a group setting, and the intensity and duration of the intervention. Practically, many strategies can be used to improve adherence (van der Have et al. 2016; Sewitch et al. 2003; Fishbein and Yzer 2006):

- Visual reminder systems, auditory reminder systems, or use of a weekly or daily pill box (phone or pager text message, phone call, video call, interactive voice response system, or electronic monitoring device with integrated reminder alarm).
- Counselling: education face-to-face or in groups with leaflets, videos, presentations, patient support groups. Using techniques like *motivational interviewing* are recommended.
- Frequency contact with the IBD nurse is another possibly efficacious strategy to promote adherence.
- E-health computer technologies can be used to tailor messages to the personal situation of the patient and could contribute significantly to the development of message strategies. The Internet is potentially a powerful medium for delivering such tailored messages.
- Recall-promoting techniques include summarizing, categorizing, structuring, providing written information, using cartoons or pictures, emphasizing and repeating information, checking with patients for understanding, and avoiding recall-hindering techniques such as technical jargon.
- Encourage question-asking behavior, and involve the patient in the problem-solving and decision-making process.
- Explore additional use of information sources.

Although there are four categories, interventions should be personalized to the needs of a patient to achieve maximum impact. It starts with communication which is a two-way process. Nurses need to develop an empathetic and active listening role and be able to provide essential IBD-related information and holistic support (Linn et al. 2013b).

32.2.3 Nurses Role

The treatment of IBD has become more complex since the introduction of immunosuppressive or biological therapy (Linn et al. 2012). Consequently, patients are more prone to forget how and when they must take their medication. A study measuring patients' knowledge of their immunosuppressive or biological therapy found that of 354 participating patients, only 60% understood the role of immunosuppressive or biological therapy. Efforts to improve patients' knowledge include the use of information leaflets or physician education (Fishbein and Yzer 2006). Patients who do not have the ability to understand or remember information are not likely to know how to take the medication as prescribed.

Nurses play an increasingly important role in educating IBD patients about their newly prescribed immunosuppressive or biological therapy. The initiation process and the implementation or execution process can be optimized particularly during consultations at which medication is prescribed. These prescribing consultations contain complex and important information which are often difficult to remember (Sewitch et al. 2003).

The IBD nurse assesses comprehension and provides education based on current evidence to patients with IBD and their relatives depending on individual needs, preferences, and coping ability. The ultimate aim is to enable and empower the patient to live as normal a life as possible. Those affected with IBD need to be provided with individualized treatment, support, and information to continue daily life while living with a chronic disease. A multidisciplinary team (MDT) and the IBD nurse in particular are key to empowering patients and advocating on their behalf (Sewitch et al. 2003; Fishbein and Yzer 2006).

The most common technique that the IBD nurse should be trained in to promote adherence is motivational interviewing (MI). MI strategies help identify the core values/goals of the patient to increase their insight regarding the role of medication adherence in achieving their goals (Greenle et al. 2013). Specific techniques used to enhance motivation include the following:

1. Convey a nonjudgmental understanding of the patient's perspective.
2. Work with the patient to see a discrepancy between their personal goals (e.g., returning

to work, being socially active) and their present behavior (e.g., not taking medication as prescribed).
3. Treat resistance to change as normal.
4. Support patient in self-management so they can identify what is important for themselves.

Motivational enhancement may be particularly useful in addressing volitional nonadherence. If the interviewer is experienced in MI! Because patients who are already invested in being adherent but experience barriers to adherence that are contextual in nature (e.g., lack of organized system and financial barriers to getting medication refilled consistently) may be less likely to benefit from motivational interviewing (Shale and Riley 2003).

It is also important to be aware of the pitfalls in communications with your patient (Sewitch et al. 2003):

– Noneffective communication.
– Recall of information.
– Barriers which are not explored (see below).
– Information is not sufficiently tailored to the individual patient.

It may be useful to consider specific questions which help in exploring the patients' barriers:

Patients' experiences, concerns, and motivations

- What are your experiences?
- How do you feel about taking your medication?
- Do you think that taking your medication is important?
- Do you have concerns about taking your medication?

Patients' daily routine barriers

- Do you manage to adapt your regimen to your daily life?

Patients' knowledge/memory barriers

- What did your GP tell you about your medication?
- Why do you need to take your medication?
- Do you often forget your medication?
- Could you repeat what I just told you?

32.3 Summary

Promoting adherence to treatment among patients with IBD is a challenging yet important task. Nurses are in a unique position to facilitate optimal adherence given their ongoing interactions with patients. Effective intervention starts with an accurate assessment of adherence. To improve adherence behavior, it is important to address the specific reasons why a patient is unable or unwilling to follow the treatment plan. From this perspective, interventions should be tailored to address the individual barriers to successful medication intake behavior. Every technique and intervention has its own value (Sewitch et al. 2003; Fishbein and Yzer 2006; Linn et al. 2013a). Exploration of barriers to adherence is critical to identify volitional and accidental reasons for nonadherence, as each may benefit from different intervention approaches. Interventions should be tailored to the specific barriers for the individual patient, and developmental factors should be considered in the choice of intervention approach (Linn et al. 2012).

▶ Patient: "I need you to listen to me, I am afraid for side-effects. I do know I need the meds, I know how they work. I just want you to listen to me, because I am just human. And from that point we will work further, together." (female, 30, ulcerative colitis)

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Constipation

33

Nathan S. S. Atkinson

Abstract

People with inflammatory bowel disease (IBD) may experience constipation whether in remission or at times of flare for a variety of reasons: medications, slower bowel transit due to inflammation, dietary changes, and more. It is important that IBD clinicians are able to appropriately recognize, assess, and manage constipation. This chapter details

- symptoms of constipation,
- types of constipation,
- functional GI disorders,
- assessment of colonic transit, and
- management of constipation.

33.1 Introduction

Patients with inflammatory bowel disease (IBD) seek medical assistance to relieve gastrointestinal symptoms, but not all their symptoms are due to their inflammatory burden. Functional bowel disorders, 'symptoms in the absence of obvious anatomic or physiologic abnormalities' (Lacy et al. 2016), are common in the general population with an estimated worldwide prevalence of 11.2% (Lacy et al. 2016). Constipation is frequently an adverse effect of many medications, and altered bowel transit time is commonly seen in the presence of active inflammation. Delayed transit of the faecal stream also alters the delivery of medications to the colonic epithelium and impacts disease response. Attention to the multiple factors that contribute to intestinal dysfunction allows relief of our patient's noninflammatory symptoms.

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33.2 Symptoms of Constipation

Although widely used, the term 'constipation' can have multiple meanings, and exploring these features whilst taking a history helps guide management recommendations. People may allude to:

- Infrequent spontaneous bowel motions (SBM); the normal range is considered between three SBM per week and three motions per day (Lacy et al. 2016). Consider how many movements may be stimulated by laxatives when interpreting a frequency history.

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- Hard or firm stool; a majority of Bristol stool form chart types 1–2 are considered abnormal, even if there are episodes of looser stool at times.
- Difficulty initiating defecation; this may include excessive straining or a long wait on the toilet before defecation occurs.

Other symptoms often occur in conjunction with constipation. These include:

- Feelings of incomplete emptying; 'tenesmus'
- Sense of pushing against a closed door; 'anismus'
- Urgency to defecation; considered as the time between first sensation to the latest moment one can hold for example: <5 min, 5–10 min, >15 min, up to an hour, etc.
- Passage of mucus
- Abdominal bloating; purely the reported sensation
- Abdominal distension; the visible appearance often associated with the sensation of bloating
- Abdominal pain; particularly when on the left side or radiating to the back

Very clearly these symptoms overlap with features of active IBD, and thus there is some art in putting together the patient's history, disease course and recent therapies, the previous response to therapy, lab results, and radiological and endoscopic findings to make a diagnosis. As is discussed below, it is important to clarify whether active IBD is present, particularly in the context of ulcerative colitis, and whilst endoscopic evaluation is most reliable, patients and clinicians often avoid repeated invasive investigations, by using blood or radiology findings as surrogate measures.

33.3 Types of Constipation

It helps to consider the mechanism of bowel disturbance causing constipation, before tailoring advice to the individual patient situation.

33.3.1 Slow Transit Constipation

Slow transit constipation is defined as prolonged transit of the faecal stream through each of the colon segments, in the absence of dysfunctional defection.

In health the faecal stream takes between 24 and 60 h to transit through the colon to the rectum (Maurer 2015). The more time the faecal stream spends in the colon, the more water is withdrawn. Colonic motility is highly complex with at least four different types of contraction waves described by modern high-resolution manometry studies; many contraction waves move in a retrograde (backward) direction (Dinning et al. 2014). Motility can be slowed by changes in the enteric nervous system with generally decreased motor activity, altered autonomic and reflex arcs and alterations in colonic smooth muscle tone and function. There is circadian variation, whilst general exercise activity and microbiota interactions also contribute. Multiple additional factors also impact on colonic motility (the secondary causes of constipation) as described in Table 33.1.

Slow transit constipation typically presents as infrequent firm stool. Management starts by addressing any coexistent secondary causes, optimising stool consistency and providing general lifestyle advice.

33.3.2 Outlet Dysfunction (Dyssynergic Defecation)

Similar to an automatic garage door opening as an advancing car drives out from an underground car park, the anorectal sphincter and pelvic floor muscle complex must act in a coordinated fashion, to pass stool.

In health the defecatory mechanism includes:

- The internal anal sphincter; an involuntarily controlled smooth muscle sphincter, which relaxes when the rectum is distended by the recto-anal reflex.
- The external anal sphincter; skeletal muscle under voluntary control, which can be damaged during labour or surgery.

Table 33.1 Common causes of secondary constipation

Medications
Analgesics
NSAIDs
Opioids
Antihypertensive agents
Diuretics
Calcium channel blockers
Beta-blockers
Antidepressants
Particularly amitriptyline and imipramine
Antihistamines
Serotonin antagonists
Ondansetron
Antiparkinson agents
Antipsychotic agents
Quetiapine and clozapine
Metallic ions
Iron supplements, aluminium antacids
Neuropathy
Autonomic neuropathy
Hirschsprung disease
Amyloidosis
CNS lesion
Metabolic disorders
Diabetes
Hypothyroidism
Hyperparathyroidism
Metabolic and electrolytes imbalance
Hypocalcaemia
Hypokalaemia
Hypomagnesaemia
Idiopathic and other associated conditions
Parkinson's disease
Paraneoplastic syndromes
Eating disorders
Dietary deficiencies
Low fibre
Low volume intake
High protein
Colonic obstructions
Mass lesions
Pseudo-obstruction (Ogilvie's syndrome)

- Puborectalis; a skeletal muscle originating at the pubic symphasis and looping around the rectum just above the sphincter complex. When contracted this pulls the rectum anteriorly, increasing the angle between the rectum and the anal canal, improving continence. This must also relax to allow defecation to occur.
- Rectal muscle fibres; these circular smooth muscle fibres peristalse to propel stool forwards.
- Rectal wall integrity; the anterior rectal wall may prolapse into the vagina (rectocoele) creating a pocket stool gets caught within. Alternatively rectal mucosa or walls may prolapse into the lumen, narrowing the anal canal and restricting stool passage out of the body. When marked, this mucosal prolapse produces a characteristic solitary rectal ulcer; however, the absence of ulceration does not exclude a degree of prolapse.

Dyssynergic defecation results from impaired coordination of these muscle groups causing constipation symptoms. Typically patients describe waiting long periods on the toilet, straining, feeling a lump descending, or needing to use a finger to stimulate defecation by pressing on the perianal tissues (digitation) or digitally removing stool from the rectum. Patients may report tenesmus or the need to return promptly to the toilet (double voiding). Patients may go on to develop an associated slow transit phenomenon. Management therefore must improve defecation technique whilst also optimising stool consistency. Only the more severe mucosal prolapses benefit from surgical correction, and in the context of IBD, this must be considered very carefully indeed.

33.3.3 Secondary Causes of Constipation

Table 33.1 lists common conditions associated with constipation that should be screened for and treated. Particularly as IBD patients age, they are at increased risk of colorectal cancer, inflammatory strictures, post-operative anatomical complications and medications to treat comorbid conditions.

Transient constipation, seen in travellers particularly but also with life stressors, changes in diet and after endurance exercise, is oft easily managed. Hospitalisation is often associated with constipation because of the change in diet, reduced mobility, pain, analgesia and physiological stress.

Painful perianal conditions including anal fissures and haemorrhoids are both caused by and

contribute to constipation through toileting avoidance. Likewise social avoidance of defecating in public spaces can be difficult to manage.

Many *medications* are associated with GI side effects, often constipation.

- Opiates are particularly notorious offenders as mu-receptor activation centrally causes analgesia, whilst mu-receptors in the gut reduce both fluid secretion and peristaltic activity. The old adage 'the pen that prescribes an opiate, must also prescribe an aperient' is true.
- Anticholinergic therapies cause dry mouth and constipation; however, many unexpected agents also have anticholinergic effects which can cumulate, the so-called anticholinergic burden. Online calculators can help quantify the extent of this effect with any specific patient prescription.
- NSAIDs, ondanestron, cimetidine, antihistamines, antipsychotic and tricyclic agents are particularly constipating and should be looked for specifically.

33.3.4 Proximal Constipation in Active IBD

Proximal constipation is frequently recognised by physicians, where formed stool accumulates in the proximal colon. Most often this is in the context of active colitis, an effect useful in defining the proximal extent of inflammation, as no stool is usually seen within inflamed segments. At diagnosis, proximal constipation has been reported in 20–46% of UC patients (Crispino et al. 2006).

However the mechanism for this is poorly understood. Some research demonstrates proximal segment transit delay, whilst others exclude faecal stasis as a cause. Rectal fibrosis impairing transit from the left colon may play a role. There are many physiological differences between the proximal and distal colon (Travis 2006) including differences in:

- Motility patterns and transit duration.
- Mucosal blood flow.
- Neuronal density and distribution.
- Energy source; distal colon epithelium is dependent on butyrate, whilst the proximal colon utilises glutamine, glucose, and short-chain fatty acids.
- Mucosal integrity.
- Leucocyte recruitment.
- Resistance to injury.

It is intriguing that ulcerative colitis often affects just the rectum or distal colon with a sharp delineation and that the point of transition can move within a patient over the course of their illness. A threshold phenomenon may explain this abrupt cutoff of colitis activity, though a neuroimmune interaction has also been proposed.

Though we await further enlightenment as to why this occurs, clinicians recognise that in the context of active distal colitis, there is often marked delay in the transit of stool through the proximal colon. This is relevant for symptom presentation but also drug delivery, as oral therapies may be held up within the stool and not reach their intended target.

Thus patients with colitis may present with the associated features of constipation, despite frequent loose stool arising from rectal inflammation. Diagnosis of the condition requires clinicians to have a high index of suspicion. Clues include a baseline tendency to constipation, previous episodes of proximal constipation and unresponsive proctitis, particularly where bleeding has responded to treatment but other symptoms remain.

Recognition of proximal constipation in a colitis patient thereafter requires management of several aspects of care:

- The distal colonic active inflammation must be treated to correct the resultant constipation. Oral 5ASA is unlikely to be effective; thus rectal therapy or systemically active agents must be used.
- Clearance of the proximal colon loading, often with large doses of osmotic laxatives (PEG solution).
- Management of delayed proximal colonic transit until the active inflammation is in remission.
- Education of the patient to generate engagement in their management plan; patients

can be sceptical of laxatives when their primary symptoms are of frequent loose stool, unless they understand the treatment rational. Time must be spent to educate the patient in how their symptoms have been generated, to improve adherence to treatment recommendations.
- Use of an abdominal X-ray to demonstrate proximal loading can be diagnostic, informative and persuading. It is helpful to be able to interpret this as an IBD nurse specialist.

Box 33.1 Learning Points: Constipation Diagnosis and Subtypes
- Constipation is a common symptom, though patients can mean different things. Take a careful history to be sure you understand the actual problem.
- Constipation is not a diagnosis in itself, but can result from components of slow transit time, rectal outlet dysfunction and secondary factors.
- Understanding the particular symptoms and contributing factors is essential for specific and appropriate advice to be given.
- Constipation may mimic symptoms in distal UC and impacts on medication delivery.

33.4 Functional GI Disorders

The term 'functional' has come to carry an overtone of 'fictitious', 'psychosomatic' or 'challenging' when used on the ward, often because symptoms that are difficult to diagnose and treat challenge our own self-image as competent modern healthcare professionals. Functional GI disorders, of which IBS is the best known, are in fact well studied with identifiable dysfunction in multiple domains of GI physiology. Normal gut function requires the faecal stream to move through the gastrointestinal tract in a coordinated and controlled manner, but this complex process is frequently disturbed. 5–30% of children suffer constipation, and more than a third develop chronic constipation (National Institute for Health and Clinical Excellence 2017a). An estimated 11.2% of the worldwide population have suffered symptoms of irritable bowel syndrome (IBS), with an incidence of 1.35–1.5% in longitudinal studies (Lacy et al. 2016). The prevalence of IBS in IBD patients is less clear, yet anecdotal evidence suggest many IBD patients develop functional symptoms also.

It is most helpful to consider functional GI disorders within a biopsychosocial model. Susceptibility arises from genetics, social and demographic context, the environment, early life experiences, life stresses, psychological state and cognitive and coping skills (Drossman 2016).

The abnormalities that contribute to the physiology and experience of functional disorders can involve any or all of the following domains:

- Abnormal motility
  - Delayed or rapid bowel transit, incontinence, nausea, vomiting and impaired gastric distension are examples. This appears to be more complex than just altered contraction patterns, which poorly correlate with symptoms.
- Visceral hypersensitivity
  - Exaggerated pain experience to normal gut sensations, a lower pain threshold to discomfort and amplified discomfort with repeated insults occur.
- Immune dysregulation with inflammation and intestinal barrier dysfunction
  - Classically seen in postinfectious IBS, leaky mucosa allows antigens into the bowel wall, and inflammation can be seen within the bowel wall or enteric nerves.
- Microbiota alteration and interactions
  - Differences in bacterial composition are recognised between IBS patients, healthy controls, IBD patients and even their siblings.
- Diet and nutrient factors
  - FODMAPs are a good example of nutrients that alter intestinal fluid shifts, gut micro-

biota and symptoms. Patients recognise the association with food more often than clinicians.

- Brain-gut axis
  - Autonomic connections between the brain and enteric nervous system influence gut function, but 'descending control' mechanisms also restrict or alter sensations received from the gut into the brain.
- Symptom experience and behavioural responses
  - The symptom severity and degree of resultant disability are shaped by psychological factors such as concurrent stress, coping strategies and behavioural reinforcement.
  - Chronic illnesses may also cause maladaptive cognitions and emotional distress and can develop helplessness or morbid pessimism, hypervigilance and anxiety with a loss of self-efficacy and self-esteem.

The functional GI disorders are addressed in the 4th Rome Classification published in 2016. Initially designed to facilitate research, the Rome foundation has developed useful diagnostic and treatment algorithms (Lacy et al. 2016), as well as overviews of GI function (Vanner et al. 2016) and sensation (Boeckxstaens et al. 2016), the impact of culture (Francisconi et al. 2016) and the microbiota (Barbara et al. 2016) on functional disorders, which are recommended for further reading.

33.5 Assessment of Colonic Transit

There is no single test to confirm constipation or transit time, but several can be employed to help define colonic transit (Rao and Meduri 2011). A good history and stool diary, as above, are paramount, and physical examination including specific rectal examination should be considered (see reference (Talley 2008) for an excellent summary).

Perhaps the simplest test of colonic transit remains the Bristol stool form chart, which is widely available and easily applied. Passage of type 1–2 stool in the context of proctitis symptoms (frequency, urgency, mucous and blood) can be a hint at proximal colonic delay. In diagnosing proximal loading due to proctitis, endoscopic evaluation remains paramount, but due to its invasive nature, surrogate markers of disease activity, such as history and laboratory results, are often used.

Plain abdominal roentograms (AXR) and colonic marker studies are widely available and helpful, even though these involve radiation which must be considered over the patient's lifetime.

33.5.1 Abdominal X-ray

A plain abdominal X-ray gives a snapshot of colonic filling, but solid stool within the right hemicolon can be a helpful indicator of constipation. Liquid stool is not usually seen; thus visible stool in the right hemicolon may be indicative of delayed colonic transit. Faecal dilatation of colon segments may be a more significant finding, particularly if a long continuous column of stool is present. Stool can also be seen in healthy patients, so it is not a specific finding; radiologists seldom comment on faecal loading in formal reports unless it is particularly prominent, because of this variation.

33.5.2 Colonic Marker Study

A colonic marker study usually involves ingestion of radio-opaque shapes within a capsule, either daily or once off, with a plain AXR taken 6 days later. Thus for the same radiation exposure, it provides both a snapshot of colonic filling at one time and an indication of whole-gut transit time over a week. Retention of more than 20% of the markers is considered abnormal. The distribution is also notable, as clustering in the rectum suggests outlet dysfunction, whilst markers retained proximal to the splenic flexure suggest proximal colon delay, and markers distributed throughout the colon are seen in a more generalised slow transit. See Fig. 33.4.

33.5.3 Scintigraphy, Manometry and Capsule Studies

Nuclear medicine scans evaluate both small and large bowel transit times and can compensate for delayed gastric emptying as they do not require large particles to pass through the pyloris or ileo-

caecal valve. Several techniques exist, though none have proven any more useful in directing treatment than any other. Wireless motility capsules and colonic manometry have shown promise but are predominantly used for research.

33.5.4 Anorectal Manometry and the Balloon Expulsion Test

High-resolution multisensor manometry catheters provide an assessment of the pressures each anorectal muscle and nerve complex generates during rest and attempts to defecate. They aid evaluation of rectal sensation and tests of the recto-anal reflex. The balloon expulsion test involves inflating a 50 cc water into a balloon within the rectum. This can usually be passed within 2 min and is a good indicator of normal defecation sequencing. These tests are usually reserved for specialised clinics.

33.5.5 Defecating Proctography

Dynamic information about rectal and pelvic floor function can be obtained by imaging the rectum as the patient defecates. Traditionally a barium paste has been instilled and fluoroscopic (X-ray) images recorded for analysis. MRI scanners (traditional scanners requiring the patient to lie down during the procedure or sit in a chair within an open MRI) use simple gel enemas and provide enhanced anatomical detail of the surrounding structures. Either technique provides essential information regarding rectal mucosal prolapse, and anatomical and evacuation disorders, used to guide physiotherapy and surgical interventions. As invasive and potentially embarrassing studies, patient preparation beforehand is critical.

33.6 Interpreting an Abdominal X-ray

Abdominal X-rays are useful for diagnosing and educating patients about proximal constipation. It is beneficial for IBD nurse specialists to be able to understand AXRs, and depending on the correct training and accreditation, there is a range of practice among IBD nurses in ordering and acting on investigations.

A systematic approach to reading X-rays is essential, so as to train the eye to observe more than just obvious features (see Box 33.2 and Fig. 33.1).

Box 33.2 Approach to Interpreting an X-ray

- Patient identity, date and type of X-ray
- Overall bowel gas pattern
  - Dilation of loops
  - Gut wall oedema
  - Stool distribution
- Bony structures and calcifications
- Soft tissue and foreign abnormalities

The normal gas pattern includes a gas bubble in the stomach and a paucity of air in the right upper quadrant—the liver 'shadow'. Air in 2–3 loops of small bowel may be visible, which should be less than 2.5 cm in diameter; the small bowel is generally in the centre of the abdomen and has valvular (pliacae) markings which extend completely across the lumen.

The large bowel sits like a frame around the edge of the abdomen. Air is often visible in the rectum with varying amounts throughout the rest of the colon. The normal colon is up to 5 cm across, and identified by haustral folds, which do not cross completely from one side of the bowel wall to the other, are thin and alternate sides along the colon (Atkinson et al. 2017).

Formed stool is recognisable by the spotty appearance of micro gas bubbles within the bowel lumen; liquid stool allows gas to separate, forming an air-fluid level. Thus stool allows the colon width to be measured and can become distended in chronic constipation. A diameter greater than 6 cm and a column of stool in the ascending colon are commonly seen in proximal loading (see Fig. 33.1).

Active colitis can be recognised as intraluminal gas highlights a loss of, or thickening of, haustral folds and by 'thumb printing'—smooth approximately 1 cm indentations in the colon wall as if one has pressed one's thumb into the swollen

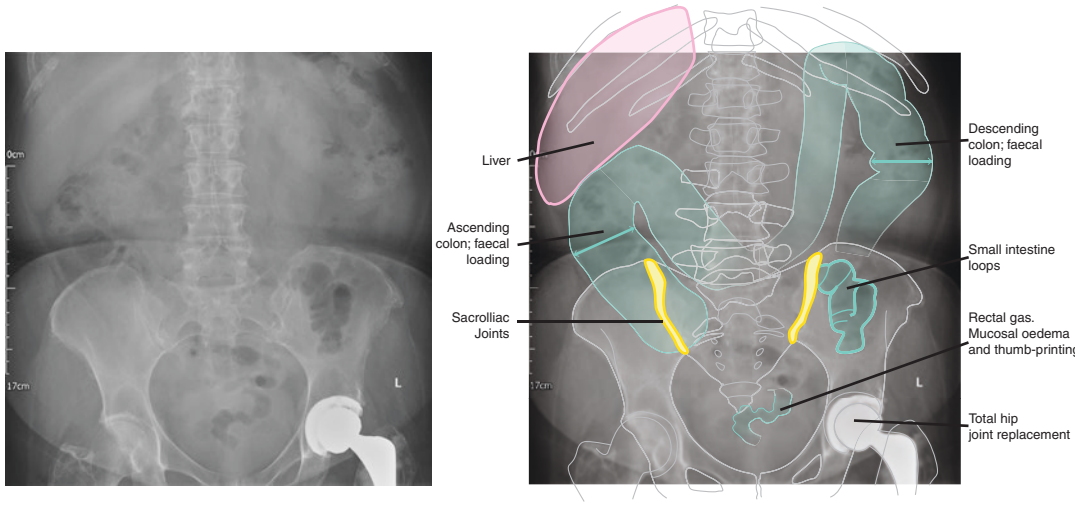

Fig. 33.1 Abdominal X-ray of proximal constipation. *Abdominal X-ray, left, and interpretation highlighted on right.* A 64-year-old patient called the advice line with right-sided abdominal pains and urgent, bloody, watery stool. Rectal mesalazine resolved the bleeding only. A supine AXR performed demonstrates oedematous thickened rectal mucosa and faecal loading in the ascending, transverse and descending colon segments, which are not dilated. The small bowel is not dilated, with no air-fluid levels seen. Crisp sacroiliac joints and spine show no evidence of extra-intestinal manifestations. A left total hip joint replacement is present

bowel wall. The inverse can also be seen as 'mucosal islands' of normal mucosa sitting into the lumen prominent of the rest of the bowel wall. Bowel wall thickening due to oedema enlarges the distance between adjacent loops of colon.

The presence of formed stool in a segment of colon suggests that segment is unlikely to be inflamed and can therefore be used as an indication of the proximal extent of colitis.

In the context of acute severe colitis, colon dilatation >5.5 cm, the presence of mucosal islands and more than three loops of small bowel with gas within them, indicative of ileus, each predict poorer outcome, with a colectomy rate of over 75% when all three are seen together (Travis et al. 2011).

In chronic disease, after years of colitis, the affected colon (usually the left) becomes 'featureless' - without haustral detail - and straightened; the 'lead pipe' colon.

33.7 Management of Constipation

Effective management of constipation usually involves addressing multiple strategies concurrently. Conservative measures to improve gut motility should not be underestimated as they are the starting point before reaching for medications.

33.7.1 Preventing Dehydration

When the kidney is unable to retrieve enough water from the urine filtrate to maintain optimal body hydration, water is salvaged from the faecal stream, and stool becomes firmer. Passing colourless urine by midday is a simple clinical measure to monitor whole body hydration. Thirst or dry oral membranes are notoriously unreliable markers of dehydration. However once hydrated, all extra water consumed is passed into urine; thus drinking large volumes of water may not benefit stool consistency.

33.7.2 Gentle Exercise

Intensive exercise, including long-distance running, intensive cardiovascular exercise or weights work, diverts blood away from the GI tract to skeletal muscles compromising GI motility. Light to moderate impact exercise however increases gut motility and faecal transit. Studies indicate increased exer-

cise improves fibromyalgia and chronic fatigue which can coexist with IBS, and smaller studies suggest improvements in IBS scores (Ford and Talley 2012). Advice for the general public is to engage in at least 150 min moderate exercise each week (e.g. fast walking, cycling on the flat).

33.7.3 Medication Review

As per Table 33.1, a medication review by the patient's general practitioner may identify drugs used for comorbidities that are no longer required or could be substituted for agents with less impact on GI motility.

Particular note should be made of iron supplements, which are often associated with constipation or less frequently diarrhoea.

33.7.4 Toilet Positioning

Most people have never considered or been taught how to sit on the porcelain throne. Most western toilet seats are 45–50 cm above the floor; however, disabled toilets are mandated higher at 52–58 cm. This usually means one's knees balance below the level of one's hips. At rest, tension in the pelvic floor, particularly puborectulis, acts to kink the rectum anteriorly enhancing continence. Elevation of the knees into a squatting position reduces this rectal angulation and therefore improves rectal evacuation time. Patients can elevate their feet by resting them on a simple stool to improve defecation—the 'brace and pump' position (Fig. 33.2). Websites such as www.squattypotty.co.uk have humorous and educational videos that can help explain this position for patients.

33.7.5 Defecation Technique

Similarly, parents seldom know or teach effective defecation technique to their children. Straining to increase intra-abdominal pressure may not necessarily aid defecation, if it actually exacerbates a prolapse or is not timed with pelvic floor relaxation. Many patients inadvertently

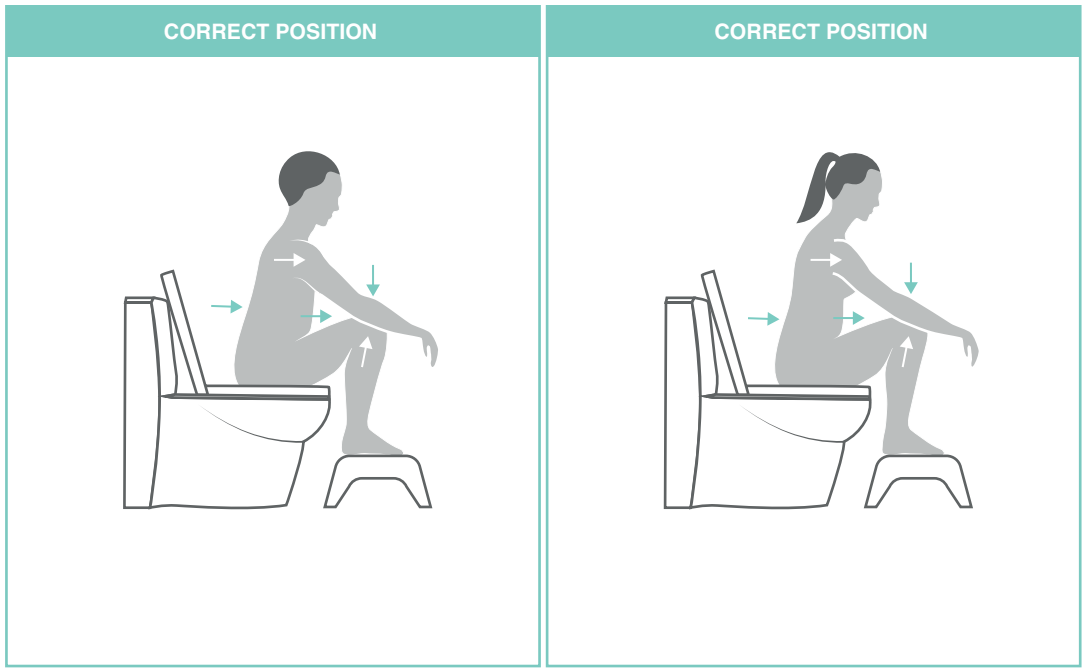

Fig. 33.2 Toilet position advice. To optimize defecation, feet rest on a stool, raising knees above the level of the hips. Elbows are rested on knees, leaning forwards, with the spine straightened—the 'brace position'. Bulging the abdomen out, rather than straining or squeezing increases intra-abdominal pressure whilst the pelvic floor muscles more naturally relax—the 'pump' technique

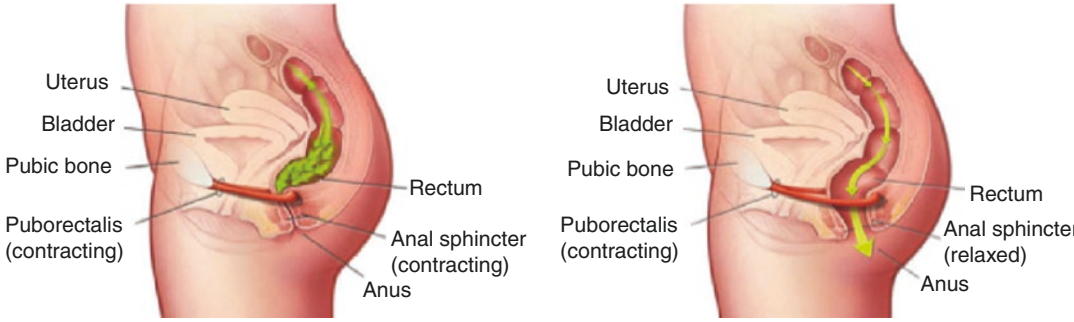

Fig. 33.3 Pelvic floor muscle function. At rest (left image) the internal (involuntary) and external (voluntary) anal sphincter muscles contract to maintain continence. Puborectalis contraction adds an anterior angulation to the rectum, which additionally holds up stool. To defecate, when the rectum senses it is distended, the internal anal sphincter relaxes and rectal muscles contract. The patient relaxes the external anal sphincter and puborectalis muscles whilst contracting the diaphragm and abdominal muscles to expel stool (right image). Dyssynergic defecation arises if rectal sensitivity is impaired, recto-anal and pelvic floor muscle coordination is lost, the anal sphincter inadequately relaxes or increases, or where inadequate propulsion force is generated. Awareness of correct technique and pelvic floor physiotherapy with or with biofeedback can improve this defecation effectiveness

squeeze the external anal sphincter to complete evacuation or whilst straining. External anal sphincter contraction is usually associated with puborectalis contraction and if tensed during defecation further restricts rectal stool passage. See Fig. 33.3.

The correct sequence of muscle actions can be relearned with biofeedback or physiotherapy input, but simple initial advice can be provided:

Patients should rest their elbows on knees, straighten their back and avoid straining. Relaxing the abdominal muscles by bulging out the stomach helps relax the anal sphincter whilst gently increasing intra-abdominal pressure. Placing hands on one's abdomen, and slowly separating the interlocking fingers as the stomach is distended, adds visual feedback to help reinforce the correct muscle pattern in this technique. 'Kegel' exercises are widely known from post-pregnancy advice and increase tone of the pelvic floor; however, this is not a cure all and needs to be supported by appropriately trained pelvic floor specialists. Further specialist advice can be sought from your local pelvic floor physiotherapist or continence nurse specialist (Fig. 33.4).

33.7.6 Fibre Supplementation

An explanation of dietary interventions on IBD is given in Chap. 29; however, evidence for the effect of fibre on bowel function is predominantly studied in the IBS literature, most relevant to concurrent constipation-predominant IBS and IBD. Dietary fibres are non-digestible carbohydrates that interact favourably with the microbiota, increase fermentation compounds and speed colonic transit time. High-fibre intake is associated with improvement in metabolic syndrome components and reduced colorectal cancer risk.

Dietary fibres have conceptually been divided into insoluble and soluble or by others as non-fermentable vs fermentable. The latter overlaps with principles used in the FODMAP (fermentable oligosaccharides, disaccharides, monosaccharides and polyols) diet. In reality most foods are mixed. Resistant starches behave similarly to fibres with regard to slow carbohydrate release but occur following cooling of cooked pasta and potato; thus cold or reheated pasta and potatoes are different to freshly cooked dishes. Any discussion or research into the effect of fibre must be therefore understood within this complexity; indeed

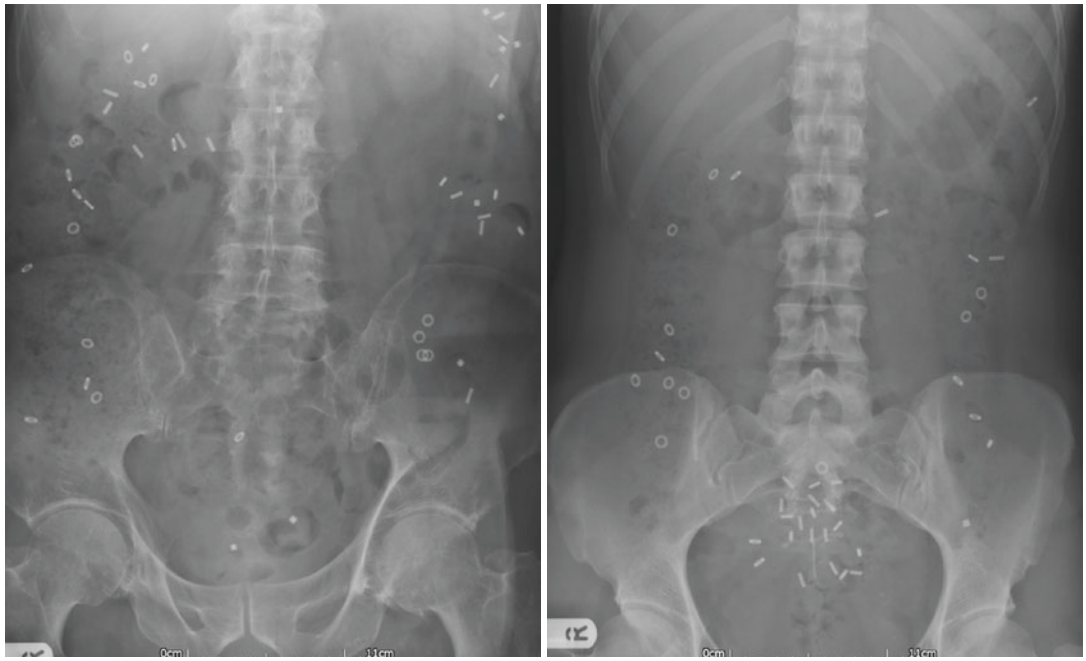

Fig. 33.4 Colonic transit studies. Abdominal X-rays taken day 7, after the patient has consumed a capsule with ten markers each day for 5 days. In health, fewer than 20 markers are expected to be seen within the colon. In a generalized slow transit constipation, an increased number of markers can be seen, distributed throughout the colonic segments (left image). In rectal outlet dysfunction, stool is delayed only in the rectosigmoid, thus markers are seen to accumulate predominantly in the rectosigmoid segment (right image)

many studies have been unconvincing or conflicting, in part due to varied definitions, leading to mixed results from meta-analyses. Nonetheless dietetic guidelines recommend 25–30 g fibre per day (McKenzie et al. 2016), which many IBS patients lack.

Insoluble fibres include brown rice or rice bran, wholemeal and seeded breads, wholegrain pasta or couscous, potato skin, quinoa, etc. which NICE advises should be reduced in IBS diets (National Institute for Health and Clinical Excellence 2017b). Wheat bran particularly should be avoided by IBS sufferers.

Soluble fibres include oats (porridge), psyllium husk (ispaghula; available as a convenient powdered or capsule formulation) and linseeds (flaxseeds: a teaspoon to tablespoon (4–12 g) built up to twice a day).

The British Dietetic Association recently summarised the evidence base of interventions for IBS symptoms (McKenzie et al. 2016). Specifically they concluded there was inadequate evidence for supplementation with psyllium husk, but 'linseeds relieved constipation, abdominal discomfort and bloating in IBS-C gradually over 3 months' (recommendation 3iii, Evidence grade C). For further reference, the BDA and British Nutrition Foundation have helpful websites.

Fibre should be consumed with non-caffeinated liquids to optimise their effect on transit time (McKenzie et al. 2016). The benefit of fibre can take up to 6 months for full effect, so aim for a sustainable change in behaviour. Importantly fibre does not improve or worsen IBD flares, but may increase total effluent volume, i.e. increase diarrhoea symptoms. Patients may therefore wish to reduce/adjust their fibre intake during a flare to improve symptom control.

33.7.7 Stimulants

Stimulant laxatives act as an irritant to the mucosa, enteric nerves or colonic smooth muscle to increase motility. Senna contains various

anthraquinone compounds, derived from plant pods (*Cassia acutifolia*) or Buckthorn bark, which have been used for millennia. Colonic bacteria activate anthraquinones; thus it takes several hours before they act, increasing migratory complexes and stimulating water and electrolyte secretion (Brunton 2011).

Bisacodyl acts directly and is minimally absorbed from the GI tract; thus it acts throughout the gut, initiating a mild inflammatory response. Oral tablets should not be taken with milk or chewed to reduce gastric irritation. Suppository forms are available; useful when patients wish to trigger defecation at a convenient time.

Picosulfate is also a stimulant laxative, but its effect varies widely between patients who may receive either no benefit or profound cramping from a standard dose.

Melanosis coli is the endoscopic finding of colonic mucosal colouring, due to macrophages becoming pigment-laden from long-term anthraquinone use. It is a reversible feature and not damaging. The so called cathartic colon continues to raise concern with many patients; it is the association of long-term stimulant laxative use with chronic constipation due to reduced colonic contractility and colonic dilatation. Initially described in women after years of use, it is at best an historic association as causality has not been proven. Nonetheless many clinicians remain cautious about using stimulants long term (De Ponti and De Giorgio 2002).

33.7.8 Osmotic Laxatives: Macrogol 3350

Poorly absorbed but osmotically active agents draw water into the bowel lumen to soften stool. In years gone by magnesium salts, mineral oil and lactulose have been widely used. Lactulose particularly is associated with bloating and flatulence and so is poorly tolerated by many IBD patients.

Box 33.3 Common UK Bowel Preparation Formulations

	Volume	Macrogol-3350	Na^+ (mmol/L)	Cl^- (mmol/L)	K^+ (mmol/L)	$Bicarb^-$ (mmol/L)	Citrate (mmol)	Other
Small intestine effluent	2–3 L/day		140	60	8	70		
Colon effluent (stool)	100 mL/day		40	15	90	30		
Laxido©/ Movicol©/ Molaxole© (1 sachet)	250 mL	13.2 g	65	53	5.4	17		
Kleen Prep©	4 L	236 g	125	35	10	20		Sulphate 40 mM
Moviprep©	2 L	200 g	181.6	59.8	14	–	60	Sulphate 52.8 mmol/L
Citramag©	400 mL		–	–	–	–	93	Magnesium carbonate 25.2 g
Picolax©/ Citrafleet©	300 mL		–	–	5	–	62	Picosulfate 20 g Magnesium oxide 7 g
Plenvu© (1st/2nd sachets)	500 mL /500 mL	100/40 g	161/297	47/70	13/16	–	0/285	

Source: www.medicines.org.uk. Normal range estimates (Brunton 2011; Sharkey and Wallace 2011)

In modern practice, polyethylene glycol (PEG or macrogol-3350) has become the osmotic laxative of choice. Low volume, safe and not fermentable, PEG produces a reliable catharsis for endoscopic procedures when balanced with isotonic electrolytes. Smaller doses are increasingly used in the management of constipation. Macrogol (Laxido© or Movicol©) is licenced for 1–3 sachets/day for constipation and 8 sachets daily for 3 days for faecal impaction.

Vitamin C (ascorbic acid) also acts as an osmotic laxative when given in large doses; it is actively absorbed by two transporters that become saturated at 1–2 g per day. Doses of 6 g per day overwhelm the transporters and produce a well-tolerated osmotic laxative effect. Ascorbic acid therefore reduces the volume of bowel preparation to drink, generating the same quality cleansing but improving patient tolerability and adherence.

33.7.9 Alternative 5-ASA Agents

The side effect profile of Olsalazine may be used to reduce recurrent constipation whilst maintain remission in ulcerative colitis.

Mesalamine is the first-line therapy for ulcerative colitis (Magro et al. 2017), acting locally on the colonic mucosa. The active 5-aminosalicylic acid (5ASA) ring is rapidly absorbed in the stomach and small bowel unless given in a form that delays release until the right time. Microgranules (Pentasa) release the 5ASA slowly throughout the small and large bowel, whilst pH-sensitive coatings (Asacol/Octasa) only release the 5ASA when they break down in the distal ileum and colon. Sulfasalazine, the first of this class, contains a 5ASA ring bonded a sulfasalazine moiety which causes many of its side effects. Balsalazide's 5ASA ring is bonded to an inert substance released more extensively in the colon. Neither are particularly associated with diarrhoea.

Olsalazine consists of two 5ASA rings bonded together with a diazo linkage, which is cleaved by bacteria in the colon releasing the active agents. 10–20% of patients however develop a watery diarrhoea to olsalazine, which is thought to be due to chloride and fluid secretion from the small bowel. This can be utilised to offset proximal constipation, conveniently managing two problems at the same time for some patients.

33.7.10 Newer Constipation Therapies

A number of newer agents have a role as prokinetics in constipation disorders, though are not licensed specifically for IBD patients.

Linaclotide activates the guanylate cyclase-C receptor on the surface of epithelial cells of the intestine. This triggers a series of intracellular processes resulting in increased chloride, bicarbonate and therefore fluid secretion from the small bowel. It is thought to also decrease abdominal pain from visceral hyperalgesia. Linaclotide is included in NICE guidance for constipation predominant IBS, as trials demonstrate 1 extra spontaneous bowel motion per week compared with placebo (number needed to treat 5–6). Thus it produces a modest effective.

Prucalopride is included in NICE guidance for chronic constipation in women who have tried two other classes of laxatives, supervised by a gastroenterologist. Prucalopride activates the serotonin (5-HT4) receptor, which stimulates colonic motility. It also has a modest effect, predominantly in women and usually within 4 weeks.

Lubiprostone, also in NICE guidance for chronic constipation, stimulates type 2 chloride channels which increases fluid secretion from the small intestine. It also has a modest effect, usually within 2 weeks, and has similarly frequent side effects.

Opiate use markedly alters GI physiology. Peripheral opiate receptor antagonists can reduce the constipation associated with opiate use, if the opiate therapy cannot be withdrawn. Naloxegol is a form of naloxol attached to PEG and is licenced where other laxatives have not been effective for moderate and severe symptoms. In trials it also increased the spontaneous bowel motions modestly, with a NNT of 6–7.

33.8 Summary

Constipation is a common and troubling symptom. Unfortunately IBD patients are not exempt from concurrent IBS which needs to be proactively managed. Constipation can be a sign of active distal colitis needing an intensification of therapy, but however more often is a concurrent problem. Secondary causes of constipation should be identified and treated (Box 33.1). A careful history is often adequate to understand the dominant mechanism of constipation, but occasionally examination or investigation such as abdominal X-ray support a clinical suspicion without the need for endoscopy. Patients often need careful education about the cause of their symptoms before a clear treatment plan is understood and adhered to. A holistic approach to bowel health and function includes diet, exercise, toileting technique and medications (Box 33.4).

Box 33.4 Practical Points: Constipation Treatment

- Constipation is often recurrent, so a sustainable management plan is required once initial symptoms are controlled.
- Treatment often requires multiple strategies.
- Engagement with the patient helps adjust expectations, encourage adherence and review progress.
- Lifestyle advice and defecation position are the key first steps in treatment.
- Make therapeutic changes gradually, allowing time for a new steady-state to develop.
- Boom-and-bust treatment strategies, such as once weekly laxatives, rarely produce consistent results. Little and often is advisable.
- Laxatives are less effective in trials, when evaluated carefully, than we assume in clinical practice.

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Part VI

Lifestyle Issues

Travel and Vaccination

34

Kay Greveson

Abstract

Inflammatory bowel disease (IBD) and foreign travel are associated with an increased risk of travel-related morbidity caused through exacerbations of IBD and acquisition of infectious diseases endemic to the destination and availability of healthcare and medicines whilst abroad (Sonnentag and Fritz, J Occup Health Psychol 12:204–221, 2007; Dolnicar et al., Ann Tour Res 39:59–83, 2012). Patients receiving immunosuppressive medication have an increased susceptibility to these infections in addition to an attenuated immune response to vaccinations. Awareness of the issues faced by the traveller with IBD is essential. The nurse working in IBD should be equipped with the knowledge and resources to provide advice, guidance and signpost to relevant organisations in order promote safe and informed travel.

This chapter aims to provide key information and practical guidance to enable effective pretravel advice and support.

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34.1 Introduction

Taking a leisure holiday can maintain quality of life by exposing individuals to new experiences and cultures as well as having a positive impact on perceived health and psychological wellbeing (Sonnentag and Fritz 2007; Dolnicar et al. 2012). In addition to questions regarding transport, accommodation and sight-seeing posed by individuals planning a holiday, a patient diagnosed with IBD would present with a different dimension of concerns. Travellers with IBD are at greater risk of travel-related morbidity caused through exacerbations of IBD and acquisition of infectious diseases endemic to the destination and availability of healthcare and medicines (Rahier et al. 2014). Despite this, having a diagnosis of IBD should not restrict foreign travel, but extra consideration and planning are essential, particularly for those on immunosuppressant medication. Immunomodulator drugs alter an individual's immune status, predisposing to an increased risk and more severe course of some vaccine-preventable opportunistic infections and a possible attenuated immune response to vaccinations, commonly advised prior to travel (Rahier et al. 2010, 2014; Wasan et al. 2010; Esteve et al. 2010). A detailed pretravel consultation and vaccination schedule are advised, provided jointly by a gastroenterologist and expert travel clinic to ensure travellers with IBD have the appropriate education and resources to stay healthy abroad (Rahier et al. 2014; Ericsson 2003; Spira 2003;

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Goel et al. 2014; Yeung et al. 2011). Healthcare professionals' knowledge and provision of this information and adherence to international guidelines have been found to be poor (Wasan et al. 2011; Gupta et al. 2009) particularly advice regarding avoidance of live vaccines for those on immunosuppressive medication (Soonawala et al. 2012a; Wasan et al. 2014). A team approach is needed involving the patient, IBD nurse, gastroenterologist and travel health specialist. The following sections highlight key elements and considerations prior to travel with IBD.

34.2 The Pretravel Consultation

The pretravel consultation should be a joint multidisciplinary approach involving IBD nurse and gastroenterologist team in addition to the wider MDT (Sonnentag and Fritz 2007), such as family doctor, travel clinic and infectious diseases teams, in the case of complex patients. Advise patients to plan ahead, particularly for travel to less developed countries where vaccinations may be required or where obtaining healthcare may be more problematic. Allowing at least 6–8 weeks to plan a trip is ideal, although longer may be needed in special circumstances such as patients on immunomodulator therapy who require a live vaccination. This is discussed later. The amount of planning and preparation required before travel very much depends on individual circumstances and the destination or duration of travel, for example, a patient who is travelling within their country or within Europe for a short holiday will need less preparation and planning compared to the patient on an immunomodulator who is travelling for an extended period to multiple countries. The travel consultation is essential in working through these aspects and ensuring safe travel. The pretravel consultation should involve the following (Rahier et al. 2014):

- Support and encouragement to travel. Inflammatory bowel disease need not restrict patients from foreign travel.
- Signposting to travel experts and travel resources specific to IBD, such as IBD passport (www.ibdpassport.com) (IBD Passport 2017).
- Discussion regarding travel destination. Travel to developing countries may carry more risk, particularly for those on immunomodulator therapy.
- Discussion regarding the importance of obtaining travel insurance to cover IBD.
- Advice regarding food and water precautions to avoid travellers' diarrhoea.
- Advice regarding avoidance of insect bites.
- Take a vaccination history in line with European guidance (Rahier et al. 2014).
- Discussion of the risk of deep vein thrombosis (DVT), particularly for long-haul flights.

There are other factors that should be taken into consideration when advising patients who plan to travel. Language barriers can be an issue and cause stress. The majority of patient charities and also some IBD centres have produced a 'toilet access card' (see Box 34.1) that explains the bearer has a medical condition, meaning they have urgency to use toilet facilities. These cards may be available in multi-lingual versions to aid with travel to other countries. Travel can be a stressful time; therefore

Box 34.1 Suggestion for an 'Emergency Kit' Taken from IBD Passport (IBD Passport 2017)

- A supply of sanitary pads,
- Change of underwear and clothes
- Wet wipes and toilet roll
- Antibacterial hand wash
- A small aerosol odour neutraliser
- Small kit of dressings, tape and saline for wound cleaning etc.
- Multi-lingual can't wait card (see above).

  Medication-keep in your hand luggage.
- Antibiotics such a ciprofloxacin for travellers' diarrhoea
- Loperamide or lomitil for diarrhoea relief (This can sometimes hide symptoms of a flare so use with caution)
- Oral rehydration salts (e.g. Dioralye).
- Buscopan or IBS relief medication
- Paracetamol to reduce fevers (beware of products containing codeine-ensure prescriptions are labelled with your name)
- Adequate supply of your regular medication, including steroids in case of a flare.

advising patients to carry an essential pack or 'emergency travel kit' (Box 34.1) with medication and supplies that they may need can ease this stress.

34.3 Obtaining Healthcare Advice Overseas

Research has shown that patients often defer a trip or change the destination of travel due to their IBD and concerns about obtaining healthcare advice abroad (Greveson et al. 2015; Soonawala et al. 2012b). Charities such as IBD Passport (IBD Passport 2017) help to address this with their website (www.ibdpassport.com) by providing a global network of IBD centres and reputable travel advice specific to inflammatory bowel disease. Most countries within Europe have a mutual 'reciprocal agreement' between their governments which allows travellers to any country covered by this agreement to receive medical treatment at a reduced cost or, in some cases, free. The agreements do not cover the cost of repatriation or routine monitoring of pre-existing conditions.

Travel within Europe is covered by the European Health Insurance Card (EHIC), which allows an individual to obtain state healthcare at a reduced cost or sometimes free in all European Economic Union countries (Europe, Iceland, Norway, Liechtenstein and Switzerland). It will cover individuals for pre-existing medical conditions and essential treatment that is needed to allow the individual to return home. It is important that the traveller have both an EHIC and a valid travel insurance policy as countries within Europe will also require travel insurance to cover any private medical healthcare or costs such as being repatriated to their home country.

Travel insurance is essential to cover any illness that may occur during travel, whether it be in Europe or elsewhere. A recent survey indicated that only 40% of respondents obtained travel insurance, with cost of premiums being cited as the main deterring factor (Greveson et al. 2015). It is essential for the IBD nurse to promote the importance of obtaining travel insurance and help to signpost the patient to relevant resources. Box 34.2 shows the key things that patients should consider when obtaining insurance. Many things can affect the insurance premium. It may be useful to make patients aware that it may be more difficult to obtain insurance in the following situations:

- Have recently had or are awaiting surgery
- Have been admitted to hospital within the last year
- Are waiting for the results of tests because of ongoing symptoms
- Have concomitant medical problems in addition to IBD

Box 34.2 Advise for Obtaining Insurance (Taken from www.ibdpassport.com)

Insurance Checklist

- Ensure your travel insurance covers your IBD!
- Shop around for the best quote. Having IBD should not equal higher premiums, especially if you are in remission.
- Read your policy! Know what your insurer will pay and more importantly, what they will not pay for!
- Know your medication—knowledge of generic names and local brands can make the difference.
- Keep names and contact details of your healthcare professionals and reliable friends.
- If you need emergency repatriation, contact your countries embassy officials.
- Ensure you take your policy documentation with you.
- Keep all receipts of everything you pay for, and further evvidence if possible such as labels and price tags.

34.4 Vaccinations and Other Destination-Specific Concern

Administration of live vaccines to those on immunosuppressant medication is contraindicated as it can cause serious and potentially fatal infections due to extensive replication of the vaccine strain; this does not happen with inactivated vaccines

Box 34.3 Table Showing Attenuated (Live) Vaccinations

Oral polio
Measles, mumps and rubella (MMR)
Chickenpox/shingles (herpes zoster)
Yellow fever
Cholera (oral version also available as inactive)
Oral typhoid (injectable version is inactive)
BCG (tuberculosis vaccination)
Flumist influenza vaccine (nasal spray only)
Rotavirus (used in infants only)
Adenovirus
Smallpox

(National Institute of Allergy and Infectious Disease n.d.). Many vaccinations for travel such as yellow fever, typhoid and BCG are only available in a 'live form'. See Box 34.3 for further details of vaccinations that are live and contraindicated in patients on immunomodulator therapy. A previous study found that 27% of immunosuppressed individuals received a live attenuated vaccine who should not have been vaccinated, and many others travelling to endemic disease areas were not given the correct vaccinations for their trip (Soonawala et al. 2012b). This highlights the importance for good communication between the IBD MDT, travel clinics and patient in order to ensure safe vaccination and travel.

Around 80% of patients will be treated with corticosteroids, 40% with thiopurines and 20% with anti-TNF therapy in their lifetime (Rahier et al. 2014). Immunomodulator drugs alter an individual's immune status, predisposing to an increased risk and more severe course of some vaccine-preventable opportunistic infections and a possible attenuated immune response to vaccinations, commonly advised prior to travel (Rahier et al. 2014). European consensus on the management of opportunistic infection in IBD (Sonnentag and Fritz 2007) recommend following a standardised checklist for immunisation for opportunistic infections. The following key elements should be considered (Rahier et al. 2014):

- Travellers should seek advice regarding their travel destination from a qualified travel health specialist.
- Vaccination is best given before immunomodulator therapy, and a vaccination history should be documented at diagnosis.
- Immunomodulator therapy should be discontinued 3–6 months before a live vaccination is given.
- Once a live vaccination has been given, immunomodulator therapy can be restarted after 3 weeks.

34.5 Travel with Medication

The majority of patients with Crohn's disease or ulcerative colitis will take some form of medication in their lifetime, ranging from tablets and topical enema/suppository treatments to injectables and intravenous infusions. This can have implications during travel, particularly with regard to transit through customs and travel on airlines. The key considerations regarding travel with medication are:

- Keep medication in their original packaging to show at customs.
- Advise to take an adequate supply of medication for the whole trip, including extra in case of delays.
- Ensure patients have a letter from their GP or IBD team outlining medical history and current medication; this will be essential during air travel if carrying medication in liquid form over 100 mls.
- Store medication in hand luggage when flying in case of lost luggage.
- Advise patients to check with the airline before flying with medication, especially injectables, to clarify their procedures about transport of medication.
- Consider long-haul travel across different time zones and the effects of this on the timing of treatment dosage.
- When travelling with medication that needs to be kept cold (i.e. adalimumab), patients can obtain a variety of useful cooling travel wallets online or via the homecare companies.

Biological medications have revolutionised the care of patients with IBD, improving symp-

toms and quality of life. They can, however, pose restrictions regarding travel overseas, particularly for extended periods due to funding and insurance problems. Travel for extended periods with biologic medication is possible but needs careful coordination. In cases where patients plan to travel overseas or into different states, the following top tips and advice should be considered to facilitate easy transition of your medical care:

- Advise patients to allow *at least* 10–12 weeks prior to departure. Arranging medical treatment abroad can be done depending on the destination of travel but does take time to arrange.
- Use resources such as IBD Passport website to obtain the name and contact details of a gastroenterologist at the travel destination. The manufacturer of the biologic drug may also be able to help locate and contact a reputable gastroenterologist at the destination.
- Provide the patient with a letter of referral outlining medical history and medications to the gastroenterologist at the travel destination. If possible send this electronically prior to departure. This is to ensure they have all the necessary information and to avoid treatment delay whilst also ensuring the patient has approval for bringing all medications into the destination country.
- Advise patients that once they arrive at the travel destination, they will usually have to either register with the local healthcare system or with a private medical insurance company, depending on local arrangements and the reason for the visit (i.e. travel for business or an education visa may be covered by private medical insurance).
- In the case of biologics, the IBD team at the travel destination may have to apply for funding according to their local guidelines before treatment can commence. Regular travel insurance policies will not cover treatment with biologics, even if the insurance policy covers pre-existing illness such as Crohn's disease or ulcerative colitis.

Special consideration also needs to be given to those on enteral or parenteral nutrition. Travel is possible but again requires planning. The following aspects should be considered:

- Allow at least 6 weeks before departure date to plan the logistics of travelling with a feed. The homecare company that delivers the feed can deliver to many overseas destinations. Exceptions to this are developing countries and those in war conflict or where delivery is not possible due to customs restrictions. Advise patients to contact the feed delivery company before they book their trip to ensure delivery is possible.
- Obtain a letter from the IBD/nutrition specialist outlining medical history, medication and an explanation of why the patient requires enteral/parenteral nutrition. A sample clinician letter for patients travelling with IV or tube feeds can be found at The Oley Foundation website (n.d.).
- Ensure patients have a written plan from their specialist of what to do in an emergency.

A complication management chart and travel advice pack that covers the symptoms and steps to take for common problems related to parenteral or tube feeding nutrition and an essential supply inventory list plus useful tips can be obtained from The Oley Foundation (The Oley Foundation n.d.). This is only available in English, but a similar version may be available in your country.

Air travel with enteral and parenteral nutrition can also pose challenges. Special consideration must be given to make air travel run as smooth as possible.

- Patients should inform the travel agent or airline of any special needs or facilities that may be required. Sometimes a medical certificate from the IBD/nutrition team confirming fitness to travel may be required.
- Advise patients to inform the airline that they will be carrying essential medical supplies and will need an excess baggage waiver. In this case, patients will have to provide the airline with details of the contents, weight and dimensions of the excess baggage containing the feed equipment and may be charged extra for this depending on the airline.

- Individuals can request special assistance for preboarding, immigration and baggage reclaim.
- Advise patients to request their feed and pumps to be hand-loaded onto the aircraft with prior arrangement from the airline via 'special handling'.
- Liaise with nutrition teams in your hospital, and ensure patients know what products they can take onto the plane and what should go in the hold.

34.6 Travel After Surgery and with a Stoma

Insurance premium will be higher for individuals who have recently had surgery or have been hospitalised for an IBD flare. Age, destination, duration of travel and other medical conditions will also influence the insurance premium. Travel after 12 months from the date of surgery will generally incur a lower premium. Several factors should be considered when counselling the patient who is planning to travel following stoma surgery. Key considerations include (Coloplast Travel Guide n.d.):

- Advise patients to discuss their travel plans with their stoma nurse as they may need additional products than they would normally need as activities such as swimming and hot temperatures that cause perspiration will mean they have to change their appliance more frequently.
- Due to increased security, carrying scissors in checked luggage is more difficult. Advise patients to precut all barriers at home. Alternatively, some stoma companies have a mouldable system which does not need cutting to size.
- As with medication, pack stoma care supplies in both carry-on and checked luggage.
- Store stoma supplies in a cool place—do not leave your ostomy products in hot places (e.g. in the car) for long periods, since the heat may damage the baseplate adhesive.
- In the case that patients may run out of supplies when abroad, advise them to take a note of the product name and code (usually found on the prescription) as well as the telephone number of their stoma supply company so that if they have a problem, they can contact them.
- Stoma passport or travel certificates *are* available from most stoma companies or stoma care nurse. These state the need for patients to carry stoma care supplies in case they are questioned at airport security/customs. In addition, it is helpful to take a copy of their prescription which shows all the product codes and description. An example of a stoma passport available from the stoma company Coloplast is shown in Fig. 34.1.
- Similarly, for international travel, the stoma companies and also the international ostomy association (Ileostomy Association Support Website n.d.) can provide stoma care and product information in different languages.

Patients who had a surgery and stoma formation may be apprehensive about travel and how this may impact on stoma function. It is important for the IBD nurse to liaise with the surgical and stoma care teams to reassure patients and provide the appropriate support and education. Many of the stoma supply companies will have information in local language regarding travel with a stoma, but concerns that patients may have and ways to reassure them are:

- The stoma bag will behave the same during air travel as it does on the ground, but cabin pressure in aircraft can sometimes cause excess flatus (wind). If the stoma appliance has a filter, it will enable air to escape and hide any embarrassing odours.
- Advise to avoid food that may cause bloating and excess wind the day prior to travel.
- Before going through airport security, it is advisable to change the stoma appliance at the last minute to ensure it is empty. Security staff are duty bound to investigate any anomalies, but this will always be done in a discreet way. Advise patients to carry a stoma passport or travel certificate as described earlier to avoid awkward situations.

TRAVEL CERTIFICATE

Personal	Medical	Supplies	Official Notice
Name:	Doctor's Name:	☐ Catheters	The holder of this card has a condition, which requires them to carry medical supplies such as Catheters, ostomy supplies, Sheaths or Anal Plugs.
Address:	Surgery Address:	☐ Ostomy supplies	These products are essential for the holder to manage their condition and should not be taken away from this person. Please be aware that they are also likely to be carrying additional supplies of products in their main luggage.
Passport No:	Doctor's Signature:	☐ Sheaths	Please be sympathetic to the cardholder and allow them to progress.
Signature:	Date:	☐ Anal Plugs	Thank you for your assistance.
		☐ Other (specify)	

French	German	Spanish	Italian	Portuguese
Le détenteur de cette carte est atteint d'une maladie le contraignant à porter sur lui/elle des dispositifs médicaux comme les cathéters, les poches à urine, les étuis péniens ou les tampons obturateurs anaux.	Der Inhaber/die Inhaberin dieser Karte hat ein Leiden, das es erforderlich macht, dass er/sie medizinische Versorgungsartikel wie Katheter, Urinbeutel, Kondom-Urinale oder Anal-Tampons trägt.	El titular de esta tarjeta padece una enfermedad que le obliga a llevar consigo dispositivos médicos tales como catéteres, bolsas de orina, colectores o obturadores anales.	Le condizioni di salute del possessore di questo Certificato di viaggio sono tali da richiedere la disponibilità di attrezzature mediche come cateteri, sacche per la raccolta delle urine, guaine peniene per incontinenza o tamponi anali.	O detentor deste cartão possui uma doença que o obriga a transportar dispositivos médicos, como cateteres, sacos de urina, pensos colectores de urina ou tampões anais.
Pour les détenteurs de cette carte, ces dispositifs constituent une aide vitale dans la prise en charge de leur maladie : il est impératif de ne jamais les priver de ces dispositifs. Merci de noter que ces personnes sont susceptibles de transporter des dispositifs de rechange dans leurs bagages.	Diese Artikel werden von dem Inhaber/der Inhaberin der Karte aufgrund seines/ihres Leidens unbedingt zur Versorgung benötigt und sollten ihm/ihr nicht weggenommen werden. Wahrscheinlich wird die Person weitere Versorgungsartikel im Hauptgepäck mit sich führen.	Estos productos son indispensables para que el titular de la tarjeta pueda controlar su enfermedad y no le deben ser sustraídos. Asimismo, es probable que esta persona lleve dispositivos adicionales en su pieza de equipaje principal.	A causa delle condizioni di salute del possessore, tali prodotti sono essenziali e non gli/le devono essere sottratti. Tenere conto del fatto che ulteriori attrezzature possono essere presenti nel bagaglio principale.	Estes produtos são essenciais para o detentor do cartão conseguir controlar a sua doença e não devem ser retirados a esta pessoa. Por favor, tenha em atenção que é provável que transportem material adicional na bagagem principal.
Merci de respecter la situation du détenteur de cette carte et de l'aider à poursuivre sa route normalement.	Bitte zeigen Sie Verständnis für den Karteninhaber/die Karteninhaberin und erlauben sie ihm/ihr weiterzugehen.	Muestre su comprensión al titular de esta tarjeta y permítale seguir adelante.	Si prega di mostrarsi ben disposti nei confronti della persona interessata e di consentirgli/le di procedere.	Por favor, seja compreensivo para com o detentor deste cartão e facilite-lhe a passagem.
Merci de votre aide.	Vielen Dank für Ihre Unterstützung.	Muchas gracias por su colaboración.	Grazie per la collaborazione.	Obrigado pela sua ajuda.

Coloplast

Fig. 34.1 Example of a stoma certificate for travel (Coloplast Travel Guide n.d.)

- Patients who have had a colectomy and ileostomy will be more susceptible to dehydration due to the reduced ability to absorb fluid and electrolytes from the diet as effectively (Crohn's and Colitis UK Dehydration Information Sheet n.d.). Advise patients to be aware of the signs of dehydration and seek medical advice if they think they are becoming symptomatic.

34.7 Key Learning and Summary

In this chapter we have examined what the impact of having a diagnosis of IBD has on patients' decision regarding travel. The importance of education and support from healthcare professionals cannot be underestimated, and promoting the patient to plan and prepare in advance of their trip is essential. The role of the healthcare professional is to signpost to useful resources and liaise with members of the multidisciplinary team to facilitate and encourage the travel experience.

Resources

IBD Passport charity www.ibdpassport.com

World Health Organisation General precautions for Travel health http://www.who.int/ith/precautions/en/

The International Ostomy Association www.ostomyinternational.org

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Smoking and Drugs

35

Fran Bredin

Abstract

Cigarette smoking, both active and passive, has vastly contrasting effects on the development and progression of both Crohn's disease (CD) and ulcerative colitis (UC). Quitting smoking also affects both forms of IBD differently. As smoking is a modifiable lifestyle factor, knowledge of its effects in IBD is therefore very important for those who care for people with IBD.

The use of recreational or non-prescribed drugs in IBD has not been widely investigated. There is some conflicting evidence as to the benefit of cannabis. Issues of legality leave this a poorly reported area.

35.1 The Effects of Smoking on IBD

35.1.1 Learning Aims

- To understand the effect of cigarette smoking on the development of both CD and UC
- To understand the effects of continued smoking on both CD and UC
- To understand the effect of quitting smoking on both CD and UC

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35.1.2 Introduction

It is believed that environmental factors play a major role in the pathogenesis of IBD with the strongest association discovered to date being with cigarette smoking. Smoking increases the risk of developing CD and reduces the risk of UC. Passive smoking may also increase the risk of CD. Following diagnosis, continued smoking has a detrimental effect in CD and a beneficial effect in UC. Quitting smoking reverses the negative effects in CD but may worsen symptoms in UC or bring on a first presentation.

35.1.3 The Development of CD

- The two most significant risk factors for CD are a family history (genetic risk) and smoking (environmental factor). Current smokers are nearly twice as likely to develop CD than never-smokers (76% increase in likelihood) (Mahid et al. 2006).
- Passive smoking may also be a risk factor for the development of CD (Mahid et al. 2007).
- Former smokers appear to still have an increased risk of developing CD, although less so than current smokers (Mahid et al. 2006).
- Regarding disease location, smokers may be more likely to develop ileal disease (Russell et al. 1998), but not all studies confirm this.

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35.1.4 The Development of UC

- As with CD the two most significant risk factors are family history and smoking, but this time the relationship is reversed.
- Current smokers are nearly half as likely to develop UC than never-smokers (42% decrease in likelihood) (Mahid et al. 2006).
- In contrast, ex-smokers are almost twice as likely to develop UC than never-smokers (79% increase) (Mahid et al. 2006).
- Smoking was previously thought to reduce the likelihood of UC extending from distal to pancolitis (Mokbel et al. 1998), but more recent studies do not confirm this (Lakatos et al. 2013; Lunney et al. 2015).

35.1.5 The Effect on Disease Course of CD

- The evidence for the effects of continued smoking on the course of CD is somewhat conflicting, possibly due to the increasing use of first immunosuppressants and then biologic therapies in recent years.
- Older studies have suggested that continuing smokers definitely run the risk of a more severe disease course with:
  - More relapses
  - Greater need for escalation of therapy
  - An increased risk of surgery
  - Shorter time to post-operative recurrence
- More recent studies have not all confirmed all the adverse effects on disease behaviour but suggest an increased need for biologics and immunosuppressants (Nunes et al. 2013a) and for surgery (Lunney et al. 2015).
- An increased incidence of joint problems has also been suggested (Lakatos et al. 2013; Lunney et al. 2015).
- Despite the conflicting evidence, it is generally agreed that continued smoking does carry the risk of worsening the disease course. This is borne out by the fact that smoking cessation is beneficial (see below).

35.1.6 The Effect on Disease Course of UC

- Continued smoking appears to reduce the severity of UC with:
  - A lower relapse rate (Hoei et al. 2007).
  - Less need for steroids and immunosuppressants.
  - There may be a reduced rate of colectomy and of pouchitis after surgery, but the evidence is conflicting (Lunney and Leong 2012).
- Additionally
  - Primary sclerosing cholangitis may be more likely in non-smokers (Loftus et al. 1996).
- However
  - Joint problems may be increased in smokers (Roberts et al. 2014).

35.1.7 Summary of the Effects of Smoking on IBD

- Current and former smoking carries a significantly increased risk of developing CD.
- Current smoking protects against the development of UC, but the effect is lost after quitting.
- Continued smoking after diagnosis worsens the course of CD but lessens the severity of UC.
- The increasing use of immunosuppressive and biologic therapies may alter the effects of smoking after diagnosis noted in older studies, but there is still broad agreement on the above statement.

35.2 Smoking Cessation and IBD

35.2.1 Learning Aims

- To understand why a knowledge of the effect of cigarette smoking on IBD is important for patients and healthcare providers
- To understand the need for a different approach when speaking to patients with CD and with UC about smoking
- To understand the role of smoking cessation in the overall management of CD

35.2.2 Introduction

Given the strong association between smoking and IBD, healthcare professionals should be aware of the clear benefit for patients with CD of quitting, and the problems a new ex-smoker with UC may face in addition to the more general health promotion role concerning smoking cessation. A clear message to quit smoking should be given to patients with CD, but whilst those smokers with UC should still be encouraged to quit, they should receive advice and support regarding the likelihood of disease relapse. As medical management in CD is not always fully effective and surgery is to be avoided if possible, smoking cessation should be seen as a treatment strategy in its own right and promoted effectively with all smokers with CD.

35.2.3 The Benefit of Smoking Cessation in CD

If patients with CD who smoke quit, there does appear to be a reversal of the negative effects of smoking. Reported benefits include (Lawrence et al. 2013; Nunes et al. 2016):

- Less relapses, becoming comparable to those of non-smokers
- Lower risk of progression to stricturing and penetrating disease
- Less need for surgery

As a modifiable factor under the control of the patients themselves for a disease which so often leaves sufferers feeling out of control, the potential benefits of smoking cessation cannot be stressed too highly.

35.2.4 Patients' Knowledge of the Link with Smoking

The links between smoking and IBD were first reported as recently as the 1980s (Harries et al. 1982; Somerville et al. 1984). Since then the number of research studies looking into the effects both of smoking and smoking cessation has steadily increased. The findings and implications of these studies have therefore gradually become more widely disseminated amongst IBD professionals and thence on to their patients. Unsurprisingly early studies assessing patients' awareness of the link showed a lack of knowledge (Shields and Low-Beer 1996; Ryan et al. 2003).

It would be expected that most specialist healthcare professionals today would discuss the impact of smoking with their patients at some point. However it has been suggested quite recently that there may still be a lack of knowledge amongst patients (van der Heide et al. 2010), despite one Irish study that found high levels of awareness (Kenelly et al. 2013). It is hoped that patients with CD are becoming more aware of the benefits of smoking cessation through a combination of professional advice and increasing use of the Internet to gain disease-related information.

35.2.5 Smoking Cessation Programmes and Referrals

Encouraging smoking cessation may take the form of:

- Simple advice on the benefits of cessation
- Advice with suggestions as to how to go about quitting
- Actual referral to a smoking cessation service where available
- The provision of a specially tailored cessation programme

The majority of IBD healthcare professionals will likely stop at simple advice, feeling that they are not the best qualified to offer further advice. The patient may be advised to contact their general practitioner or practice nurse as smoking cessation help may be offered locally. Some hospitals offer a smoking cessation service with an adviser to whom referral may be made. The effectiveness of these approaches depends on the healthcare professional knowing what support and services are available locally for their patients.

Although simple information and advice are better than no advice, in line with strategies to aid cessation in the general population advice together with active cessation therapy will be more effective (Kenelly et al. 2013; Stead et al. 2016).

The first large-scale programme to aid patients with CD in cessation was carried out as part of a study by Cosnes and colleagues from 1995 to 1999. The programme consisted of behavioural counselling with regular access to a cessation specialist and the use of pharmacological aids. A quit rate of 12% at 1 year was achieved (Cosnes et al. 2001).

The TABACROHN study across several hospitals in Spain showed the effectiveness of a concerted effort to promote smoking cessation in patients with CD. The method used to aid cessation varied with what was available locally. By the end of the study, 23% of participants had quit and remained so (Nunes et al. 2013b).

The first reported group smoking cessation initiative designed specifically for patients with CD was described by an IBD nurse working in the south of England (Challis and Surgenor 2004). The approach was to use small group support with pharmacological aids. All group members had not only CD in common but also a desire to quit smoking; the group sessions served to explore ways of coping with CD and managing symptoms. Although the numbers were small, the results were very positive. A similar approach was followed again by an IBD nurse working with a stop smoking specialist with similar good results (Bredin et al. 2011). The main problem with this approach is that numbers of patients ready and wanting to quit at any one time can be low especially in a smaller hospital. Although patients with CD will often state a desire to quit smoking, the numbers of those who are willing to take action at any given time will be, as with any population, much lower. It does appear however that once aware of the link between smoking and disease, people with CD are more amenable to a quit attempt (van der Heide et al. 2009).

35.2.6 Cost-Effectiveness of Providing Smoking Cessation Services

Providing any additional service in the IBD clinic will incur costs. Smoking cessation programmes can be labour intensive, but this must be offset against not only the service costs of managing more severe disease but also the costs to the patient in terms of reduced quality of life. Research from the Netherlands and the United States would appear to justify the use of cessation services (Coward et al. 2014; Severs et al. 2017).

35.2.7 Smoking Cessation and UC

- Those who quit smoking following onset of UC tend to experience disease flare-up with consequent:
  - Increased hospitalisation rates
  - Increased need for corticosteroids and immunosuppressants
- Resuming smoking may be seen as a valid treatment option by some patients, but this generally should not be encouraged due to the many other risk factors associated with smoking. Although one small study found good results with patients who resume low-dose smoking (Calabrese et al. 2012), this may not be a sufficient long-term benefit since there appears to be a dose-dependent effect that leaves heavier smokers better protected (Aldhous et al. 2007).
- Current studies predate the increasing use of biologic therapy in ulcerative colitis, which may impact positively on the above, enabling ex-smokers to have a better outcome.

Patients with UC who wish to quit smoking should probably be advised to wait until their colitis is in good remission (unless they have compelling reasons to quit immediately). They should be informed of the risk of relapse and offered prompt treatment and support in the event of relapse.

35.2.8 The Role of the IBD Nurse

IBD nurses who form part of the multidisciplinary team are ideally placed to promote smoking cessation in patients with CD and support smokers with UC who wish to quit. IBD nurses often have more frequent and longer contact times with patients and therefore more opportunity to discuss lifestyle issues. In order to play an active role, they should if possible:

- Be prepared to regularly discuss smoking cessation with their patients and assess when a smoker is ready to quit.
- Develop and maintain a knowledge of local smoking cessation services and how to access them.
- Be aware of the smoking cessation aids used locally and any potential side effects.
- Be aware of the problems that may initially result from a quit attempt—such as changes in eating patterns, constipation, depression and anxiety—and advise accordingly and promptly.
- Consider attending a brief intervention course with local smoking cessation advisers if available.
- Consider the feasibility of setting up a disease-specific smoking cessation group.

35.2.9 Summary of Smoking Cessation and IBD

- Stopping smoking reverses the effects of smoking on both CD and UC, with a beneficial effect on CD and a detrimental effect on UC.
- All IBD patients should be made aware of the links with smoking. All who smoke should be advised to quit; however those with ulcerative colitis must be made aware of the risk of relapse.
- All healthcare professionals caring for smokers with IBD should take every opportunity to give advice regarding cessation and support quit attempts.
- Local smoking cessation services should be utilised where possible.
- Consideration should be given to developing a robust and defined approach to smoking cessation for patients with CD which will vary from one IBD unit to another according to the resources available.

35.3 Future Research into Smoking and IBD

35.3.1 Learning Aims

- To have an understanding of the current knowledge regarding the mechanisms for the interaction between smoking and IBD
- To be aware of future possible areas for further research

35.3.2 Introduction

As yet there is no full understanding of the mechanisms behind the effects of smoking on inflammatory bowel disease. This is due in part to the fact that cigarette smoke contains literally hundreds of substances which are harmful to humans. Nicotine has been the most studied component to date with respect to IBD. An example of another substance present is arsenic—which has been used in suppository form to treat proctitis (Forbes et al. 1989).

It is suggested that smoking may interact with IBD in the following ways (Parkes et al. 2014):

- Causing alteration to the gut microbiota
- Decreasing gut permeability
- Causing alteration to the gastrointestinal immune system
- Causing alteration to epigenetic events (modification of gene expression)

35.3.3 Nicotine Therapies in UC

Several studies have assessed the benefit of using nicotine patches as treatment for UC. Overall, there was no benefit over standard therapy (mesalazine or corticosteroids). Additionally there were more adverse events in the nicotine groups (McGrath et al. 2004).

35.3.4 The Use of Electronic Cigarettes

Although not covered in the sections above due to the relative newness of the products, electronic cigarettes (e-cigarettes) may prove useful as a cessation aid. Further research into their use and safety is needed (Hartmann-Boyce et al. 2016).

35.3.5 Summary of Future Research into Smoking and IBD

- The exact mechanisms by which smoking affects IBD are as yet unknown. Further research is needed but is hampered by the sheer number of constituents in tobacco smoke.
- Within the gut, the microbiota, gut wall permeability and immune system may be affected by smoking.
- Smoking may alter gene expression resulting in changes to disease behaviour.

35.4 Drugs and IBD

35.4.1 Learning Aim

- To be aware of the current knowledge regarding the use of recreational or non-prescribed drugs in IBD

35.4.2 Introduction

Discussion of recreational drugs is limited here to *Cannabis sativa* or marijuana as it is probably the most likely to be used currently by patients within an IBD clinic. In some countries the use of cannabis is legal for symptom relief in certain chronic illnesses although illegal otherwise. Data surrounding its use outside of the clinic setting is therefore limited. There have been studies looking at the use of cannabis in IBD but further research is needed.

35.4.3 Cannabis and IBD

Patients are probably likely to try cannabis for similar reasons to other complementary and alternative medicines (CAM). A review of studies suggests that patients resort to CAM in an attempt to gain some personal control over and improvement of symptoms and/or as a result of ineffective conventional therapy (Hilsden et al. 2011). A Spanish study found that longer disease duration and extra-intestinal manifestations were factors associated with CAM usage (Fernandez et al. 2012).

Cannabis is known to have anti-inflammatory and analgesic effects and is used legally in some countries for symptom relief in cancer, multiple sclerosis and other chronic disabling conditions. Its use by patients with IBD is therefore not surprising. Estimates of the usage of cannabis vary from 10–16% for current usage and 17–50% for lifetime usage (Ahmed and Katz 2016). Reported benefits include relief of abdominal pain, relief of diarrhoea and improved appetite.

35.4.4 Risks Associated with Cannabis

Unlicensed use of cannabis carries the risks associated with an unregulated substance lacking quality control. Known side effects of cannabis are concerning; those reported in studies looking at usage in IBD populations include euphoria, heightened awareness, paranoia, memory loss, anxiety, dry mouth, increased appetite and drowsiness (Lal et al. 2011; Storr et al. 2014). It has also been suggested that cannabis may have a fibrosing effect which could lead to increased need for surgery in CD (Storr et al. 2014). Additionally, cannabis may mask symptoms and lead to delay in seeking help in active disease or to cessation of maintenance treatment.

35.4.5 The Current and Future Use of Cannabis in IBD

The potential benefits of cannabis in IBD should be further studied as it may have a place in symp-

tom management. Patients with IBD should however be made aware of the possible risks associated with the use of cannabis. The use of cannabis may not be reported to the healthcare team due to legality issues. Developing an open and honest rapport with patients and a non-judgemental approach to CAM usage may encourage disclosure.

35.4.6 Summary of Drugs and IBD

- Cannabis is the most widely studied recreational drug in IBD.
- Cannabis may help with pain control, improve appetite and reduce nausea.
- There are known side effects and risks associated with cannabis usage which may be increased with the use of unregulated supplies.
- There may be a risk of worsening of CD long-term due to increased fibrosis.
- The illegal status of cannabis in many countries leads to under- or non-reporting of its usage; IBD teams should encourage non-judgemental disclosure and honest discussion regarding the risks and benefits.

Resources

The Cochrane Tobacco Addiction Group in the United Kingdom http://tobacco.cochrane.org/welcome provides systematic reviews of tobacco control interventions.

Treatobacco.net http://www.treatobacco.net/en/index.php also based in the United Kingdom provides information on the treatment of tobacco addiction with a translation facility into ten other languages.

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Stress and Psychological Support

36

Yoram Inspector and Tracey Tyrrell

Abstract

It is widely acknowledged that inflammatory bowel disease can seriously affect all aspects of daily life. Furthermore, many patients report that stress exacerbates their symptoms (Mitchell and Drossman 1987; Robertson et al. 1987) and this is supported by clinical studies which indicate that chronic stress and life events can cause relapse in patients with IBD (Mawdaley and Rampton 2005). Therefore better management of stress has potentially crucial implications for patients and healthcare professionals. It can improve resilience and develop more adaptive coping mechanisms. However when this is not achieved, psychological distress in the form of depression, anxiety and post-traumatic stress disorder can take over which in a vicious cycle impairs further the ability to handle stress.

This chapter will look at the various stress factors which are unique to IBD and how the IBD nurse can psychologically support the patient in daily practice and in turn looking at how the nurse can be supported in order to support the patient.

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36.1 What Is Stress?

> You can't stop the waves but you can learn to surf—Jon Kobat Zinn (1994)

Stress is a natural response which has been alluded to for many centuries. We cannot eliminate stress especially as it has a vital survival function, but we can learn how to live with it and even use it to our advantage. This is obviously easier said than done yet not unachievable. "Stress can be described as a circumstance that disturbs, or is likely to disturb, the normal physiological or psychological functioning of a person". In the 1920s, Walter Cannon (1871–1945) conducted the first systematic study of the relation of stress to disease. He demonstrated that stimulation of the autonomic nervous system, particularly the sympathetic system, readied the organism for the "fight-or-flight" response characterised by hypertension, tachycardia and increased cardiac output. This was useful in the animal that could fight or flee; but in the person who could do neither by virtue of being civilised, the ensuing stress resulted in disease.

Hans Selye (1907–1982) developed a model of stress he called the general adaptation syndrome. It consisted of three phases:

1. The alarm reaction
2. The stage resistance, in which adaptation is ideally achieved

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3. The stage of exhaustion in which acquired adaptation or resistance is lost

He considered stress as a nonspecific bodily response to any demand caused by either pleasant or unpleasant conditions. Selye believed that stress, by definition, need not always be unpleasant. He called unpleasant stress: *distress* (Sadock et al. 2015).

36.2 Stress the Mind and the Body

> …A body that could never rest,
> Since this ill Spirit it possest—Andrew Marvell (2013)

Distress is caused by too much mental or emotional pressure (NHS Direct Wales 2017). Pressure turns into distress when the person feels that they are unable to cope. It is important to remember that people have different ways of coping with stress, so a situation that feels stressful to one person may motivate someone else into a positive action. This is the basis of the **Perceived Stress Scale** which was developed to measure the degree to which situations in one's life are appraised as stressful. Psychological stress has been defined as the extent to which a person perceives that their demands exceed their ability to cope (Cohen et al. 1983).

Life is stressful. Day-to-day demands can cause stress, particularly work, relationships and money issues. Stress can affect how the person feels, thinks and behaves and how their body works. Stress causes a rush of hormones in the body. These stress hormones are released to enable the person to deal with pressure or threats—called the "fight-or-flight" response.

Once the pressure has passed, the stress hormones levels will usually return to normal. However, if there is a constant stress, these hormones will remain in your body, leading to the symptoms of stress (NHS Direct Wales 2017). Common physical symptoms of stress can include sleeping problems, sweating, loss of appetite and headaches, muscle tension and dizziness (NHS Direct Wales 2017).

This in turn can lead to people feeling anxious and irritable, and/or they may have racing thoughts and difficulty concentrating, worry constantly, lose their temper more easily and act unreasonably.

Being overwhelmed with the above can lead to feelings of helplessness, hopelessness and worthlessness which are the three states that perpetuate and maintain depression. Hopelessness is the factor most related to suicidal ideation (Beck et al. 2006).

36.3 Stress the Gut and IBD

> I am poured out like water, and all my bones are out of joint: my heart is like wax; it is melted in ***the midst of my bowels***—A Psalm of David (2005)

In the 1950s, Harold Wolff (1898–1962) observed that the physiology of the gastrointestinal tract appeared to correlate with specific emotional states (Sadock et al. 2015). Hyperfunction was associated by him with hostility and hypofunction with sadness. Wolff regarded such reactions as nonspecific, believing that the patient's reaction is determined by general life situation and perceptual appraisal of the stressful event. Earlier, William Beaumont (1785–1853) an American military surgeon had a patient named Alexis St. Martin, who became famous because of a gunshot wound that resulted in permanent gastric fistula (Sadock et al. 2015). Beaumont noted that during highly charged emotional states, the mucosa could become either hyperaemic or blanch, indicating that blood flow to the stomach was influenced by emotions. Going further back in time, we find that already King David in the Old Testament noticed that his psychic stress is concentrated in his gut as quoted above. Psalm 22 opens with the poignant words: "My God, My God, why hast though forsaken me"? So one can say that all David's emotional suffering that is concentrated in the "midst of his bowel" is the embodiment of the experience of being abandoned. It is not uncommon to have experienced abandonment at some point of one's life and the

psychic stress-gut connection which accompanies it. Nothing has changed since biblical times: Our twenty-first-century language still demonstrates the knowledge about the inseparable connection between our deepest emotions and the gut. Human beings are still "gutted" by psychological traumas that they "cannot digest" that makes their stomach "to be knotted with fear" (Inspector and Burns 2016). We all feel the "butterflies" in our stomach when we are anxious. Psyche in the Greek mythology was a princess with butterfly wings; therefore when we feel the butterflies in the stomach, we feel "psyche" in our stomach.

As regards to the specific link between stress and IBD, to date, there is still no evidence from human studies that IBD is caused by stress. In animal studies, however, there is evidence for it: the cotton-top tamarin, a new world monkey from Columbia, developed ulcerative colitis and colonic cancer only in captivity. The unique social unit has been changed and so were the temperatures that were lower than the jungle habitat—social isolation and cold stress, physical restraint, prolonged swimming, premature weaning and conditioned anxiety have all been shown to produce acute or chronic gut inflammation in several animal models (Wood et al. 1998).

Human studies have shown that adverse life events, chronic stress and depression can increase the possibility of relapse in patients with quiescent IBD (Mawdaley and Rampton 2005).

Patients report that they feel that there is a link between stress and their flare-ups. A survey of a random sample of 1000 members of the American Gastroenterological Association showed that physicians believed that psychological factors do not contribute to the cause of IBD but that psychological factors affect the clinical exacerbation of symptoms (Wood et al. 1998). Conversely, more than half of the patients with IBD believe that stress or personality is a major contributor to the development of their disease, and >90% think that stress influences their disease activity (Robertson et al. 1987). For example, one patient at St. Mark's 2014 (St. Mark's patient 2014) even expressed her concern regarding becoming stressed as she was afraid "that this will trigger a flare-up".

36.4 Stress and the IBD Patient

> It is much more important to know what sort of a patient has a disease than to know what kind of a disease a patient has—Willian Osler (1982)

It is "important to know what sort of a patient has the disease" as no two patients will experience their disease in the same way. The unique individual experience of the disease is actually what defines illness.

There is subtle difference between disease and illness. Disease is the objective pathological disorder of the structure and/or the function of our organs, whereas illness can be understood as our subjective experience of our disease (Chang et al. 2016). Another way to approach these subtle differences is to say that disease refers to the medical establishment perspective wheras illness to the way the patient perceives their condition (Suchman 1963).

However there are common experiences that are special to IBD patients. Apart from dealing with their own stress of day-to-day life, the patient needs to now deal with having IBD.

Here is a partial list of the unique stressors of IBD:

- Coming to terms with having an autoimmune condition
- Unpredictable nature of the condition
- Cancer risks
- Side effects of medical treatment
- Social embarrassment/shame of having a "dirty disease" (or as one patient defined it a "yucky disease")
- Taboo subject, unappealing socially
- Fistulas
- Permanent stoma
- Rectal bleeding
- Using enemas
- Subjective invisible disabling symptoms—pain, fatigue, cramps
- Faecal incontinence (was reported to be worse than death by palliative patients (Rubin et al. 2016)

Looking at this list of stressors that our patients have to deal with, it is no wonder they are at times extremely distressed.

Without the ongoing professional help and support of the IBD nurse, the patient can feel overwhelmed and trapped by all the above conditions and symptoms. Being and or feeling trapped is a major stress as can be demonstrated in the following experiment done with mice by the French surgeon Professor Henri Laborit. The experiment was the basis for Alain Resnais film "Mon oncle d'Amerique" which translates into English as "My American Uncle", in which the mice are used as an illustration to the humane condition. What happens in the experiment? There are three stages:

1. A mouse is put in a cage but the door of the cage remains open. The mouse received a disturbing but not a dangerous electrical shock. As the mouse can escape, it avoids further pain and its health is not affected (see Fig. 36.1).
2. A mouse receives an electrical shock, but this time the door of the cage is locked, it cannot escape and is **alone!** This **lonely, trapped** mouse starts to become ill—it develops alopecia and a peptic ulcer (see Fig. 36.1).
3. Two mice are in the locked cage and are electrocuted. They cannot escape like in the first stage of the experiment but they are **together. Not alone. They interact with each other, discharge their pain on each other and share it. They remain physically healthy.** (see Fig. 36.1)

There is scientific evidence that "Stressed mice look like depressed humans". This is a subtitle in a very recent textbook on *The New Mind-Body Science of Depression* (Maletic and Raison 2017) which explores fascinating and surprising interlinks between inflammatory processes and depression. Not being alone and interacting with others has a healing potential for depression and according to the above textbook even for inflammation.

There is no escape from the cage of IBD for the IBD patient but also not for the IBD nurse.

How to interact with the patient in the "electrocuted cage" of IBD? In order to help, healthcare professionals need to be ready to be "electrocuted", being ready to compassionately take the patient's experience in. Compassion does not require one to achieve complete understanding of the other's perspective and circumstances, engendering exactly the same feelings; it merely calls on one to imagine what it might be like to suffer in the way that the other is suffering. If achieved this will engender the corresponding emotion, which can then be conveyed (Heath 2016).

If a good nurse-patient relationship is established, the patient can be your second mouse. It works both ways; if the patient validates our professional help and advice, we feel reassured and more motivated to continue to provide our service.

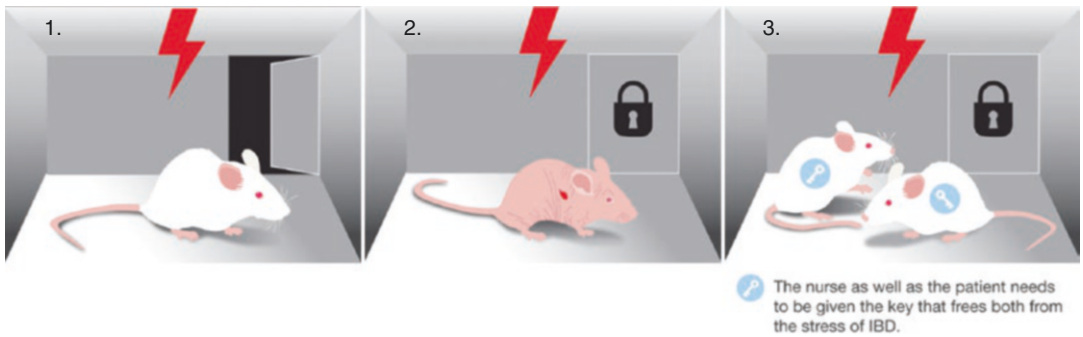

Fig. 36.1 The stage experiment

We should not forget that although we are put in the position of the "invincible saviour", we are human beings with our unique vulnerabilities. This however can actually work in the favour of providing a more compassionate treatment. Carl Gustav Jung's concept of "The Wounded Healer" comes to mind, which has been already noted by Shakespeare:

> Men can counsel and speak comfort to that grief which they themselves do not feel; but, tasting it, their counsel turns to passion (Shakespeare, Much Ado about Nothing, Act 5, Scene)

36.5 Stress and the IBD Nurse

> -"Tell me in one word how you are?"
> -"Fine".
> -And in two words?
> -"Not fine"! (Anonymous corridor conversation)

The IBD nurse's role is vital in supporting the patient with IBD. However, how do you know when the patient is psychologically distressed? Distress can be expressed by the patient feeling worthless, hopeless and helpless. With the right approach, the IBD nurse can play a pivotal role in helping the patient to feel less worthless, less hopefulness and less helpless. These are the three mental and emotional states that lead to and maintain depression. Major depression was found to be the most common mental disorder in IBD patients (Graff et al. 2009).

36.5.1 Assessment

When assessing patients, whether over the phone or face to face, you will find the majority of the time is spent talking about clinical symptoms. However it is important to carry out a holistic assessment. The holistic assessment involves asking open-ended questions from the patient's perspective covering their physical symptoms, the psychological effects these have on their daily lives and also about the social aspects which include employment and education (Bach and Grant 2009). In turn the nurse will address all aspects of a patient's life, which then allows the nurse to assess the consequences of living with IBD. Health-related quality of life (HRQOL) can measure the impact of living with a specific disorder. It allows the patient to self-report their symptoms and concerns rather than a clinician-directed interview.

36.5.2 Validated Assessment Tools in IBD

- Inflammatory Bowel Disease Questionnaire (IBDQ) (Guyatt et al. 1989)
- Rating Form for Inflammatory Bowel Disease Patients' Concerns (RFIPC) (Drossman et al. 1989)
- Gastrointestinal Quality of Life Index (GQL1) (Eypasch et al. 1995)

The nurse can assess the mood and anxiety in patients with the hospital anxiety and depression scale (Zigmond and Snaith 1983). It consists of 14 questions related to anxiety and mood and is completed by the patient. However, it is important to introduce this tool with sensitivity and explain to the patient why you are asking the questions as the patient may feel that their symptoms are being judged as being psychological. This tool will help to highlight and understand how their disease affects their emotional state.

36.5.3 How and What to Ask?

The reason why to start with the how before the what, is due to the fact that if you find the right tone, music, the right way to ask the question, one can ask nearly anything. There are a variety of professional techniques of how to do it yet if we are compassionately and empathically attuned with the patient's emotional state, this will happen naturally.

Asking IBD patients about their bodily symptoms might at times be experienced as intrusive and embarrassing to the patient and the nurse alike as they are centred on hidden bodily parts and functions that are closely related to shame. Again if one is genuinely caring, the right tone will emerge and the patient will open up to the question.

The next question is what to ask? The advice is to ask about whatever you as a nurse find relevant for the treatment of the IBD but also about what is relevant to the quality of life of the unique person you meet. It can be helpful to simply ask the patient's permission to discuss personal and sensitive topics. Embarrassment and shame are core feelings to the experience of IBD, so many patients might feel relieved when you say: "I know that some of the symptoms you experience might be socially embarrassing" as their experience will be recognised and validated. If you feel like it, you can use what the author Ann Patchett said about shame:

> Shame should be reserved for the things we choose to do, not the circumstances that life puts on us. (Patchett 2005)

We heard from many clinicians that they are afraid to open the "Pandora's box", meaning being afraid of all sorts of overwhelming difficulties and frightening things that will come out of it. Health care professionals may feel that they do not have the specific training to be able to address very difficult psychological problems.

It is important to reflect about the questions we might avoid asking as these might be the ones the patient is longing for someone to ask them. Not all patients have the support network within which they can share the experience of having to live with IBD. Having IBD can be a very lonely place. If you still are anxious about asking directly intimate questions, a good way to start is by simply asking the patient the following:

- "What do you want to get from the session?
- How does having IBD affect your life?
- How are you coping?

The recommendation is to overcome these professional anxieties mentioned above and to open the "Pandora's box" (see Fig. 36.2). This in turn can save time in the long run as crucial issues will be addressed quicker; it will also deepen the bond between you and the patient and will generate hope:

In the Greek mythology, from the box Pandora opened flew every trouble and sickness known to humanity (probably IBD was in the box as well). Pandora managed to keep one spirit in, a timid spirit named "Elpis", usually translated as "Hope". So if you do not open Pandora's box, you do not get access to hope.

Fig. 36.2 Pandora's box

Hope as far as we know is uniquely humane. It is not about "everything will be alright". It is about "It might be alright". To have access to hope enables us, nurse and patient alike, to be able to carry on.

When it is difficult to introduce sensitive topics, using a questionnaire can be a handy alternative to facilitate the discussion. It is useful to send the HRQOL to the patient with their appointment letter as it can help to form an agenda for the clinical appointment and a focus for the assessment. It helps the nurse to be able to gauge the patient's response to a certain question and decide whether they are ready to discuss them at the time or at a later date. It can be difficult to address all aspects of the patient's care in one clinic or telephone slot, and the questionnaire can help both the patient and the nurse to prioritise the issues that need to be talked about.

36.5.4 Now Pandora's Box Has Been Opened, What Do You Do with the Information?

The IBD nurse is not a counsellor but can still therapeutically support the patients on their journey to remission by following the simple but effective tools:

1. Be there. (We are in this together. The nurse is the "second mouse".)

The mutual engagement of the nurse and the patient is crucial for the compliance with the complex and the difficult medical treatment. To begin with, you do not need to use any manuals or formulations. If you will just be present as an empathic, compassionate human being who is deeply interested and curious about what the patient is going through, you will make a good start.

At Diagnosis

Most patients' reaction to diagnosis is a mixture of shock, anxiety and uncertainty and in some cases relief (Crohn's and colitis UK 2014). Patients have been informed that they have a chronic/ongoing condition, something that they are "stuck with". The patient may develop an anxiety at the thought of taking daily medications for an uncertain amount of time if not indefinitely and unsure of what to expect. Patients may feel concerned and confused particularly when a doctor or a nurse does not know what the actual causes of IBD are.

At Flare-Ups

IBD is an unpredictable condition. Just when patients have come to terms with the condition and are feeling that they are beginning to get on top of things, a new situation develops. For example, a patient may develop a sudden flare-up or an unpleasant side effect to a medication that is difficult to live with. Patients may find that their medication is not working and other medications or surgery may be recommended. Uncertainty and feeling out of control start again.

2. Validate.

Remember most symptoms of IBD are opaque and therefore IBD is often called an "invisible illness". Therefore it is important that the IBD nurse listens and takes note of the patients reported symptoms. The patient **knows** and experiences the condition; the nurses and doctors **know about** it and have the information. Hence embracing the patients' subjective experience has the potential to redeem them from feeling lonely and alienated.

3. Provide information.

As described in the opening section of this chapter, stress can lead onto anxiety. Anxiety is made of a combination of uncertainty and an intense fear of something being irreversible. In order to reduce anxiety, you need to reduce uncertainty. The IBD nurse can help to reduce the uncertainty by providing information. Patients may be relieved to find that their symptoms have a known name and that the condition can be usually managed with medication or surgery if necessary. Known knowledge is powerful.

4. Involve the patient in the care plan.

> Tell me and I will forget, teach me and I may remember, involve me and I learn—Benjamin Franklin (https://www.goodreads.com/quotes/21262-tell-me-and-i-forget-teach-me-and-i-may)

Involving the patient in the care plan will help to further reduce the uncertainty as the patient will feel less helpless and hopeless. During a flare-up the nurse will work with the patient to see if they can make adjustments and take time to recuperate. It is not easy coming to terms and accepting a chronic medical condition. Making the patient aware that there may be times when they have to take things more easily can help them keep a balance in their life. It may help the patient feel more in control of their condition.

Remind the patient that they are not alone. This is reinforced by informing the patient of the prevalence of the condition. It is estimated that 2.5 million people in Europe have IBD (Kaplan 2015). The nurse should find out from the patient what support network they have. IBD is an embarrassing condition and this may prevent some patients discussing this with their family or friends. Encourage the patient to discuss with their family and friends, offer the patient the option to bring them to the next hospital appointment or ask them to read charity websites.

5. Treat the patient as well as the condition.

Nurses need to meet also the person and not just the condition. Empathy—putting yourself in the shoes of the patient—is the basis of any good therapeutic relationship. It will encourage openness and honesty which will allow you as the nurse to make sure that the patient has the right treatment.

6. Positivity

Being positive is important. The patient is dealing with a condition with no cure; however reminding them that research is continuing to find better treatments for patients is important. Encourage the patient to be open and honest about their condition.

7. Manage expectations and decision-making.

It is important to provide the patient with a "road map" that will inform them about the challenges ahead whilst keeping a realistic hope regarding remission. The decisions that IBD patients need to take are complex and difficult, and each carries within it potential health benefits but also potential scary side effects. The professional support of the nurse at these crucial junctions of the treatment journey is invaluable. Provide the professional advice, but allow and create space, for the patient to process her/his own thoughts and views about the treatment options.

When it seems to us that patients make "stupid" decisions, it is important to remind ourselves that the word "stupid" stems from to be "stupefied" with fear. When we are afraid, we enter into a fight-flight-freeze mode and can no longer think.

In the Greek mythology, Perseus overcame the petrifying gaze of the monstrous Medusa through observing her reflection in the shield of Athena the goddess of wisdom. It is the mutual compassionate curious reflection process of the nurse and the patient that helps to overcome the fear and make better informed decisions.

36.6 Support the Supporter

At times looking after IBD patients can be difficult for the IBD nurse as some patients need a lot of support. We are working in a pressurised environment, and it is vital that we recognise our own stress levels and how it affects our work with colleagues and patients.

Therefore it is important for the nurse to have an opportunity to discuss any worries or concerns that they have about a patient or work related situation. This can be done through Clinical Supervision.

Clinical supervision is a formal process of professional support and learning which enables individual practitioners to develop knowledge and competence, assume responsibility for their own practice and enhance patient protection and safety of care in complex clinical situations (Department of Health 1993). It supports nurses by exploring emotions and feelings experienced during patient care. This can prevent burnout (Royal College of Nursing 2002). It is recommend setting up regular meetings with a work colleague, preferably someone who works at the same level or higher and who has had supervision training.

If there is the opportunity to work with a counsellor in your clinical area, then use it. Set up regular sessions so you have a forum to discuss any difficult patient experiences. At St. Mark's Hospital, the IBD nurses have weekly group supervision with the consultant psychiatrist of the Psychological Medicine Unit.

Furthermore network with other IBD nurses in your local area, sharing ideas and talking about experiences with your peers, is just as effective and helps to reduce your own uncertainties (see Chap. 46 on networking).

Finally, due to the constant demands involved in treating and caring for IBD patients, a sense of inadequacy can develop that also involves feelings of guilt as regards to not being able to help enough. We can find ourselves therefore constantly self-criticising, and this corrodes further our self-confidence and self-esteem which then in a vicious cycle might affect our motivation and performance. Professor Paul Gilbert says in his book *The Compassionate Mind* about how to move from self-criticism to self-compassion which involves, among other things, giving ourselves "encouragement, support and kindness". This starts from the simplest things such as firstly "seeing what we did well and only then considering learning points". It is easier said than done, but as Gilbert highlights it is a gradual process of moving towards a more self-compassionate position (Gilbert 2009).

We probably find it easier to be more compassionate towards the suffering of our patients than towards ourselves. A sense of altruism or selflessness is a core part of our work that for many of us is a vocation rather than just a way of making a living. This very often leads us to "walk the extra mile" for our patients, but we must be careful that by doing that we do not lead ourselves to burnout and "compassion fatigue". In the long run, this will harm ourselves and then, vicariously, our patients, who depend on us being fully there for them (Moberly 2017).

36.7 Summary

Addressing stress and distress in IBD patients is a core part of their holistic care. It has the potential to improve the compliance to treatment and quality of life. This chapter explored the nature of stress and distress and how it affects the patient and the IBD nurse alike. In order to reduce the distress of IBD, it is important to keep the following key points in mind:

- A good nurse-patient relationship is based on actively listening to the patient's thoughts and concerns with empathy and compassion.
- Providing the information which suits the unique interest and needs of the patient.
- Help patients to be aware and adapt to stressors. Knowing and recognising the association between bowel symptoms and psychological stress may help patients to modify all factors affecting the illness conditions.
- Help patients take responsibility for their healthcare.
- Reinforce health-promoting behaviours.
- Healthcare professionals must identify psychosocial factors unique to each individual that contribute to the clinical expression of the disorder.
- It is important for the IBD nurse to be supported by regular supervision and networking in order to contain and manage their stress and distress levels.

Acknowledgements Finally we would like to thank our patients for teaching us every day about the courage and the resilience needed in order to face the adversity of IBD. This turns working with the IBD patients into a humbling and a deeply rewarding experience.

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Communication Skills

37

Stephanie Fry, Kathryn Burrell, and Tamie Samyue

Abstract

Communication is a vital component of the nursing role and is essential for the delivery of successful, quality healthcare. Good interpersonal communication increases the accuracy of information shared between nurse and patient and can amplify elements that are crucial in achieving positive health outcomes.

Effective and open communication is a key factor when liaising with a multidisciplinary team and can result in a collaborative and collegial approach to patient care.

Health literacy needs to be considered when communicating with patients. Knowledge of how to ensure patients understand basic health information will enable the delivery of information that is appropriate, effective and tailored to the individual's needs.

In this chapter, the practical skills required to facilitate good communication will be reviewed and common barriers to communication explored, along with how to maintain effective communication via telephone and electronic mail. Communicating effectively within a professional capacity will also be discussed.

The importance of health literacy and the impact it has on communication with the patient will be highlighted and practical ways of providing information and education to patients explored.

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37.1 Communication Between Healthcare Professional and Patient

Communication is a process by which information, or a message, is exchanged between individuals. It requires the sender to be able to communicate the message in a format that the receiver understands and the receiver to be able to interpret the message in the context that it was sent. There are many steps along the way where the messages can be misrepresented or misinterpreted, leading to communication breakdown. Communication between healthcare professional and patient can either facilitate a therapeutic relationship or create barriers (Balzer-Riley 2017).

Effective communication is a skill that can be difficult to master. It often needs to be learnt and at times requires maximum effort (Miller and Rollnick 2013). Training in communication enhances the efficacy and efficiency of this skill for use in patient consultation and chronic disease management (del Rio-Lanza et al. 2016). It also significantly and positively correlates with improved patient adherence to treatment (Panes et al. 2014).

Communication is vital for building patient-clinician relationships and rapport (O'Connor

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et al. 2013). It increases accuracy of information shared and amplifies empathy, trust and respect which are crucial elements in achieving positive health outcomes (Miller and Rollnick 2013).

37.2 Communication Basics

Communication with all patients should be empathic, compassionate and person-centred (Miller and Rollnick 2013; Pulvirenti et al. 2011). It is important to ensure that the environment is comfortable, quiet, private and free from distraction. Provide undivided attention, as being distracted whilst communicating can show disinterest and disrespect towards the patient.

Non-verbal behaviours are an essential part of the communication process and can include messages conveyed by eye movements, facial expressions and body language (Balzer-Riley 2017). They influence the outcomes of communication and are a significant contributor to its success or failure (Burgoon et al. 2016).

When greeting a patient:

- Introduce yourself and your role to new patients in a friendly manner.
- Establish open communication through informal chatting during initial minutes of the interaction.
- Inform the patient of the reason for the consultation if it is unclear.
- Inform the patient how much time you have together.
- Outline clearly what needs be achieved during your time together.

37.2.1 Active Listening, Asking and Informing

Active listening, asking and informing are three basic but important communication skills (Rollnick et al. 2008). When mastered, they can improve the efficacy and efficiency of communication. The process of informing and actively listening has positive effects on patient self-efficacy, increases patients proactively seeking health information, and has been shown to increase shared decision-making (del Rio-Lanza et al. 2016).

Active listening is a communication skill that lets the patient know they are being heard.

The acronym SOLER can be utilised to facilitate active listening (Iedema and Manidis 2013):

- S—Sit squarely facing the client.
- O—Observe an open posture.
- L—Lean forward towards the client.
- E—Establish eye contact.
- R—Relax.

Offering a reflective listening response is how a clinician can check their understanding of the patient's message, rather than assuming they have understood. Utilising active listening and providing reflection gives the patient opportunity to clarify in case the clinician has misunderstood and encourages them to explore and reveal more information in a short period of time (Rollnick et al. 2008).

Asking a question places a demand on the person to give an answer. It can be used to guide the patient in a particular direction or area of interest to the questioner. Closed-ended and open-ended questions can elicit succinct or elaborated responses (see Table 37.1). Utilising a balanced combination facilitates the communication process and can gather concise information and allows the patient to contribute to the interaction.

Table 37.1 A comparison of closed- and open-ended questions

Closed-ended questions	Open-ended questions
• Elicits a 'yes' or 'no' response • Allows a succinct response • Ideal for assembling factual or specific information • Offer little opportunity for the patient to interact • Overuse can block the patient from contributing to the conversation	• Does not predict or narrowly confine the response • Allows the patient to respond more freely • Ideal for eliciting views, opinions and feelings • Seeks elaboration or further clarification • Overuse can lead to a conversation that easily gets off topic or avoids discussing important issues

The tone, pacing, wording and clarity of questioning, along with good listening skills, are some of the foundation skills of quality communication (Rollnick et al. 2008).

Informing is the most commonly used communication skill used in healthcare. When providing information to a patient, remember:

- Be friendly.
- Seek permission to give advice.
- Provide information in a clear, concise manner and check the patient's understanding.
- The patient may not have the ability to absorb information.
- The patient may not be interested or ready to receive information.
- The patient may not agree with you about the importance of the information provided.

37.2.2 Communication Via Telephone and Electronic Mail

Telephone and electronic mail (email) services are considered to be a key element of the IBD nurse's role, acting not only as an access point for patients seeking information and support but also as a suitable platform to provide multiple aspects of care (O'Connor et al. 2013).

There can be specific challenges communicating when the patient and nurse cannot visualise each other, as the effect of gestures and other non-verbal communication is lost (Balzer-Riley 2017). By enhancing communication skills in these formats and tailoring your style of communication for each setting, you can develop strong, trusting and effective therapeutic relationships in the non-face-to-face setting (Knox and Cooper 2015).

Some tips for communicating with patients over the telephone and email include:

Via *telephone*:

- Compensate for the lack of non-verbal cues by amplifying the tone and expression of your voice.
- Provide regular verbal cues that let the patient know you are listening.
- Clarify that what has been heard is correct.
- Summarise any agreed plans at the end of the call.
- Ensure that information provided is understood.

Via *email*:

- Acknowledge receipt of the contact, even if it cannot be responded to immediately.
- Use a warm and empathetic approach to written communication.
- Clarify the content if required.
- When responding to queries with multiple parts, make it clear which query you are responding.

It is essential that all communication including advice, education and implemented plans are documented in the patient medical record and accessible to all members of the multidisciplinary team.

37.2.3 Barriers to Communication Between Healthcare Professional and Patient

Barriers to communication can stop the patient from communicating freely and candidly, decrease rapport and distract from active listening.

Some of the barriers that should be avoided include (Miller and Rollnick 2013; Iedema and Manidis 2013):

- Confrontation.
- Giving unwanted advice, suggestions or solutions.
- Ordering, commanding, cautioning or threatening.
- Persuading with logic, arguing or lecturing.
- Moralising (approving or disapproving).
- Rejecting, criticising, blaming and defending.
- Placating (agreeing, approving, praising, reassuring, sympathising and consoling).
- Shaming, ridiculing or labelling.
- Interpreting or analysing the patient's experience.
- Questioning or probing when the patient does not wish to discuss an issue.
- Withdrawing, distracting, humouring or changing the subject.
- Making stereotyped comments, clichés and trite expressions.

37.3 Communication in the Professional Health Setting

Effective communication between healthcare professionals is essential to deliver a high standard of care to patients. Clear and accurate communication will ensure patients receive consistent and adequate treatment in a timely manner (Crohn's and Colitis Australia 2016).

Ineffective communication between healthcare professionals can adversely affect patients through poor continuity in the quality and type of care being provided. Conflicting or poorly communicated assessments, treatments and management plans can lead to medical errors, adverse events, injuries, delays, incorrect treatment and death. Within a multidisciplinary team, ineffective communication can also create a culture of mistrust and an unwillingness to collaborate and work together (O'Daniel and Rosenstein 2008).

Barriers to effective communication between healthcare professionals include:

- Different communication styles.
- Professional hierarchy and workplace culture.
- Qualifications and professional experience.
- Multiple teams involved in the management of complex patients.
- Fear of discipline if errors arise.
- Use of medical terminology and acronyms.
- Poor recording and sharing of patient information.

Overcoming barriers to effective communication:

- Promote openness and a team-based approach to patient care.
- Share responsibilities and accountability amongst colleagues.
- Build positive relationships through collaborative projects.
- Establish communication standards that define behaviours and procedures within the organisation.
- Utilise standardised communication tools to record and disseminate information.
- Establish formal or informal routes of communication between providers:
  - Multidisciplinary meetings
  - Ward rounds involving multiple specialists such as a gastroenterologist, colorectal surgeon, IBD nurse and dietician
  - Team debriefing after significant patient or professional events

Effective communication between healthcare professionals can result in a collaborative and collegial approach to patient care. Hence, staff achieve greater work satisfaction, reduce errors and provide better outcomes for their patients, such as reduced hospital admissions, improved patient satisfaction and better treatment compliance (O'Daniel and Rosenstein 2008).

37.4 Understanding Health Literacy

Health literacy is an important factor when managing patients with chronic conditions such as IBD. Health literacy is the degree to which individuals have the capacity to obtain, process and understand basic health information (Carlisle et al. 2011). It is estimated that 60% of the population can be identified as having low health literacy (Australian Commission on Safety and Quality in Health Care 2014). Optimal communication between the clinician and patient is imperative to ensure patients understand the health information they receive and can utilise it to make appropriate health decisions.

37.4.1 Impact of Low Health Literacy on the Individual

Health literacy can impact a patient's ability to understand and successfully manage their disease (Table 37.2).

People with low health literacy are at increased risk of (Australian Commission on Safety and Quality in Health Care 2014):

Table 37.2 How health literacy can impact patient disease management

Low heath literacy may lead to	Good health literacy may lead to
• Limited understanding of the management of their condition • Being unaware of a medication regime • Not following up primary health maintenance such as vaccinations, bone density scans, skin cancer screening, etc.	• Knowing medications and dosages • Being aware and up to date with immunisations • Attending appointments and having regular blood tests • Being aware of the importance of primary health maintenance

- Needing emergency care
- Becoming seriously ill
- Not having vaccinations or preventative care
- Presenting to hospital
- Inadequate understanding of disease
- Poor medication management
- Poor health outcomes
- Increased risk of mortality

Identifying patients with low health literacy can be difficult, and it is important not to presume patients will understand all information presented to them. In doing so we can promote better health outcomes for the individual (Adams et al. 2009). Whilst several formal health literacy assessment tools are available, informal cues can often prompt the clinician to identify a patient with low health literacy.

Some cues that a patient may have low health literacy include (Centre for Health Care Strategies 2013):

- Missing appointments
- Inability to answer simple questions about medication
- Failing to have scans and tests
- Not asking questions during consultation

Populations who are vulnerable to low health literacy include (Australian Commission on Safety and Quality in Health Care 2014):

- Older adults
- Migrant, culturally and linguistically diverse populations
- Lower socio-economic population

Example: Consider Health Literacy with Mr. Brown

Mr. Brown is a 60-year-old man with Crohn's disease, diagnosed 3 years ago. He does not attend regular appointments or adhere to his medication regime. Recently, he experienced a disease flare requiring admission to hospital. During his admission, Mr. Brown displays a limited understanding of his disease and how he should be taking his medication.

37.4.2 Using Knowledge of Health Literacy to Improve Communication with Patients

Some methods and tools to use that promote health literacy include (Australian Commission on Safety and Quality in Health Care 2014):

- Assume most patients will have difficulty understanding medical terminology and complex health information.
- Present information simply and through different formats such as visual or decision aids if required.
- Assess that the patient has understood the information presented.
- Repeat information if necessary.
- Listen to patients and allow them to ask questions.
- Regularly evaluate how information is being delivered.
- Encourage patients to access available resources such as an IBD nurse advice line.
- Use the teach-back technique to ensure patients understand information.

37.4.3 The Teach-Back Technique

The teach-back technique is a practical and simple communication strategy that clinicians can implement that ensures patients understand their disease and disease management (Carlisle et al. 2011). Generally, patients retain only about 40–80% of information presented during medical appointments, and half of the information retained

is not correct (Kessels 2003). With this technique, the clinician asks the patient to repeat 'in their own words' what they have understood. The teach-back technique should be used with every patient for consistency and to ensure there is no bias from the clinician as to which patients are presumed to understand health information and which are not (Carlisle et al. 2011).

A practical guide to teach-back (Watts et al. 2016):

- Keep the message simple!
- Give information in clear plain language.
- Stop frequently to assess patient understanding.
- Put the burden of understanding back on clinician by asking the patient to teach-back new information. 'To make sure I have explained everything correctly, would you mind repeating back our plan for …'.
- Always repeat or find new ways to provide information if the patient has not understood and then reassess their understanding.
- Avoid asking closed-ended questions.

Example: Using the Teach-Back Technique with Mr. Brown

Mr. Brown was reviewed by an IBD nurse. His prescribed medication regime was discussed verbally. Throughout the consultation, the IBD nurse stopped regularly to ask Mr. Brown to state in his own words what he understood about his medications, when he should take them and when he needed monitoring whilst ensuring that Mr. Brown did not feel uncomfortable if he did not know the answer. Mr. Brown recalled incorrectly and omitted important information about the times he needed to take his medication. The information was provided again in a written format and his understanding reassessed. By the end of the consultation, Mr. Brown could confidently and correctly state what medication he was taking, the times they needed to be taken and what monitoring was required.

End Summary

- Effective communication is a skill that can be difficult to master and often requires training.
- Communication should be empathic, compassionate and person-centred.
- Non-verbal cues, listening, asking and informing are key skills that facilitate effective communication.
- When using telephone and email communication, the absence of non-verbal communication needs to be compensated.
- Barriers to communication should be avoided.
- Effective and open communication results in a collaborative and collegial team approach to patient care.
- Recognising and accommodating low health literacy promotes better health outcomes for patients and healthcare systems.
- Keep the message simple and use the teach-back technique with all information provision.

Resources

Websites are available that convert medical terms into simple language. For example, many patients may not understand the term 'immunosuppression'. These websites suggest alternative terms or context related to immunosuppression that most would understand.

A helpful website can be found at https://hso.research.uiowa.edu/medical-terms-lay-language.

There is enormous wealth in seeking further training in different communication techniques. One style of communication or counselling that has proven to be very effective in assisting patients make positive changes to their negative health practices is *motivational interviewing* (Miller, W. & Rollnick, S., (2013). *Motivational interviewing: Helping people change.* 3ed. New York: The Guildford Press).

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Sport

38

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Abstract

This chapter seeks to describe how sporting activities can benefit patients during their life with IBD. Pros and cons for possible activities will be provided. Motivation and the fun factor play a crucial role in maintaining continuous activity. Several different studies were evaluated. This summary determined that patients with IBD tended to have quite low levels of routine physical activity. Various training programs correlate well with decreasing disease activity, resulting in better health-related quality of life.

Patients with chronic inflammatory bowel diseases should be strongly encouraged to engage in a sporting activity. Sporting activity should be part of the entire treatment concept for IBD patients.

38.1 Introduction

Patients living with chronic inflammatory bowel disease (Crohn's disease/ulcerative colitis) have to cope, not only with the limitations of the direct symptoms of the disease, but they also have to cope with its impact on many aspects of day-to-day life, social relationships, and the psyche. Improving quality of life is one of the main goals of the medical care and treatment teams as well as of the patients themselves. This chapter seeks to describe how sporting activities can benefit patients in the long run and which types of sport can be best recommended to patients. But it also points out that, for IBD patients, limitations may apply to certain sporting activities or disease situations. Motivation and the fun factor play a crucial role in maintaining continuous activity. So, how can the care team (e.g., physician, IBD nurse, clinician) help to keep patients motivated to exercise within their physical limitations?

38.2 Definition of Sport and Exercise

The term sport covers various forms of movement, play, and competition in connection with human physical activity. The word itself derives from "disport," which essentially means "to carry away" in the sense of to entertain or dispel (Onions 1966). Since the beginning of the twentieth century, the term sport is in common usage worldwide. A precise or even conceptual delimitation cannot be carried out. The definition of the word in day-to-day life can vary widely from person to person: long walks or gymnastics can just as well be referred to as sport as

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regular visits to the fitness studio, jogging, or even high-performance sports. For many people, sport is an essential part of leisure-time activities, either alone or in the company of family and friends.

38.3 Effects of Sport on IBD

Regular physical activity is known to reduce the risk of colon cancer (Shepard 2016), but there is little information available about the benefits of such activity for the prevention and treatment of chronic inflammatory bowel diseases. In principle, sport and IBD are not mutually exclusive, but there are IBD-related limitations which may restrict sporting activity. Study results were able to show that regular physical exercise reduces disease activity and medication use. Sport does not adversely affect the course of the disease and does not trigger attacks (Fischbach et al. 2009; Zillessen et al. n.d.). In a Canadian study, IBD patients reported being less stressed after regular training (walking 3.5 km three times a week). Their BMI score improved, and they also reported improvements in their quality of life (Narula and Fedorak 2008). The immune system is strengthened by adapted endurance training, and the immune cell count increases. In a study that used an online survey (n = 677), many respondents reported that IBD restricts their physical activity due to abdominal/joint pain (70%), fatigue/tiredness (69%), disease flare-ups (63%), and increased urgency (61%).

Regular moderate exercise can have a positive effect on IBD. In one study, Crohn's disease patients who exercised regularly over a period of 6 months exhibited significantly lower levels of disease activity than patients who performed no exercise. In addition, self-motivated physical exercise was shown to have a positive effect on IBD patients' mood, weight reduction, and osteoporosis. On the other hand, depending on the intensity and duration of the exercise, a temporary/transient mild systemic inflammation can potentially be triggered and the inflammation-inhibiting release of cytokines enhanced, possibly leading to a worsening of the gastrointestinal symptoms (Bilski et al. 2016).

In a systematic review of data collected from 1996 to 2015, several different studies were evaluated. On the whole, this summary determined that patients with IBD tended to have quite low levels of routine physical activity. Various training programs correlate well with decreasing disease activity, resulting in better health-related quality of life (Shepard 2016). The fact that exercise (low-intensity walking program) has a positive effect on quality of life without causing an exacerbation of disease symptoms could be demonstrated in a prospective study in which a stress index and the Harvey Bradshaw index were measured monthly in Crohn's disease patients belonging to either an exercise group or a non-exercise group (Ng et al. 2007). Patients in the exercise group experienced a statistically significant ($P < 0.05$) improvement in their quality of life.

According to the Nurses' Health Studies I and II, in which a total of almost 195,000 women were enrolled, physical activity is inversely correlated with the risk for Crohn's disease. Exercise had no influence on the risk of developing ulcerative colitis. Every 2–4 years, the study participants were asked about their physical activity and other lifestyle factors. The most physically active women had a 37% lower risk for Crohn's disease than the least physically active (a disease incidence of 6 versus 16 per 100,000 person-years). Age, smoking status and BMI had no influence on chronic inflammatory bowel disease (Chan et al. 2013).

38.4 Which Types of Sports Are Suitable?

Basically, patients can engage in any type of sport they like—the most important factor to consider when choosing a sport is enjoyment. That is easier to achieve, especially when the patient's motivation is not very high.

The amount of exercise performed depends on patients' individual capabilities and aspirations. Everything is possible—nothing is a must!

Patients with chronic diseases normally know their own limits very well; they should listen to their own bodies and not set themselves sporting goals that are overly ambitious. Individual disease activity, and in some cases also comorbidities or current complications, must always be taken into consideration. The following are some examples of sporting activities that IBD patients readily engage in:

Running or walking is always an option: outdoors or indoors, alone or in a group. These forms of endurance exercise top the list of the most popular sports. Suitable clothing should be worn. Good shoes are important—they provide support. Patients should begin with short distances, taking breaks every now and then, if necessary. Distances can be increased gradually and speed can be controlled individually. Above all, the muscles of the legs and buttocks are strengthened. The use of trekking poles in Nordic walking means that muscles above the hip are also trained while taking pressure off the back and joints. Forces are distributed evenly. Hiking is also highly recommended as a form of physical exercise.

Swimming should also be strongly recommended as a gentle form of endurance exercise because buoyancy and the reduction in body weight associated with it takes the strain off the joints. Almost all muscle groups are trained.

Dance and other exercise routines involving music increase fitness and offer exceptionally high levels of enjoyment. This means that the intensity of the workout can be increased, but it can also be controlled by the individual. In addition, posture and coordination are improved. There is another advantage to exercising in a group—it's a great way to get out and meet people.

During a game of *golf*, players often cover distances of many kilometers; here, the focus is on social interaction in combination with exercise in the fresh air.

Apart from a few exceptional cases, IBD patients can almost always engage in *ball sports* such as badminton, tennis, volleyball, or football, without any misgivings. Ball sports build team spirit and improve coordination as well as reaction times. They can be played indoors or outdoors at any time of year. A sense of accomplishment sets in quickly. Exercise intensity should be determined by the individual.

Those who like to hold a racket in their hand might be better off choosing badminton over tennis as the badminton racket is lighter than the tennis racket and therefore puts much less strain on the playing arm.

Autogenic training is a recognized and popular relaxation method. Even though the training itself does not involve physical exercise, several processes are activated in the body. It is a good way to relieve stress and increase well-being. Patients should always be advised to seek guidance from a professional so that they learn the correct techniques.

Yoga aims to bring the body, mind, and spirit into harmony. There are various forms of yoga; the various emphases may be on meditative elements, physical training, and breathing exercises.

Yoga stretches the muscles, strengthens the body, and mobilizes the joints. Breathing exercises improve lung capacity and the supply of oxygen to the organs; the meditative elements provide relaxation. The training focus can be determined by the individual. When starting off one needs a good instructor who will adapt the exercises to the needs of the individual participants. Yoga can be practiced at home and in almost all phases of the disease. It helps reduce stress and increase body awareness.

38.4.1 Advice Before Exercising for the First Time

Patients should speak openly with their trainer about their illness, existing limitations, and aspirations. Teammates should also be informed. Speaking openly at the beginning makes everyday sporting life easier. When others are aware that a teammate needs to go to the toilet more often, or that their stomach might make noises, they generally don't have a problem with it.

Training sessions must be individually adapted, but this can be done constructively when instruc-

tors know exactly who they are dealing with. In addition, where applicable, an initial internist or orthopedic examination should be advised in order to identify any circulatory regulation disorders or musculoskeletal malalignment. It also makes sense to discuss the exercise plan with the patient's IBD care team as they are familiar with the disease course and can provide advice.

It is very important, especially in the beginning, to put all sporting ambitions aside and set *realistic goals*. It is better to start small and build up gradually. That way success will come naturally. Setting one's expectations too high can soon lead to disappointment, and then there is the risk of giving the sport up again quickly. The initial physical condition plays a role: if you have never run before, in 6 months you still won't be able to finish a marathon, but you will be able to accomplish a personally defined distance in a better time.

For many people, being able to track one's personal progress is important in order to stay motivated. This is easy to do for sporting activities, e.g., use markers that are directly measurable such as lifting more weights, increasing the number of repetitions, higher speeds, or better body flexibility.

Another way to stay motivated is to record results in a "diary" or electronic medium. That way, patients can see their progress documented.

Progress can also be measured by a change in others' perception of the person: "You're looking very well" or decreasing consumption of medication.

38.5 Restrictions

Acute flare-up: The body needs time to recover. Patients should not participate in sports at all or only to a limited extent. In case of increased diarrhea, sufficient intake of fluids and minerals should be ensured, especially in summer.

Osteoporosis: Sports that place excessive strain on the skeletal system should be avoided. Swimming, cycling, or even isometric exercise may be recommended.

Joint pain: Sports that put pressure on the joints should be avoided. However, in general, exercise is a good thing because smooth movement normally reduces symptoms.

Overweight/poor nutritional status: Reduced, light training may be beneficial. Ensure sufficient intake of carbohydrates and minerals.

Stoma: Sports that put stress on the abdominal wall or where contact to the abdomen could occur through kicks and punches, or the impact of a ball should be avoided due to the risk of causing a rupture/hernia or prolapse (e.g., weight lifting, judo, handball, football).

After surgery: Immediately after surgery sport is off limits. The type of operation performed may affect the patient's fitness to perform sport. How much and which type of sport can be performed must be decided on an individual basis. After abdominal surgery, any stress on the abdominal muscles should be avoided in order to minimize the risk of rupturing the scar. Similarly, care should be taken to avoid any external force on the abdomen (e.g., through the impact of a ball).

Fistulas: In the case of perianal fistulas or abscesses, all forms of sport that put pressure on the perineum (e.g., cycling) should be avoided.

38.6 Summary Tips

Providing support and motivation in the patient care setting, all clinicians can also be a key point of contact for patients on the topic of sport.

What *tips* can be given to support patients?

- Show understanding; it often seems hard in everyday life to find time for sports and more exercise.
- Suggest looking for like-minded individuals to get together with.
- Emphasize the fun factor. Patients should choose a sport that gives them pleasure.
- Set realistic goals.
- Motivate patients to "stick with it."
- Start slowly; the rewards are not always immediate.

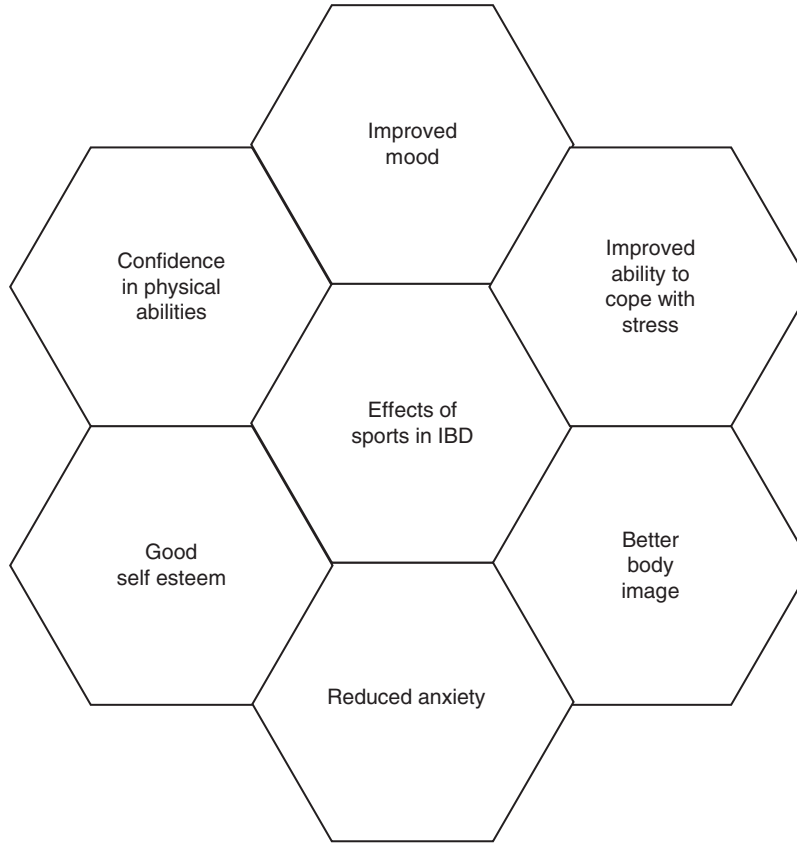

Fig. 38.1 Effects of Sports in IBD

- Stress the importance of rest phases.
- Discuss special sporting goals (high-performance sport) with the treating physician.

Arguments in favor of sport (Fig. 38.1):

- Increases quality of life
- Improves stress resistance
- Helps to stabilize normal weight
- Reduces inflammatory activity
- Acts as an antidepressant
- Prevents osteoporosis
- Reduces risk for colon cancer
- Improves mobility (important for patients with joint pain)
- Reduction of anti-inflammatory medication
- Strengthens the immune system

38.7 Summary

Various publications on the topic of IBD and sporting activities report not only a positive influence on patients' quality of life but also a preventive effect on the initial manifestation and progression of the disease. Patients with chronic inflammatory bowel diseases should be strongly encouraged to engage in a sporting activity. The choice of exercise/sport should be made on an individual basis depending on the patient's circumstances, personal preferences, and physical condition. When making this decision the patient's current disease status but also the long-term course of the IBD should be considered. Sport has a favorable influence on emotional and mental health, and people of all ages benefit from its positive effects. Sport is not an actual

treatment for chronic inflammatory bowel diseases, rather it belongs to the realm of complementary therapies. Nevertheless, the many positive effects of any kind of activities must be communicated to each patient and encouraged by the IBD nurse as well. In summary, it must be stated that, in this day and age, sporting activity should be part of the treatment concept for IBD patients.

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Sex and Intimacy

39

Charlotte Ford, Lucy Medcalf, and Alexandra Kent

Abstract

IBD affects patients of all ages, but onset is often during the first 2–3 decades of life. Consequently the diagnosis often coincides with when individuals are developing relationships and becoming sexually active. It is well-recognised that chronic diseases can impact on sexual function. Unfortunately this subject is rarely discussed with IBD patients in busy clinics, despite increasing evidence that it affects these patients. Various factors impact on sexual function including psychological factors (anxiety, depression and body image), disease activity and symptoms, medications and sexual health. Discussing concerns and problems with patients is important, and there are simple measures that can be made, and resources available, to help these patients remain in successful relationships.

39.1 Introduction

The need for intimacy and the development of relationships affects everyone, from birth to death. Beyond age-related laws, functioning as a sexual being is not restricted by age. IBD is most commonly diagnosed between the second and fourth decade, coinciding with when many people have their first sexual experiences and embark on new relationships. Symptoms of fatigue, diarrhoea, abdominal pain and incontinence alongside recognised complications such as surgery and fistulae can impact a patient in terms of body image, self-confidence and physical health. The European Crohn's and Colitis Organisation provide guidance that states: 'The psychosocial consequences and health related quality of life of patients should be taken into account in clinical practice at regular visits' (Caprilli et al. 2006). Barriers may impede discussion around relationships and intimacy: age, culture, language, time pressures of consultation, awareness, gender mismatch of doctor-patient, skills and confidence of medical professionals. Quality of life tools have few questions relating to intimacy, thereby reducing recognition of problems in relationships or sexual function. There is limited support available for patients, with this area of care being poorly advertised. It is important to be aware of the impact on patients and have open discussions with the patient, GP, gastroenterologist and IBD specialist nurse. Various factors specific to IBD impact on relationships and sexual function. These include an increased incidence of anxiety and depression, impaired body image, gastrointestinal symptoms, physical features of IBD (stomas, fistula, scars, etc.), medications and the effect of IBD on sexual health. This chapter highlights these areas and provides practical advice in ways to approach and/or treat these problems.

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39.2 Symptoms

Active disease may present in a number of ways including diarrhoea, abdominal pain, fatigue, arthralgia and weight loss. Disease flares can have a significant impact on libido, sexual attractiveness, level of sexual activity and enjoyment of sex (Moody et al. 1992). Studies have also shown correlation of disease activity with erectile and ejaculatory difficulties. Specific symptoms related to disease activity are discussed below.

39.2.1 Fatigue

Fatigue is an extremely common symptom in patients with IBD. Underlying mechanisms are multifactorial and may relate to active disease with a systemic inflammatory response, anaemia and/or depression. Fatigue correlates strongly with quality of life, and studies have shown it can impact on sexual motivation (Timmer et al. 2007a). Patients may report feeling too tired for sex or too tired to even discuss this with their partner.

Practical tips:

- *Patients should be encouraged to discuss symptoms such as fatigue with their GP and specialist team as this may prompt assessment of disease activity and vitamin/nutrient deficiencies.*
- *Patients may want to consider the timing of sex and planning this at times of day when they may be less tired.*
- *Instead of trying sexual intercourse, patients may consider other ways of being intimate with their partner,* e.g. *massage or sharing a bath.*

39.2.2 Abdominal Pain

Abdominal pain is commonly experienced and burdensome in patients with IBD (Sweeney et al. 2017). A substantial proportion of patients continue to experience abdominal pain even when their disease is in remission. Chronic abdominal pain can cause sexual inhibition and limit sexual pleasure.

Practical tips:

- *It may help for patients with chronic abdominal pain to consider alternative sexual positions.*
- *Persistent or unexplained abdominal pain should always prompt referral to specialty team for assessment of disease activity and consideration of alternative causes.*

39.2.3 Diarrhoea, Faecal Incontinence and Urgency

IBD is associated with unpredictable bowel movements, flatus, urgency, increased stool frequency and incontinence, particularly during active disease. For many patients a fear of incontinence or faecal urgency during sex can create anxiety and fear and consequently inhibit sexual motivation. Diarrhoea may make sexual activity difficult to plan and reduce frequency of sexual intercourse.

Practical tips:

- *Patients may find it helpful to empty their bowels before sexual intercourse to reduce anxiety around faecal incontinence.*
- *For some patients use of anti-motility agents* (e.g. *Imodium) may be appropriate when timing sexual intercourse, although its use should always be discussed with a gastroenterologist.*
- *Patients may enjoy non-penetrative sexual activity (masturbation, oral-vaginal, oral-penile or oral-anal).*
- *The use of a dental dam (a small plug of vinyl material which is placed over the vulva or anus) can provide a safer barrier to faecal leakage. This may ease concerns and additionally can reduce the risk of some STIs.*

39.2.4 Dyspareunia and Proctalgia (Pain in Rectum and Anus)

Females with IBD may experience dyspareunia (pain on intercourse). This is more common in those who have undergone previous abdominal or pelvic surgery leading to pelvic adhesions.

Adhesions can cause dyspareunia due to repositioning or 'fixing' of the pelvic organs. Proctalgia (rectal pain) is common in patients with IBD particularly in the context of active disease. Some women and men enjoy participating in anal intercourse which may exacerbate rectal or anal pain. Patients with perianal fistulae or anal fissures should be aware that anal intercourse can exacerbate these symptoms.

Practical tips:

- *The use of lubricating gels may assist patients with dyspareunia on penetrative sex.*
- *Patients should try different positions and/or may enjoy oral sex (oral-vaginal, oral-penile or oral-anal) when disease is active.*
- *While there is no evidence to suggest that anal sex may trigger a flare of IBD, in the context of active disease affecting the rectum (proctitis) or active perianal fistulae, anal intercourse should be strongly discouraged.*

39.3 Physical

39.3.1 Stomas

Stomas can have a negative impact on body image and self-consciousness (Cohen 1991). Patients may worry about how their long-term partner or any new partners will react to the stoma. During sexual activity patients may be fearful of leakage or odour.

Practical tips:

- *Colorectal stoma care nurses are a vital resource for discussing emotional, practical and physical aspects of living with a stoma. Patients should have contact details provided.*
- *Preoperative counselling by stoma nurses is fundamental. They can counsel and advise a patient and work together to choose the correct location for the stoma on the abdominal wall.*
- *Colorectal nurse specialists will be involved in stoma care and patient training post-operatively. They will ensure the dressings and bags used are suitable for each patient. Patients can be reassured that the bags are strongly adhesive and can withstand physical contact.*
- *Patients can empty bags or replace in advance of sexual activity.*
- *Clothing/pouch covers can be worn or sexual positions can be adapted until patients have developed the self-confidence to expose their stoma.*
- *Patients should be encouraged to make contact with patient support networks and charities, including Colostomy UK and Stomawise.*

39.3.2 Surgery and Post-operative Risks

Surgical procedures invariably cause pain, especially around wound sites, and patients are advised to avoid strenuous activity for ~8 weeks post-operatively. This can impact all physical activity including sexual function, but should resolve with time. Persistent abdominal pain may be due to adhesions, and scars can have a negative effect on body image and body confidence. Complications of pelvic surgery (including pouch formation) include impotence and reduced fecundity (Cornish et al. 2007).

Practical tips:

- *Patients should receive clear advice from surgeons or stoma nurses regarding when they can resume sexual activity post-operatively.*
- *Preoperative counselling should include complications of pouch surgery, including a discussion about whether delaying pouch formation until a later date is appropriate.*
- *Preoperative counselling should involve partners where possible.*
- *Ensure colorectal nurse specialists have details of resources for patients undergoing surgery.*
- *Adhesiolysis may be considered in extreme cases of abdominal pain related to adhesions, but only under the guidance of experienced IBD surgeons who are able to discuss the benefit of these procedures.*

39.3.3 Perianal Disease and Fistulising Disease

Fistulae can be embarrassing for patients and make sexual intercourse painful. Setons are surgical threads which may be left in a fistula to 'keep it open'. These may allow abscesses to drain and fistulae to heal. Fistulae and setons allow the passage of discharge which can be odorous or perceived as such. This may make patients feel 'smelly', unhygienic or less attractive to their partner. Patients with active perianal disease may experience additional pain and discomfort which limits sexual enjoyment.

Practical tips:

- *Patients should be encouraged to ask questions about their specific disease pattern (*e.g. *perianal disease) so that concerns may be explored.*
- *Procedures such as seton placement should be discussed fully including the risk/benefit and potential consequences for psychosexual elements of their disease.*
- *Patients with active perianal disease (abscesses, fistulae, setons) or anal stricturing should be strongly advised to avoid penetrative anal sex.*

39.3.4 Joint Disease

Patients with IBD may have associated arthropathies (disease of joints) or arthritis (inflammation of joints) which may impact on sexual satisfaction and sexual activity. Studies have identified a strong correlation between active joint disease and quality of life indices. Sexual activity may be limited by pain, joint stiffness, swelling, fatigue, decreased range of movement and decreased libido (Aguair et al. 2013).

Practical tips:

- *Patients with persistent joint symptoms should be investigated for associated arthropathies and ideally reviewed by a rheumatologist.*
- *Advice should be given regarding appropriate analgesia, exercises and/or physiotherapy.*

39.4 Psychosexual Consequences of IBD

The most consistently reported risk factor for sexual problems in IBD patients is co-existing mood disorders (O'Toole et al. 2014). Depression and anxiety are more common in IBD and may result from symptoms secondary to disease activity, side effects of medication (e.g. corticosteroids), concerns regarding cancer risks and surgery and stoma formation. Men who are depressed may struggle with erectile dysfunction (Timmer et al. 2007b). Smoking correlates with depression, and both have been associated with worsening disease activity in patients with Crohn's disease. Patients may struggle with body image due to physical changes, which may be a consequence of their disease or its treatment, e.g. changes in weight, scars and stomas. This may lead to self-consciousness, anxiety, sexual inhibition or patients feeling undesirable. Patients with a stoma may report fears related to intimacy and other aspects of sexuality and body image, including loss of sexual drive, ostomy-related odours, inability to perform sexually, feeling unattractive, dirty or smelly and losing control of bowel movements.

Practical tips:

- *Medical professionals should screen for depression in patients presenting with sexual dysfunction.*
- *Consideration should be given to medications such as antidepressants and drugs to treat anxiety.*
- *In some patients a referral for counselling may be appropriate.*

39.5 Medication

39.5.1 IBD Medications

IBD is treated with a variety of medications, and patients should be counselled on the risk of side effects before new drugs are prescribed. Patients are rarely warned about potential effects on sex-

ual function. Steroids can affect mood and lead to depression which may impact on libido and cause a loss of interest in sex. Long-term steroid use can result in changes to body habitus which can impact on body image. Enemas and suppositories administered per rectum are often prescribed in the evening, and their timing may need to be considered around sexual activity. Methotrexate has been associated with impotence in patients with rheumatoid arthritis, and erectile dysfunction has been reported with infliximab, adalimumab and thiopurines, although thought to be uncommon. Antidepressants have a significant sexual side effect profile with SSRIs associated with erectile and ejaculatory difficulties, orgasmic and arousal disorders. Opiates have an adverse effect on erections and can cause premature ejaculation.

Practical tips:

- *A detailed medication history is crucial to the history of a patient with sexual dysfunction with IBD.*
- *It should be recognised that non-adherence is common, particularly in young patients, and this may negatively impact on disease activity.*

39.5.2 Sildenafil

Sildenafil (Viagra) is a well-established treatment for erectile dysfunction. It is an effective for treatment in patients with erectile dysfunction following rectal excision for IBD. Sildenafil is safe to use in patients with IBD, and there are no recognised interactions with IBD medications, although gastrointestinal side effects have been reported.

39.6 Relationships

Rates of partnership among IBD patients appear to be similar to the general population, but patients with IBD report that they feel it has an adverse effect on relationship status. This is greater in patients who have undergone surgery for IBD. Active IBD can impact on the ability to socialise, interact and meet people, which can leave patients feeling socially isolated. Family planning for patients with IBD can also be challenging. Fears around infertility are common, concerns regarding congenital malformations and conferring genetic risk to offspring (Mountifield et al. 2009). Some studies have suggested these fears are higher in female patients, patients with Crohn's disease versus UC and in patients who have undergone previous resection. Voluntary childlessness has been shown to be more common in females with ulcerative colitis. This may prompt difficult discussions between patients and their partners.

Practical tips:

- *Patients should be well informed and supported by the medical team.*
- *Patients should be encouraged to discuss their concerns openly with their partner and may wish to attend appointments together.*
- *Crohn's and Colitis UK produce specific information for patients with IBD around relationships and intimacy.*

39.7 Sexual Health

Immunomodulators used in IBD are associated with an increased risk of infections, including corticosteroids, thiopurines, methotrexate, calcineurin inhibitors, anti-TNF agents and other biologics. For corticosteroids, a total daily dose equivalent to 20 mg of prednisolone for 2 weeks is associated with an increased risk of infections. Steroid use is commonly associated with fungal infections such as vaginal thrush (caused by the organism *Candida albicans*); this may cause vaginal discharge and irritation. It is possible for thrush to spread during sex, but it is not classified as an STI (sexually transmitted infection). Male partners do not need to receive treatment unless experiencing symptoms. However, in females experiencing recurrent infections, both sexual partners may need thrush treatment to prevent reinfection. Reinfection from a female partner is common.

39.7.1 Screening for Infection

Screening for opportunistic infections prior to initiating immunomodulator therapy in IBD patients is crucial. Guidelines published by the European Crohn's and Colitis Organisation recommend screening for infections including hepatitis B (Hep B), HIV, tuberculosis (TB) and varicella zoster virus (VZV). Genital herpes is a common infection caused by the herpes simplex virus (HSV). It causes painful blisters on the genitals and the surrounding areas. While screening for HSV infection is not necessary prior to initiation of immunomodulator therapy, oral antiviral therapy should be considered in patients with recurrent oral or genital HSV infection at commencement or arising during immunomodulator therapy. Regular gynaecologic screening for cervical cancer is strongly recommended for women with IBD, especially if treated with immunomodulators.

39.7.2 Vaccination

Hepatitis B (HBV) vaccination is recommended in all HBV anti-HBcAb seronegative patients with IBD. HPV is the most widespread of all sexually transmitted viruses; four out of five (80%) of the world's population will contract some type of the virus once in their life. HPV is associated with an increased risk of cervical cancer. In patients with IBD, routine prophylactic HPV (human papilloma virus) vaccination is recommended for females and males according to national guidelines to reduce the risk of cervical cancer.

39.7.3 Risk-Taking Behaviour

Young people with any chronic illness are three times more likely to engage in high risk behaviour than healthy peers. High-risk behaviour includes high number of sexual partners and sex without condom use. These behaviours confer risks of sexually transmitted infections, unplanned pregnancy plus additional psychological distress/morbidity. One study has suggested that young people with IBD are more likely to have high levels of alcohol misuse and illegal drug use compared to other chronic health conditions and healthy peers (Brooks et al. 2016).

39.7.4 Sexually Transmitted Diseases

There is no evidence to suggest that patients with IBD have a higher prevalence of sexually transmitted diseases. Patients often don't disclose their sexual history because they may feel embarrassed to do so or not feel it is important. Key risk factors for STIs include young age (less than 25 years at highest risk), people from or who have visited countries with higher rates of STIs, men who have sex with men (MSM), frequent partner changes or multiple concurrent partners, early-onset sexual activity, previous STI and concurrent alcohol or substance misuse. Anal sex has a higher risk of spreading STIs than many other types of sexual activity (including gonorrhoea, syphilitic, chlamydia and herpes simplex virus). The lining of the anus is thin and can easily be damaged, which makes it more vulnerable to infection. STIs including gonorrhoea, syphilis, chlamydia and herpes simplex virus can present with rectal symptoms. In patients with IBD, the symptoms of STI proctitis (e.g. anorectal discharge and bleeding) may be misdiagnosed as active IBD (Lamb et al. 2013).

Practical tips:

- *A full sexual history is crucial to identify patients at risk for STIs and these patients should be referred promptly to the GUM (genito-urinary medicine) clinic for diagnosis and treatment.*
- *Specialists in GUM medicine and sexual health should be consulted in cases of confirmed or suspected STI for advice on treatment, further screening (*e.g. *for co-infection including HIV, hepatitis B and C) and partner identification if appropriate.*
- *Patients should be encouraged to practice safe sex. Using condoms helps protect against STIs when having vaginal or anal sex.*
- *If using lubricants, water-based ones should be advised. Oil-based lubricants such as*

lotion and moisturiser can cause condoms to break or fail.

- *Persistent proctitis and symptoms of proctalgia should always prompt a full sexual history.*
- *When taking a sexual history, speaking to the patient alone may allow them to speak more openly about their symptoms.*

39.8 Summary

There is clear evidence that IBD can impact on relationships and sexual functions in a multitude of different ways. Failure to provide patients with an opportunity to discuss concerns openly can impact on the ability to form meaningful relationships. This should be seen as a failing in patient care. These problems should be broached, especially in young adults who are more likely to exhibit risk-taking behaviour.

This chapter provides information on the areas that impact on sexual function in IBD, including anxiety, depression, impaired body image, gastrointestinal symptoms, physical features of IBD (stomas, fistula, scars, etc.), medications and the effect of IBD on sexual health.

Opening conversations with patients regarding the impact of their disease on relationships and sexual functioning can be difficult. However, simply starting the conversation may help patients identify potential problems and prevent them feeling isolated. There are simple measures that can be made, and resources available, to help these patients remain in successful relationships. Patient information leaflets should be readily available in clinics directing them to further resources.

Additional Patient Resources

- Crohn's and Colitis UK: Sexual relationships and IBD (available Crohn's and colitis.org.uk)
- http://www.colostomyuk.org/
- NHS sexual health clinics: http://www.nhs.uk/NHSEngland/AboutNHSservices/sexual-health-services
- http://www.iasupport.org/
- http://www.stomawise.co.uk/
- www.facebook.com/groups/CCUKforum
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Patient Support Groups

40

Sanna Lönnfors and Marco Greco

Abstract

Inflammatory bowel diseases are often considered socially stigmatizing and embarrassing and can be uncomfortable for patients to talk about. Support from peers is therefore important, and its benefits have been shown in numerous studies. Patients can meet face-to-face or online in very different settings and participate in different activities together without even having to talk about the illness. Although patient support especially online can be a wonderful resource, it must be clear for patients that the information found online may not always be scientifically proven and that online forums must not replace medical care.

40.1 Introduction

Inflammatory bowel diseases (IBD) are often considered socially stigmatizing and embarrassing due to the nature of the symptoms they cause. People with IBD may consider it uncomfortable to talk about their talk about their illness with friends or even family member since they may not fully understand what an IBD patient is going through. According to an American study of the support-seeking behavior of people with different chronic illnesses, peer support seeking is highest among people with diseases regarded as embarrassing, stigmatizing, or disfiguring (Davison et al. 2000). Embarrassing symptoms such as increased stool frequency, potential incontinence, or (even) worse put IBD directly into this category. Due to these symptoms as well as the unpredictability of the disease, people often see it as stigmatizing (Frohlich 2014). Furthermore, although inflammatory bowel diseases per se may not be disfiguring illnesses, it may have a significant effect on a person's body image: for example, those IBD patients who have undergone a surgery, either stoma or nonstoma forming, experience more body image dissatisfaction (McDermott et al. 2014).

40.2 Benefits of Peer Support

The benefits of peer support for people with IBD have been showed in numerous studies. A Europe-wide online patient survey of almost 5000 people with IBD, carried out by European Federation of Crohn's and Ulcerative Colitis Associations (EFCCA), found out that the majority of those who had participated in patient association activities felt that the participation had made an improvement in their life as someone with IBD (Lönnfors et al. 2014). Summer camps for young people with IBD organized by EFCCA under the "E.S.C. Program" and its

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member associations internationally have also shown to be efficient. A small retrospective online survey for young people who participated in one or more summer camps showed that for most participants, the camp improved their confidence in dealing with the illness, their acceptance of the illness as well as overall quality of life. The majority of respondents found that meeting other young people with IBD was the most supportive part of the camp (Lönnfors and McCombie 2015). A pilot support program for teenage girls with IBD and their mothers resulted in the girls reporting a better quality of life and emotional and social functioning even when there was no change of IBD symptoms. The program consisted of monthly meetings which included (a community) dinner followed by an educational program (Szigethy et al. 2009).

For people with IBD, it is reassuring to know that they are not alone and that there are fellow patients to turn to for support, understanding, and encouragement (Coulson 2013). Indeed, the IBD-specific summer camp attendees named meeting other IBD patients as the most enjoyable experience of the camp (Lönnfors and McCombie 2015). As a consequence, people with IBD reported improvements in sense of control, confidence, and resilience as well as positive attitude (Coulson 2013). Furthermore, it is not only patients that need support from peers; their family members may also benefit from it. This may be especially true for parents of children with IBD as well as partners of IBD patient.

40.3 Peer Support Face-to-Face

Peer support can be found in different ways, and support groups can have very different styles and structures. First and foremost, there are the patient associations; these organize different events and activities where their members can come together. The first time that an IDB patient meets others in the same situation and socialize freely without fears of being stigmatized or misunderstood can be absolutely life changing. Meeting with other people with IBD does not necessarily have to revolve around talking about the illness but can consist of participating in different activities together (e.g., doctor-patient meetings, recreative activities, and self-help groups). In such get-togethers where everyone knows what it means to have IBD, talking about the illness may not even be necessary.

40.4 Peer Support Online

In these modern times, peer support groups do not have to be face-to-face meetings; in fact, meeting other people with IBD could be difficult for a patient in an active phase when symptoms may make leaving home quite challenging. Luckily, online technologies and especially the emergence of various social media platforms allow not only searching for information online without having to go to a library but also interacting with other people with IBD from within one's own home.

Online peer support can take many forms. It is possible to ask questions and share information and experiences in real time through various chat rooms, discussion forums, or social media communities. Meeting other people with IBD online can be done at any time of the day, and the possibility of speaking about one's illness anonymously may be attractive to those who would find going to physical meetings embarrassing or uncomfortable—or if IBD symptoms prevent going out.

According to Coulson (2013), the most common reasons for accessing an IBD online support community are finding others in a similar situation, learning new information about the condition, sharing experiences and information with others, seeking emotional support and advice, and asking questions about the condition. While sharing experiences and interacting with peers is of great value, healthcare practitioners should advise patients that online platforms may be full of commercial ads for various self-help products in addition to people promoting them. Patients should practice caution since these products as well as accompanying health tips may not be based on any evidence (Fortinsky et al. 2012). Many online platforms and websites may not go

through any editing or censoring, and the success stories may be very subjective.

An international online survey of 249 people living with IBD showed that participation in an online IBD community gave people access to knowledge about all aspects of living with IBD, which helped them to accept the illness and learn to manage it (Coulson 2013). The survey also showed that being a part of the online community helped people to see the illness in a more positive light and improved their subjective well-being. Thus, online communities may give people with IBD access to both informational and emotional support, which may not be available via traditional healthcare.

40.5 Potential Problems with Support Groups

Healthcare practitioners should, as a rule, help patients find support groups in their community since such groups can be an important resource for patients and their families. However, make sure the patients understand that advice heard in these groups must not replace medical care. Patients also need to be aware of warning signs that the group may be driven by someone's personal interests—an offer to cure an incurable illness such as IBD or advice to stop medical treatment and purchase an alternative product instead should be clear warning signs, especially when the alternative product is a not tested solution.

Online support groups may have their dark side as well; as reported by Coulson (2013), people with IBD tend to spend more time in online forums during a flare-up, which could mean that the negative sides of IBD are more present in the discussions. Reading such "horror stories" could be particularly scary for those recently diagnosed. Furthermore, the information shared on such online forums by patients may not always be of high quality or accuracy. Although it is advisable that healthcare personnel facilitates the access of people with IBD to peer support groups, they should also be aware and, if necessary, inform people with IBD of the potential problems in such groups.

Another common problem with support groups is the lack of quality in the scientific information provided. In addition, there is the risk that potential side effects are discussed only within the forum, without the affected patient sharing any adverse event or reaction through the proper channels. This is a loss of valuable information that would be otherwise available to the entire IBD community. Finally it must not be undervalued that there is a potential privacy issue, particularly when groups are not hosted by well established and official patients' support group.

40.6 Conclusion

Patients support groups are an important resource for people with IBD. Studies have shown that an improvement in an IBD patient's quality of life does not necessarily require an improvement in symptoms; just knowing that one is not alone may be a great help for someone with IBD. Healthcare professionals should be aware of this and facilitate access to such communities by supporting people with IBD in finding them.

Peer support can be given in different settings, but patient organizations play a major role in creating reliable support groups that are not driven by anyone's personal agendas. Policymakers should ensure that such organizations are supported in a way that allows them to cooperate and share.

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Part VII

Research

Clinical Studies

41

Susann Wienecke and Bianca Deparade-Berger

Abstract

Medical and surgical therapy for complicated IBD patients is often unsatisfactory, and the disease burden remains high despite optimal therapy. To optimise medical therapy, clinical research is necessary in order to develop new therapeutic options as well as diagnostic procedures to understand how diseases begin, progress and can be treated. This is where clinical research becomes an essential aspect of IBD care looked at from a wider perspective. It can be performed either by observation or prospective clinical trials. Clinical trials generate data on safety and efficacy of new drugs or procedures. Understanding different trial approaches is important for IBD nurses; many of whom are directly involved in the care of these patients. Any such nurse is the essential link between patients, physicians and sponsor. Clinical knowledge in IBD is critical not only to detect and document adverse events but also to meet the given endpoints of a clinical study. Study knowledge is important to help patients and colleagues navigate increasingly complex study designs which must appropriately address a wide variety of research questions. While clinical knowledge is addressed elsewhere in this manuscript, this chapter will address key designs, trial terminology and the application of:

- The four phases of clinical trials
- Study designs and key aspect of these such as endpoints
- The practicalities of setting up a clinical trial
- Ethical principles practically applied throughout a study, particularly in discussion with participants
- How studies deal with adverse events
- Individual roles in the study team

Abbreviations

AE	Adverse event
CRA	Clinical research associate
CRF	Case report form
CRO	Clinical research organisation
CSR	Clinical study report
CV	Curriculum vitae
DAL	Drug accountability log
EC	Ethics committee
eCRF	Electronic case report form

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EDC	Electronic data capture
EOS	End of study
EOT	End of therapy
ET	Early termination
eSR/SD	Electronic source record/Source data
EUDRA	European Union Drug Regulatory Authorities—EUDRA CT Nr.
FDA	Food and Drug Administration
GCP	Good clinical practice
IB	Investigator's brochure
IC	Informed consent
ICF	Informed consent form
ICH	International Conference on Harmonisation
IF	Investigator file
ISF	Investigator site file
NIS	Non-interventional study
NA/NK	Not applicable/Not known
ND	Not done, not documented
PI	Principal investigator
SAE	Serious adverse event
SAR	Serious adverse reaction
SD	Source data
SDV	Source data verification
SF	Screening failure
SC	Study site coordinator
SUAE	Serious unexpected adverse event
SUSAR	Suspected unexpected serious adverse reaction
TMF	Trial master file
WHO	World health organization

41.1 Introduction

Clinical trials are conducted in all areas of medicine and are the only way to reliably assess the efficacy, tolerability and safety of new active substances and previously approved medicinal products. Clinical research enables the development, improvement and marketing of therapies and medicines that can be used to help patients later on. Participants in therapy studies make an important contribution. The efficacy of a medicinal product can only be verified by sufficient documentary evidence.

41.2 The Three Phases before a Clinical Trial

41.2.1 The Quest for a Suitable Substance

At the beginning of any clinical trial is the quest for a substance for a new medicinal product. This demands much time and patience: a pharmaceutical company must examine on average 5000–10,000 substances to identify something suitable from which a new medicinal product can be created. The process can involve testing materials from plants, microorganisms or animal tissue, for example, but may also include substances that have been developed entirely from scratch.

41.2.2 Preclinical Development

Once a promising substance has been identified, it goes through a process known as preclinical development. This involves testing the substance for potential adverse effects, e.g. if it is toxic, causes disease or alters genes. To determine this, the substance is first tested in cell cultures and later in animal experiments. Only when this preclinical phase has been completed successfully and without raising concerns can the substance be tested on humans in phase I trials. In order to obtain approval for a clinical trial, the pharmaceutical company must submit the results of the preclinical trial to the competent authority.

41.2.3 The Different Approval Phases

Clinical trials are divided into phases I to IV (Fig. 41.1). In general, these phases are described as follows:

Phase I trials: healthy (voluntary) subjects, first-in-human study

- 10–40 participants
- Testing for tolerability and toxicity
- Evaluation of the respective pharmacokinetics—absorption, distribution, mechanism of action in the human body

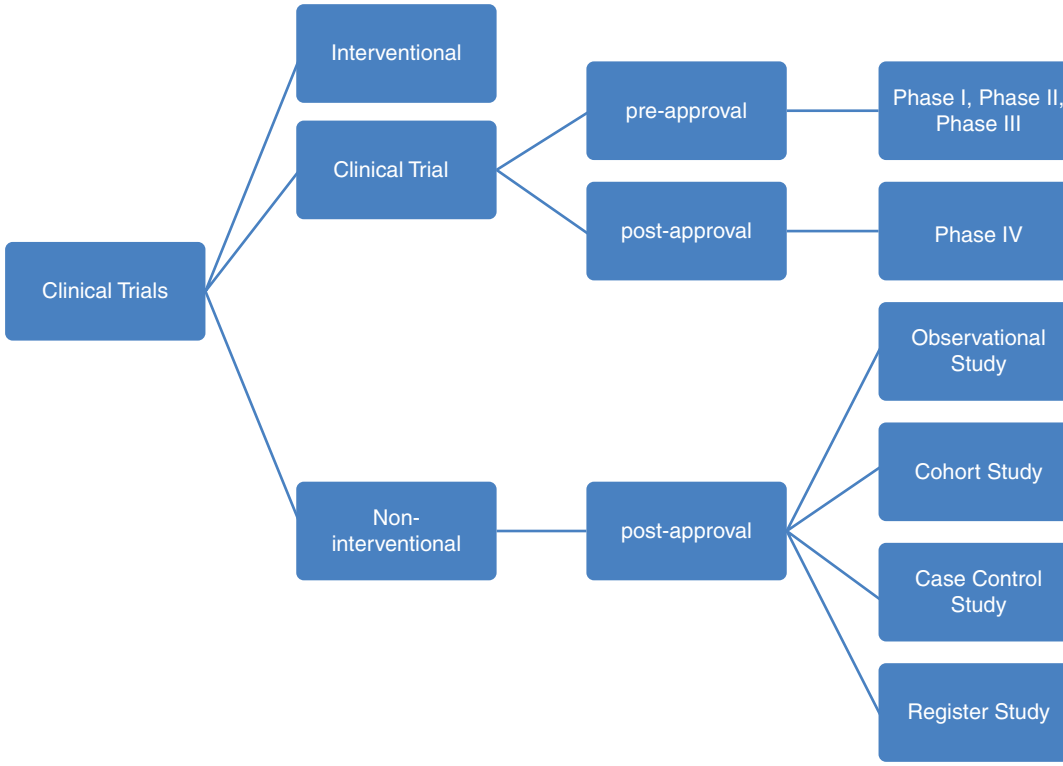

Fig. 41.1 The different study designs

- Definition of dosage form (tablet, inhaler, infusion)
- Determination of dosage

Phase II, IIb trials: smaller patient populations

- 50–100 patients
- Proof of concept
- Controlled study
- Evidence of efficacy compared to placebo or standard therapy
- Recording of side effects/interactive effects
- Risk-benefit analysis
- Finding the optimal dose
- Determining the safety/tolerability profile

Phase III trials: large patient populations

- 100–1000 patients
- Multicentre, controlled, randomised
- Detection of side effects/interactive effects
- Proof of efficacy and tolerability

Phase IV trials: cohort trial, observational, post-marketing trial

- Testing for approved indications with a large patient population
- Assessment of long-term tolerability
- Confirmation of risks/benefits
- Detection and characterisation of rare side effects
- Interaction with other drugs
  - The pharmaceutical company may only submit an application for authorisation of the drug after the study phases I–III have been completed successfully.

41.3 Study Design

41.3.1 Endpoints

▶ The *primary endpoint* is the aim of any particular clinical study or trial. This endpoint answers an important question for which

subjects are randomised and the trial is powered, for example, the proportion of patients in clinical remission after 8 weeks. *Secondary endpoints* are endpoints like mucosal healing, drop of calprotectin or quality of life that are analysed post hoc and may not have been the primary endpoint for which the trial was powered or randomised. A *clinical endpoint* refers to the target outcomes of the trial (induction of remission, drop in disease activity, mucosal healing, surgery rates, quality of life, laboratory abnormalities). A so-called non-inferiority study is designed to prove that one drug is not inferior to another in the treatment of a disease.

When an experiment involves a control group, the proportion of individuals who reach the clinical endpoint after an intervention is compared to the proportion of individuals in the control group who did not receive the intervention but still reached the same clinical endpoint.

41.3.2 Interventional Studies: Clinical Trials

In interventional studies, participants receive a type of intervention such as a new drug (or placebo) in order to evaluate it. In the drug development process, drugs are evaluated by carrying out interventional studies, known as clinical trials (depicted in Fig. 41.1).

41.3.3 Non-interventional Studies

- ▶ A non-interventional trial is a study in which findings resulting from persons' treatment with medicinal products are analysed using epidemiological methods; the treatment, including the diagnosis and monitoring, shall not follow a predetermined trial protocol but shall result exclusively from current medical practice.
- ▶ §4(23) AMG (German Medicinal Products Act)

- The treating physician is not given any study-specific guidelines regarding treatment such as when or whether a therapy is discontinued or altered or which dose and route of administration is selected. The treatment given reflects current clinical practice (standard of care). Once the decision to treat is made, the physician can decide if the patient can be included in the observational study. While all clinical trials must be approved by an ethics committee and approved by the appropriate authorities, non-interventional studies need only be reported to the competent authorities. However, consultation with an ethics committee is necessary before starting the study.

41.3.4 Open-Label Extension

Open-label extension (OLE) studies allow continued prescribing of unlicensed drugs after a randomised control trial (RCT) and can provide information on long-term safety and tolerability of new medication.

If the sponsor offers an OLE, participants are invited to enrol in an extension study. All participants in the extension study are given the study drug of which both they and the investigators are aware. The objective is primarily to gather information about safety and tolerability of the new drug in long-term, day-to-day use. An additional purpose is to make the (now proven) effective but as yet unlicensed drug available to participants who were randomised to placebo. Furthermore, prolonged observation may disclose adverse effects that were not observed in the randomised controlled study.

It may also be useful to demonstrate that participants randomised to receive the active treatment during the OLE phase achieved outcomes similar to those participants who received the drug from the beginning of the parent RCT.

41.3.5 Randomised Controlled Trials: Phases I, II, III, and IV

A randomised controlled trial (RCT) is a scientific experiment, testing usually a medical intervention against a comparator. The patients (or healthy vol-

unteers) participating in the trial are randomly allocated to either the group receiving the treatment under investigation or to a group receiving standard treatment (or placebo treatment) as the control. Randomisation minimises selection bias, and the different comparison groups allow the researchers to determine any effects of the treatment when compared with the no treatment (control) group, while other variables are kept constant. RCT has been proven to be the best study design to obtain a precise statement about a clearly defined study question.

41.3.6 Cohort Studies

A cohort study is a particular form of longitudinal, prospective observation that samples a cohort (a group of people who share a defining characteristic, typically who experienced a common event in a selected period, such as birth or graduation). The comparison group may be the general population from which the cohort is drawn. Cohort studies are useful for revealing causal relationships because exposure occurs before the disease event.

41.3.7 Case-Control Studies

A case-control study is a type of observational study (not randomised) in which two existing groups differing in outcome are identified and compared on the basis of some supposed causal attribute. They require fewer resources but provide less evidence for causal inference than a randomised controlled trial (Wikipedia). Case-control studies proceed in reverse order to cohort studies. The starting point is an existing event (exposed) and the investigator tries to figure out its cause in the past.

Example: Patients with and without infusion reactions are compared to determine whether those patients showing an allergic reaction did or did not get prophylactic medication.

41.3.8 Observational Studies

Observational studies are designed to collect information relating to the practical application of pharmaceuticals that have already been approved and registered.

- No control group, no study protocol—observation protocol only.
- Existing data material is reviewed and medical records studied.

41.4 Planning and Organisation

41.4.1 Suitability of a Trial Site

The suitability of a trial site is established by the sponsor/contract research organisation (CRO). This involves completing a so-called *feasibility questionnaire* to determine whether or not the site has the necessary study qualifications. The following information is necessary and, in particular, the trial group is described: How many participants does the trial group consist of? What professional qualifications and clinical trial expertise do the site personnel have? A CV as well as proof of continuing education and an overview of trials carried out so far is also presented. Particulars on the infrastructure of the site and the funding and/or materials and equipment available are also needed to assess the suitability of the site. After that, a personal *pre-study visit* takes place at the site. *Initiation* of the site only takes place after the selection process is over and the sponsor has given a positive vote.

41.4.2 Pre-study Phase

Requests are made to the individual trial sites by the study sponsor or by a contracted institute (Fig. 41.2).

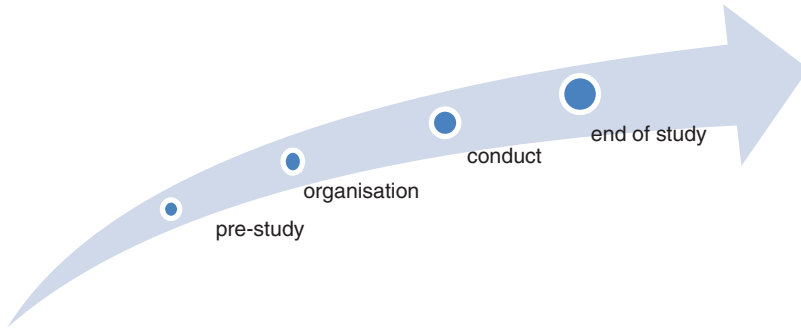

Fig. 41.2 The different phases of a clinical trial

- First inspection of the study protocol.
- Study is discussed with the team before being accepted – requirements, expectations, equipment/facilities.
- Decision to participate in or decline the study.

41.4.2.1 Feasibility

The *objective* is to find out whether a study centre has the required study qualifications.

- Is a patient cohort available?
- Capacity—personnel (qualifications, availability).
- Are other specialist departments (e.g. radiology, laboratory) available?
- Are there competing studies?
- Are the inclusion and exclusion criteria of patients feasible?

41.4.2.2 Pre-study Visit

The *objective* is to find out whether the study centre is suitable to participate in the clinical trial. This mostly takes place through personal contact at the centre.

- Qualifications of investigators/personnel
- Recruitment rate, recruitment strategy
- Study design, criteria
- Start and duration
- Technical and spatial conditions at the study site
- CV/study experience
- Documents for application for ethical approval
- Infrastructure

41.4.3 Planning

Who will assume which tasks: contract negotiations, talks with the required specialist disciplines, patient recruitment, documentation, drafting worksheets, completing training courses, laboratory work, diagnostics, etc (Fig. 41.2).

- Time calculation
- Material and human resources

41.4.4 Conduct

> ▶ Clinical studies should be conducted in accordance with the ethical principles that have their origins in the Declaration of Helsinki, and that are consistent with GCP and the applicable regulatory requirement(s). ICH/GCP E6

41.4.4.1 Initiation

All persons participating in the study must be involved in the initiation. The approval of the ethics committee and all official authorisations must be on hand at this point in time. The contract, which has been approved and signed by all specialist disciplines involved, should be on hand. Patient insurance is also required.

Procedure
Detailed discussion of the final protocol, study procedure, study design, objective, inclusion/exclusion criteria, concomitant therapy, study duration, recruitment phase, administration of the investigational product:

- Complete all necessary documents, logs.
- Discuss the legal and regulatory requirements, ICH-GCP.
- Determine if all equipment is complete: laboratory, necessary equipment, materials.
- Control the investigational product.
- Discuss the study documentation, especially the essential documents.
- Duties of the principal investigators (PI).
- Duties of the study nurse.
- IVRS, eCRF, access.
- Tasks of other departments such as laboratory, pharmacy and other specialist fields, e.g. radiology.

41.4.4.2 Prescreening/Screening

After a clinical study has been initiated at the study centre, the *prescreening process* can begin. The inclusion and exclusion criteria specified in the protocol are considered and, where appropriate, patients are identified in an existing database (such as in the outpatient department or on the hospital ward).

This way the PI can inform the subjects/patients in advance and give them enough time to think about participating in the trial. Once the informed consent form has been signed, the actual *screening process*, which follows from the "study procedures" section of the study protocol, can begin. A designated period of time during which this process can take place is also noted.

41.4.4.3 Randomisation

- The process of assigning trial subjects to treatment or control groups using an element of chance to determine the assignments in order to reduce bias.
- ICH-GCP 1.48 Randomisation

Randomisation is the day on which the patient is assigned to the investigational drug or placebo group. It is the first time the investigational drug is administered.

If all of the inclusion and exclusion criteria determined in the screening process are met, patients can be successfully randomised. From that point on, *visits* take place at intervals precisely defined in the study protocol, requiring patients to attend the study centre. The time window for these visits should be strictly adhered to as not doing so would constitute a protocol violation. If a patient is unable to attend, e.g. due to travel plans, the trial monitor must be informed in order to ensure that the study procedure is maintained and the subject continues to take his/her medication. The necessary examinations, blood samples, etc. are specified in the protocol.

41.4.4.4 Unscheduled Visits

During the course of the study, unexpected complications relating to the general condition of the study participant can always occur. If such complications occur outside the visit window, an *unscheduled visit* can be carried out. The procedure for such a visit is also precisely defined in the protocol.

41.4.5 End of Study/Termination of Study

Studies are sometimes terminated sooner than planned. There are several possible reasons for this:

- The investigational drug proved to be highly effective at an early stage. The study question has thus been answered very positively.
- Some participants experienced serious adverse events from which others ought to be protected.
- During the course of the study, the investigational drug was already found to be less effective than the comparator treatment.
- Patient withdraws consent (possible at any time).
- Accumulation of serious adverse events (SAEs) or unexpected AEs.

At the end of the study, a final monitoring visit known as the *close-out visit* takes place. This includes the following:

- Completion of the documentation/documents
- Transfer of all data
- Destruction of the investigational product
- Archiving of the study documents
- Deregistration of the study with the competent authority

▶ The sponsor shall notify the competent authority, the competent Federal authority, the competent ethics committee and the competent authorities of other Member States of the European Union and other Contracting States to the Agreement on the European Economic Area in whose territory the clinical trial is being conducted, of the end of the clinical trial within 90 days. If the clinical trial was terminated or suspended by the sponsor, notification shall be sent within 15 days, stating the reasons for the termination or suspension.

▶ GCP-V § 13(8)

A letter of confirmation of ethical approval is forwarded by the sponsor and filed in the ISF.

41.5 Decision to Participate in a Clinical Trial

41.5.1 Informed Consent Discussion

▶ In a **detailed discussion between the principal investigator and the potential study participant a**ll the details of the study should be addressed. The patient's questions should be clarified and an individual **risk-benefit analysis** should be performed. The research plan should be made transparent to the potential participant so that they can make their own decision. A one-to-one discussion with the study participant is the most effective way towards a better understanding of the contents of the informed consent discussion. The intention is to ensure that the study participant is in a position to recognize the importance and implications of the clinical trial. An important point that should be already clarified at this time is the **voluntary nature of participation.** The study participant can stop participating in the study at any time, and without giving any reasons, without incurring any disadvantage.

▶ GCP-V § 3(2)

41.5.2 Risk/Benefit

▶ Before a trial is initiated, foreseeable risks and inconveniences should be weighed against the anticipated benefits for the individual trial subject and society (Fig. 41.3). A trial should be initiated and continued only if the anticipated benefits justify the risks.

Important Note In all clinical trials, protecting the safety of the participants is the first priority.

41.6 AE/SAE

41.6.1 Adverse Event

▶ An adverse event is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment.

▶ ICH-GCP 1.2.

▶ During and following a subject's participation in a trial, the investigator/institution should ensure that adequate medical care is provided to a subject for any adverse events, including clinically significant laboratory values, related to the trial. The investigator/institution should inform a subject when medical care is needed for intercurrent illness(es) of which the investigator becomes aware.

▶ ICH-GCP 4.3.2

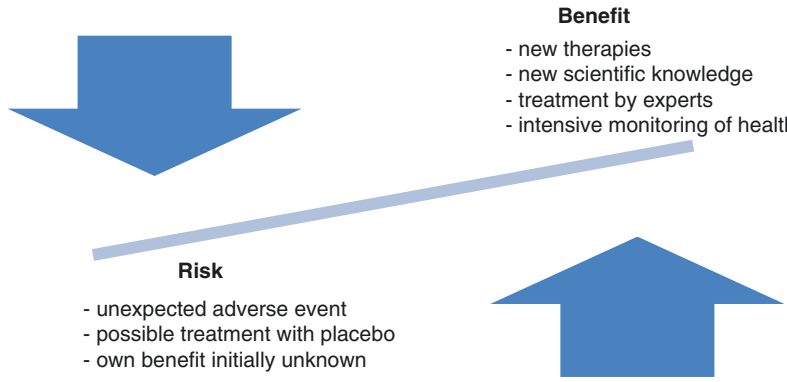

Fig. 41.3 Risks and Benefits of a clinical trial

For example, 4 weeks after taking the investigational drug for the first time, the patient suffers from headaches which was not known previously in the patient history. The precise point in time at which this symptom appeared for the first time, with what degree of intensity, whether a medication was taken and whether a possible connection to the study medication exists must be precisely documented by the investigator. Furthermore, the patient will be asked about this AE, and, where applicable, the course and/or outcome will be added giving a precise stop date.

41.6.2 SAE: Serious Adverse Event

Every adverse medical event which, independent of the dose:

- Leads to death
- Is life-threatening
- Requires the study participant to be admitted to hospital for treatment or prolongs their stay in hospital
- Results in permanent or significant injury/disability
- Represents a congenital defect or birth defect

Important!!!

- As soon as notification of an SAE reaches the study centre, it must be documented immediately and forwarded to the sponsor within 24 h.

The procedure by which the initial report must be sent, whether electronically, using the eCRF or by fax, is specific to the study and part of the respective study protocol.

It is important to bear in mind that this is the duty of the PI. If the PI is not on site, this task may be performed by the SI. However, the PI must be informed of this development without delay. All other information shall be sent to the sponsor as a follow-up report and/or on request.

41.7 Protection of Participant Safety

The obligation to protect the well-being of study participants does not end when a study receives Institutional Review Board (IRB) or Data and Safety Monitoring Board (DSMB) approval or when a participant signs the informed consent form. The interests of study participants must be safeguarded *at all times*, and by many entities, throughout a clinical research study. Ultimately, no single individual or institution can provide

complete protection for trial participants. A systematic plan must be followed for each trial to ensure that everyone involved understands and fulfils his or her responsibilities. Research team members who have adequate knowledge of clinical trials, statistics, the clinical disorder and the investigational product being studied must review the study data regularly to ensure that events are being properly interpreted and reported. Ongoing communication amongst all study staff is an essential part of ensuring participant safety.

41.8 Duties/Responsibilities of the Study Team (Fig. 41.4)

41.8.1 Principal Investigator/PI

▶ A person responsible for the conduct of the clinical trial at a trial site. If a trial is conducted by a team of individuals at a trial site, the investigator is the responsible leader of the team and may be called the principal investigator. See also Subinvestigator.

▶ ICH-GCP 1.34 Investigator

41.8.2 Subinvestigator (SI), Deputy

Any individual member of the clinical trial team designated and supervised by the investigator at a trial site to perform critical trial-related procedures and/or to make important trial-related decisions (e.g. associates, residents, research fellows).

Because the responsibilities of the investigator/subinvestigator are so wide-ranging, they are not specified here. For further information, please refer to the ICH-GCP guidelines (http://ichgcp.net/4-investigator).

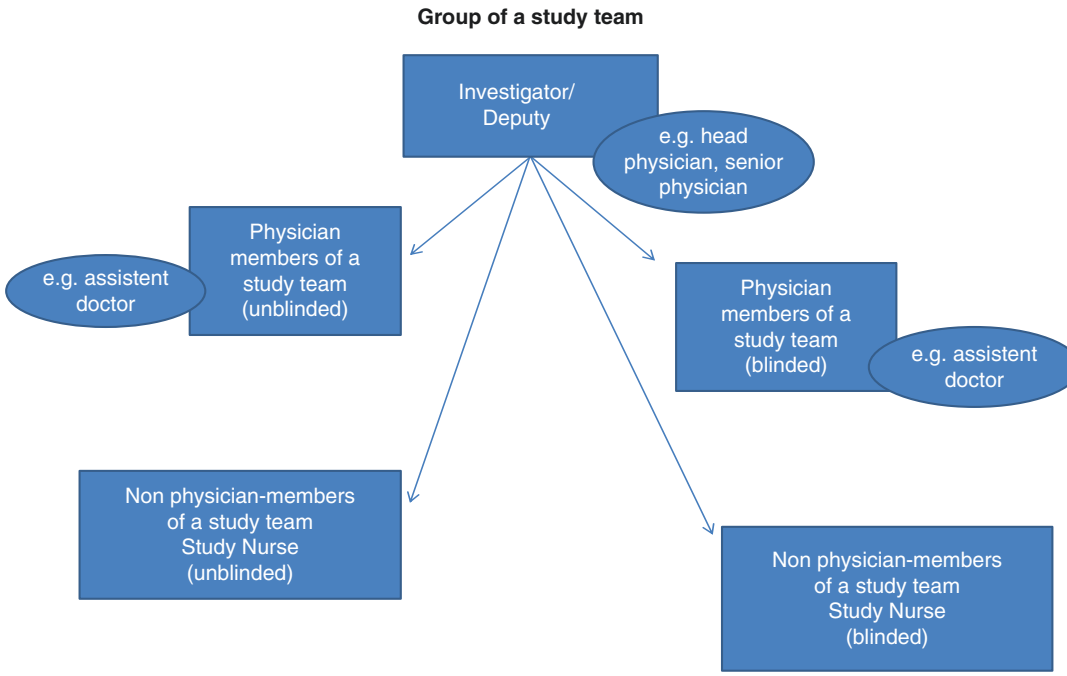

Fig. 41.4 The study team

41.8.3 Clinical Trial Nurse/Clinical Trial Coordinator

The clinical trial nurse plays an essential role in the day-to-day running of the trial and acts as an important link between the sponsor, CRO/monitors, investigators, other specialist departments and the trial subjects/patients. She/he works on site at the study centre and is jointly responsible for the organisation and administration of the daily routine of the study and for ensuring that the trial procedures conform to the protocol.

In order to be eligible to participate in further training to become a clinical trial nurse, a basic education in a medical field is beneficial. During this training, all relevant study-specific themes around clinical trials will be introduced and explained. After successful completion of the basic course and a final exam, a GCP certificate is awarded. This has to be "refreshed" every 2 years.

41.8.4 Clinical Monitor/Monitoring

The *clinical research associate* (*CRA*) is responsible for monitoring clinical trials. This includes checking that the trial is conducted in compliance with the principles of good clinical practice, the Declaration of Helsinki and the respective laws and provisions (amongst others, the law on medicinal products and the law on medical devices) of the individual countries in which the clinical trial is being conducted. The CRA is also responsible for controlling the conduct of the trial in accordance with the provisions of the investigational plan, the documentation of the respective documentation forms (case report form, CRF) and the use of the investigational drug.

The *CRA* acts as an important link between the study centre and the sponsor and contributes significantly to the success of a clinical trial. Consequently, good collaboration is highly beneficial.

Monitoring It is necessary to monitor the progress of the clinical trial as well as ensure that the trial is conducted, documented and reported in accordance with the investigational plan, the standard operating procedures (SOPs), GCP and the relevant legal requirements. Monitoring is the responsibility of the sponsor and consists of making periodic visits to the trial site. This involves, amongst other things, checking the informed consent of the trial subjects, ensuring that the treatment complies with the protocol and comparing the source data in the patient files with the entries in the data collection forms.

In collaboration with the trial site staff, the aim is to ensure that the conduct of the study complies with the investigational plan and GCP-ICH standards.

Monitoring visits must be announced in advance and an appointment arranged. This can be done by telephone or e-mail. An appointment is confirmed by means of a letter of confirmation which includes the following points:

- Trial title/protocol number
- Place and time
- State which person(s) will be available during the monitoring visit (when making the appointment, check that the principal investigator will be present)
- Monitor's name
- Description of what will be monitored—visit schedule
- State which documents must be made available, e.g. CRF, ISF, source data, computer workstation for the monitor

41.8.4.1 Monitor's Report

A report, which is drafted after each visit to a trial site and/or after every trial-related contact in accordance with the SOPs of the sponsor, is written by the monitor to the sponsor. Included in the final report are all open points which should be

dealt with by the time the next monitoring visit takes place at the latest. Both the letter of confirmation and the final monitoring report are to be filed in the ISF.

Beforehand, where applicable, the original files should be sourced, any open queries in the eCRF answered, and any open points dealt with. During the monitoring visit, it is primarily the clinical trial nurse who provides assistance to the monitor. The trial nurse and the investigator are available to answer questions, document any ambiguities and make copies of any documents that might be of importance to the monitor.

41.9 Storage/Archiving

Storage All study documents should be stored in lockable, fireproof cabinets. It is also recommended that only members of the study team have access to those rooms.

Archiving relates to all essential clinical trial documents (investigator site file according to ICH-GCP, Chapter 8) (1) but also to the patients' medical files and, where applicable, study-specific patient records (source data, ICH-GCP, 1.5.1 and 1.5.2), which must be archived by the medical institution.

Pursuant to GCP-V §13, the responsibility for archiving lies with the sponsor who may delegate some of these tasks to the investigator. Additionally, depending on the setup of the trial, the law on medical devices and the law on radiation protection must also be taken into account since the retention periods stipulated by the legislator vary.

Documents to be archived at the trial site:

- Investigator study file (ISF), outsourced sections, identification lists of the participants, informed consent declarations (originals)
- Study-specific documents (consultation notes, status reports, correspondence, newsletters)
- Study-specific patient files, source data, laboratory reports
- Participant identification lists
- Informed consent declarations (originals)
- Completed CRFs and queries (copies) or burned and checked CDs with patient-specific data

41.9.1 Retention Periods

Important Note In general, the sponsor specifies the retention period because if the drug is approved, it is the sponsor who is responsible for extending the retention period to 15 years. In addition, the study protocol or the clinical trial agreement can provide information on this.

41.9.1.1 Archiving Time Point

1. All patients have completed all visits and the follow-up phase has ended.
2. The CRF is complete, all queries have been processed and the databank closed.
3. A close-out visit has taken place.
4. The sponsor has given approval for archiving.

In addition, it is recommended that an SOP be written for the archiving process. The location at which the trial documents are stored should also be noted in the SOP. The contact details for the archive are to be communicated to the sponsor as well. If the location changes during this time, the sponsor must be informed.

41.10 Conclusion

In the age of evidence-based medicine with increasing expectations and hurdles for clinical studies, it is becoming more and more difficult to perform high-quality clinical studies as required by the authorisation agencies to investigate and finally approve new therapeutic options. Thus, the IBD research nurse is the most important link between patients, physicians and sponsor. Their broad knowledge in IBD is critical not only to detect and document adverse events but also to meet the given endpoints of a clinical study.

Nursing Research

42

Lars-Petter Jelsness-Jørgensen

Abstract

Nurses play an increasingly active role in clinical research in IBD. By reviewing existing literature on the topic, this chapter provides a brief overview of some main concepts related to research in nursing. In addition, the chapter provides some general advice in relation to implementing evidence-based practice, as well as carrying out independent research.

42.1 Introduction: Research in Nursing

Nurses play an increasingly important role in the follow-up of IBD patients. This makes nurses perfectly situated in order to develop and improve clinical practice, not least through their knowledge of the patients' problems or concerns.

Research and science have an essential place in our society. The fruits of this research include, among other things, longer life expectancy and better material as well as technological conditions than ever before in history. When we conduct research, we use our senses and abilities to reason in the same way as in everyday life, but in a more systematic manner. The ultimate goal is of course to refine or expand on existing knowledge (Polit and Beck 2017).

According to Denise Polit and Cheryl Beck, the term *nursing research* is defined as: "a systematic inquiry designed to develop trustworthy evidence about issues of importance to the nursing profession, including nursing practice, education, administration, and informatics" (Polit and Beck 2017). This definition is, however, too narrow to encompass the breadth of research that nurses currently are involved in. Nurses are not only involved in research within their line of work/specialty but also increasingly involved in interdisciplinary research; some examples are connecting genetics with health interventions or clinical medicine with patient-reported outcomes. Consequently, the term clinical nursing research or research by nurses may be more accurate to describe the focus and activities of nurses involved in IBD research.

In a historical context, there is a long tradition of systematically collecting and interpreting data within the nursing profession. An obvious example is the work that Florence Nightingale performed during the Crimean War, where she developed a special interest related to the importance of environmental factors on physical and emotional health (Polit and Beck 2017). In this sense, Florence Nightingale was not only one of

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the founders of the nursing profession but also an epidemiologist. Since these early stages, research in nursing has gone through various developmental phases, and, as the literature points out, things like increased visibility, enhanced interdisciplinary collaboration, and a focus on evidence-based practice will be important priorities in the coming years (Polit and Beck 2017). The aim of this chapter is to provide insight into aspects of evidence-based practice, research from idea to publication, critical appraisal, and IBD-related research by nurses.

42.2 Methods

A review of existing literature forms the basis for the chapter. The following databases were used to search literature relevant to nursing research in IBD: PubMed, EBSCO, CINAHL, and PsycINFO.

42.2.1 Evidence-Based Practice

The most common definition of evidence-based practice (EBP) comes from Dr. David Sackett. EBP is "the conscientious, explicit and judicious use of current best evidence in making decisions about the care of the individual patient. It means integrating individual clinical expertise with the best available external clinical evidence from systematic research" (Sackett et al. 1996). More specific, evidence-based practice should integrate the following three elements:

- Best scientific evidence
- Patient preferences
- Clinical experience

Besides research, practical knowledge is a cornerstone of nursing. This kind of knowledge is learned through reflexive processes where practitioners learn from experience (Abrandt Dahlgren et al. 2004). Often such knowledge is described as tacit knowledge, clinical expertise, or intuition. On the other hand, clinical expertise requires that nurses are able to find, evaluate, and use knowledge based on research in the follow-up of individual patients. Although Sackett clearly asserted the need for evidence-based medicine, the concept has also been criticized (Sackett and Rosenberg 1995). Not least, it has been pointed out that this is already the way patient care is handled. However, as Sackett argues, findings have highlighted that patient values rarely are included in clinical decision-making (Sackett et al. 1996). In recent years, however, there has been a gradual evolution from typical paternalistic healthcare services, where healthcare personnel decides what is the best for each patient, to active patient participation in decision-making. This is known as "shared decision-making" (Elwyn et al. 2016). So how can nurses go forward step by step to work knowledge-based? Table 42.1 is based on the recommendation of Melnyk et al. (2010).

When looking at the steps in evidence-based practice, there are some basic conditions that must be present in order to foster this process. Very basic is the ability to question both existing clinical practice and to be curious about, e.g., various patient phenomena. Potential questions might include: Does IBD nursing have any effect on patient adherence to treatment? Or does IBD nurse follow-up reduce the risk of disease recurrence compared to standard care? The answers to these examples will be important, not only for nurses but also for patients, doctors, and administrators.

The next step involves formulating a focused and explicit question related to what the nurse wants to focus on. Since many may experience this process as difficult, the PICOT structure can be helpful in this context. PICOT take into

Table 42.1 The seven steps of evidence-based practice

Step 0: Cultivate a spirit of inquiry
Step 1: Ask clinical questions in PICOT format
Step 2: Search for the best evidence
Step 3: Critically appraise the evidence
Step 4: Integrate the evidence with clinical expertise and patient preferences and values
Step 5: Evaluate the outcomes of the practice decisions or changes based on evidence
Step 6: Disseminate EBP results

account patient population of interest (P), intervention or area of interest (I), comparison intervention or group (C), outcome (O), and time (T) (Melnyk et al. 2010). The various steps are exemplified below:

- P = What kind of patient or patient group does the question concern?
- I = What type of intervention is in focus? The term intervention should be interpreted broadly and may, for example, include advice to patients, preventive measures, or actions in daily practice.
- C = Should the intervention be compared to another? Sometimes we want to compare the practices we have today with another measure.
- O = Which outcomes or endpoints are of interest? What is the aim of the intervention?
- T = What kind of time frame?

However, it is not always necessary to use all these stages. The application of these different stages is dependent on things as research design and outcome of interest. For example, if the target population is IBD patients who have undergone stoma surgery (P) and the aim is to investigate postoperative level of depression (O), only P and O will be necessary to use. On the other hand, if the interest is in whether IBD patients (P), using combotherapy (I) compared to monotherapy (C), have an increased risk of lymphoma (O), both P, I, C, and O are used.

Once a clear question has been formulated, the next step in the EBP process is the literature search. To conduct a literature search, it may be sensible to involve a librarian. They often have long experience in searching different databases and are generally happy to help. If there is no access to a librarian, databases such as PubMed may be used to do an independent literature search. An important principle in evidence-based practice is to use summarized research. Researchers at McMaster University in Canada have made a pyramid consisting of six levels of knowledge sources (Dicenso et al. 2009). This is commonly known as the S-pyramid (Fig. 42.1).

The next step in EVP process is to critically evaluate the literature found. Such a critical evaluation is essential even though the literature has been peer reviewed, particularly in order to consider the validity, methodological quality, results,

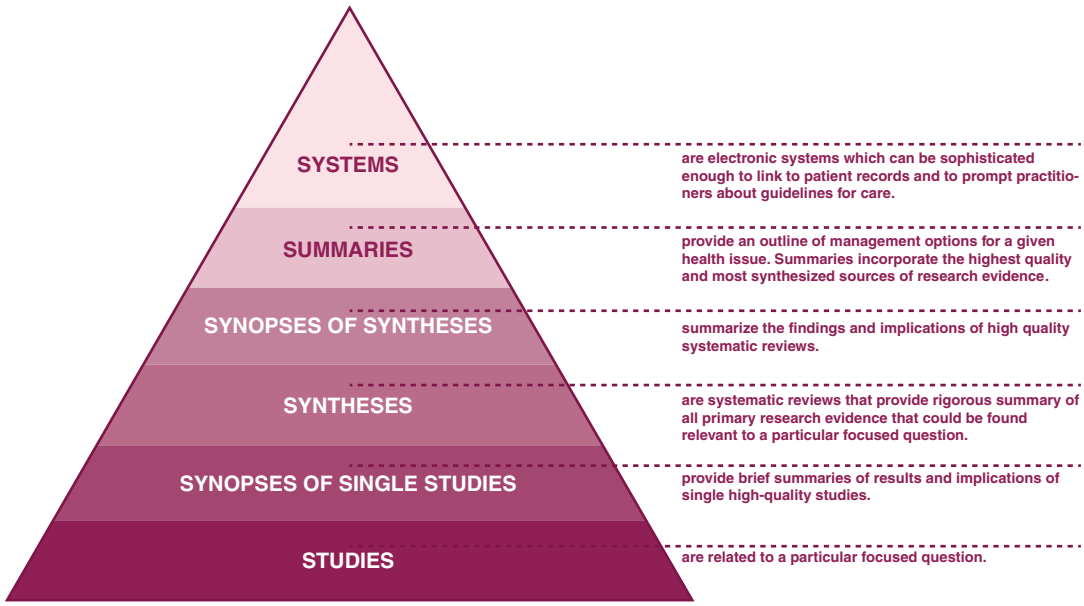

Fig. 42.1 The S-Pyramid (By permission of The National Collaborating Centre for Methods and Tools. The 6S pyramid. Retrieved from: http://www.nccmt.ca/capacity-development/6s-search-pyramid)

and transferability. Additionally, it may be necessary to practice how to critically evaluate research papers. A Norwegian study, for instance, found a considerable variation in how students read a scientific article. Some students only read the abstract, others merely the conclusion (Jelsness-Jorgensen 2015). Consequently, many may not be able to assess whether the method is appropriate to answer the research question or if the results are justified based on the methods. Although this process may seem complicated, it developed tools that can be of help. One example is the Critical Appraisal Skills Programme (CASP). On the websites of CASP, checklists specifically developed for qualitative and quantitative research designs can be freely downloaded.

Table: Suggestion to exemplify with one of the CASP tools in the text, e.g., http://media.wix.com/ugd/dded87_25658615020e427da194a325e7773d42.pdf

Table 42.2 display examples on what kind of design that is corresponding to each of the research questions. This short overview may be helpful when reading and assessing scientific papers.

The successful implementation of EBP is dependent on a number of variables. Individual experiences, attitudes, and professional, organizational, and workplace factors may all act as barriers to the translation of empirical knowledge into practice. Williams et al. (2015) found, in a review of the literature, that the following factors were of significant importance for the implementation of EBP in nursing care:

- Workload
- Other staff/management not supportive of EBP
- Lack of resources
- Lack of authority to change practice
- Workplace culture resistant to change

Some of these factors are obviously also crucial in the research process. Indeed, the support from colleagues and the academic community is absolutely essential for the success of a clinical research project.

Table 42.2 Core questions with associated designs

Core questions		Preferred design
How does it feel?	Experiences and attitudes	Qualitative methods
How many?	Prevalence	Cross-sectional studies
What is the development over time?	Prognosis	Cohort studies
Why do some get sick, while others remain healthy?	Cause (etiology)	Cohort studies Case-control studies
What can be done?	Effect of interventions (treatment, prevention, rehabilitation)	Randomized controlled trials (RCTs)

42.3 Undertaking Research: From Idea to Publication

To practice reading scientific papers can provide valuable knowledge when doing independent research. Some of the essential parts of EBP are also important when planning research. For example, a literature search will always be essential to get a better picture of what publications exist in the field to be studied. It is not necessary to research findings that have been (already) described several times in the literature. Moreover, using sound scientific methods to address relevant research questions is critical. A few years ago the Norwegian Research Council appointed a panel of international scientific experts to review the various research environments in Norway. Among those with the poorest evaluation was nursing research. These experts named the main problems as small research environments that have little ability to define clear questions, using partly weak scientific methods and producing unoriginal research without interest to anyone. What makes this especially bad, according to the research group, is a politically created expectation that employees should be using these weak research results in the teaching of their own students (Translated from news coverage in the Norwegian Newspaper

Aftenposten: http://www.aftenposten.no/norge/Sterk-kritikk-av-norske-forskningsmiljoer-174260b.html).

It is therefore essential to constantly strive toward improving the quality of research in and among nurses. An important step is to network with other nurses, allied health professionals, and physicians. Networking can result in multicenter data collection, which does not need to increase the complexity but may increase quality. So how should you proceed in the research process?

42.3.1 Idea/Hypothesis/Question

Ideas can arise from clinical experience as well as something that has been observed or read (about). These ideas should then be formulated in such a way that they can be examined in a research project. Roughly speaking, it is possible to distinguish between three different kinds of research questions. These include questions that want to explore something, questions that will describe something, and questions that want to explain something (causality). Independent of what kind of question that may be applicable to each specific project, the question must be clear and specific (Polit and Beck 2017). It is important to clarify:

- What are we interested in? (e.g., a phenomena, a process, or treatment)
- Who are we interested in? (e.g., outpatients, patients undergoing surgery, patients receiving home care nursing)

A research problem may also include a primary aim and up to several secondary aims. In cases where we want to test something, it is natural to start with a hypothesis. Hypotheses are tested through statistical analysis. According to Polit and Beck (2017), a hypothesis "is a prediction, almost always involving a predicted relationship between two or more variables. Qualitative researchers do not have formal hypotheses."

Discuss ideas with someone who has research experience. Finding a skilled supervisor is essential in order for the research process to be as good as possible. The supervisor will also provide experience in methodology, analysis, and publication.

42.3.2 Literature Search/Review

It is of course possible to search the literature both unsystematically and systematically. Anyway, it is recommended that you take time to learn the steps in a literature search. Once again, a librarian may be helpful. As described under EBP is important to start with a specific search strategy. If the goal is to make a systematic review of the literature, specific guidelines may be helpful. These are easy to obtain by searching the Internet, but Harvard University Library provides a nice overview: http://guides.library.harvard.edu/meta-analysis/guides.

42.3.3 Methods and Design

An important step is to determine which method is suitable to answer the research question. Table 42.3 presents some of the basic differences between some of the most commonly used research designs.

42.3.4 Ethics and Formal Approval

All research must be assessed to see if it involves ethical challenges. Sometimes it can be difficult to see this clearly, and it is therefore very important to seek formal approval before the project is initiated. This is primarily to avoid patient harm. Although nurses are not studying the effect of drugs, there may be sensitive information that needs to be handled in the proper manner. In addition, data must be stored securely, so that patient identification and sensitive health information are protected.

42.3.5 Analysis/Statistics and Interpretation

There are many different computer programs that can be used in the statistical analysis, such as the

Table 42.3 Description of commonly used research designs

Design	Description
Cross-sectional	Data collected at one point in time. This design is suitable if one wishes to investigate a phenomenon at a given time
Cohort design	A defined group of people (a cohort) is followed over time to study various outcomes
Randomized controlled trial	Experimental test of an intervention. This should include a random allocation to either treatment or placebo to avoid bias. In some cases (such as in pharmacological studies), both researchers and participants are blinded
Case-control study	Compares "cases" with matched controls (e.g., IBD patients to matched controls without IBD)
Retrospective	Looking back in time to try and establish factors that might explain the current outcome (e.g., factors associated with lung cancer)
Qualitative	In-depth investigation of a phenomena, e.g., through the collection of narratives

Statistical Package for the Social Sciences (SPSS) (http://www-03.ibm.com/software/products/en/spss-statistics). There are also tools that can help to sort qualitative data, e.g., NVivo (http://www.qsrinternational.com/nvivo-product). Generally speaking, the individual hospital or academic institution may have access to such tools. It is consequently advisable to consult with the individual institutions to see what is/would be recommended.

42.3.6 Publication

Publication of research results is a very important part of the research process. Scientists have a moral obligation to share their results with others, even when research results are different than expected. The most common would be to publish in a scientific journal. The selection of journals depends on several things, such as the impact factor, the journal's focus, and whom the message is directed to. Criteria have also been established related to co-authorship, which is vital to know before you send the article for review (http://www.icmje.org/recommendations/browse/roles-and-responsibilities/defining-the-role-of-authors-and-contributors.html).

42.3.7 Dissemination

Making research visible has become more and more important in recent years. This dissemination no longer takes place only in traditional scientific settings, such as scientific journals, popular science papers, or conference presentations. Social media, e.g., Twitter, Facebook, or ResearchGate, play an increasingly important role in these strategies. ResearchGate, for example, is a social network for academics to list their publications and interact with each other. In addition to these networks, creating research blogs has also become quite common.

Patient participation in research has become increasingly recognized as important. Patient engagement may lead to research findings that are more pertinent to patients' concerns and dilemmas (Domecq et al. 2014). It is now almost mandatory to involve patients at some level in the research process. Patients can potentially provide valuable insights in all stages of the research process, from the idea, design, methods, analysis, interpretation, and dissemination.

42.4 Nursing Research in IBD

It would not be possible in a single chapter to outline all of the research done by nurses in IBD, but until now the thematic focus seems to concentrate on (a) the role of the IBD nurse; (b) various patient phenomena and symptoms, such as pain, fatigue, health-related quality of life, and coping; and (c) intervention research (Jelsness-Jorgensen et al. 2011a, b, c, 2012a, b; Bager et al. 2011, 2012; Czuber-Dochan et al. 2013a, b, 2014a, b; Younge and Norton 2007; Opheim et al. 2014a, b; Coenen et al. 2017; Lindberg et al. 2013; Oxelmark et al. 2007, 2016; Jaghult et al. 2007, 2011; Dibley and Norton 2013; Norton and Dibley 2013; Woodward et al. 2016).

Since 2007 the N-ECCO (Nurses-European Crohn's & Colitis Organisation) has been an active member of the ECCO (European Crohn's

& Colitis Organisation). The overall aim has been to provide nurse education and the opportunity for nurses to network internationally (O'Connor et al. 2013). The N-ECCO consensus statements on the European nursing roles in caring for patients with Crohn's disease or ulcerative colitis highlighted that research should be viewed as an inherent part of the advanced IBD nursing role (O'Connor et al. 2013). Although research is a recommended activity in IBD nursing, limited time seem to be dedicated to it. The lack of dedicated time is also viewed as one of the most important barriers for IBD nurses to get involved in research (O'Connor et al. 2013). Since the goal has to be to increase the proportion of nurses involved in IBD research, it is essential that managers integrate research in role descriptions and job plans. Indeed, the N-ECCO consensus statement 4B also highlighted that "further research is needed to assess the impact of IBD specialist nursing interventions. To achieve this, the Advanced IBD Nurse needs to participate in and conduct research activities appropriate to their role" (O'Connor et al. 2013).

As a direct result of the N-ECCO consensus statements, the N-ECCO research network forum was established in 2014 (https://www.ecco-ibd.eu/education/n-ecco-research-forum.html). The aims of the first meeting were to encourage networking between nurses across Europe and internationally, to share development, to enable nurses to design and collaborate on research studies, and to mentor new nurses in research within IBD. Since its first development, the N-ECCO research network has had annual meetings in connection with the ECCO conference, in order to facilitate methodological discussions and help with practical aspects of undertaking nursing research within IBD. The main agenda is to:

- Support nursing research in IBD.
- Generate new knowledge and evidence.
- Encourage Europe-wide/international networking.
- Provide inspiration, collaboration, and opportunities.
- Enhance awareness of IBD nursing within ECCO.
- Narrow the gap between academic and clinical IBD care.
- Offer linkage between those doing research and those wishing to do so.
- Develop a cadre of academic clinical IBD nurses.

In addition to the factors already mentioned, an important goal of the research network was to identify central research priorities within IBD nursing. Therefore, a multinational research panel consisting of IBD nurse researchers from the United Kingdom, Denmark, Ireland, and Norway, in cooperation with the ECCO, aimed to establish topics to guide future IBD nursing research across Europe. The top five research priorities were interventions to improve self-management of IBD; interventions for symptoms of frequency, urgency, and incontinence; the role of the IBD nurse in improving patient outcomes and quality of life; interventions to improve IBD fatigue; and care pathways to optimize clinical outcomes and patient satisfaction (Dibley et al. 2017). In future research efforts, nurse researchers should involve patients in every step of the research process, in order to focus on aspects of importance to the patients and not merely the healthcare professionals.

42.5 Summary

Research is fundamentally important in bringing about new knowledge that can improve clinical practice, patient follow-up, and care. This requires the ability to ask questions, to seek documentation, and to systematize knowledge. This chapter has emphasized simple steps that can be used both if you want to establish independent research projects, as well as systems to help the individual researcher to keep a critical eye on all phases of their own research process as well as existing research.

42.6 Conclusions

Nurses are perfectly situated in order to contribute to research, both as independent researchers and as project collaborators. However, such an

involvement requires both self-interest, dedication, necessary skills, and a working environment that supports the focus on clinical research. The proportion of chronically ill is estimated to increase over the years to come, and it is therefore essential to strengthen multidisciplinary research that can facilitate good resource utilization, optimal patient follow-up, coping, and symptom control, as well as person-centered healthcare.

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Part VIII

IBD Nursing

Training and Education

43

Veronica Hall

Abstract

There is a European mandate for education and training in inflammatory bowel disease (IBD), endorsed by United Kingdom IBD Standards (IBD Standards Group, Quality Care: Service Standards for the healthcare of people who have Inflammatory Bowel Disease (IBD), 2013) and NECCO (O'Connor et al., J Crohn's Colitis 7(9):744–764, 2013) who support the premise that nurses in an IBD role need to have basic and specialist IBD knowledge. Due to the variation in boundaries and scope of practice of those involved in IBD patient care the type of training and education needs to be tailored to suit the needs of both the service and the professional. Whilst some countries such as the Netherlands have very specific academic courses and qualifications for IBD nurses, most countries are still in varying stages of development. Therefore a hybrid of training approaches can be useful. This chapter refers to UK resources due to the location and expertise of the author. However the focus includes principles and practicalities of delivering training that are fit for purpose and could be transferrable to the training and development needs of a specific service or individual. It will include:

- In house, on the job training utilizing competencies and supervised practice.
- Formal academic training at bachelor's and Master's level including the advantages of e-learning
- Professional bodies role in education and training
- Corporate sponsorship learning opportunities
- Portfolio development

43.1 Introduction

It is evident that a variety of healthcare professionals, operating at differing levels of autonomy are involved in the delivery of care to people with IBD. It is acknowledged that there is a European mandate to deliver education and training in IBD; there is no consensus on the most appropriate way to deliver it to practitioners whether in Europe or elsewhere. There is also no right or wrong way but it has to be fit for purpose and tailored to the needs of a particular service. It is expected that the reader may adopt an approach which is suitable for their situation and setting from the variety of approaches that are exemplified here.

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43.1.1 Competency Based Training

The UK Nursing and Midwifery Council (NMC) (Nursing and Midwifery Council (NMC) 2017) uses competence to describe skills and ability to practice safely without the need for supervision. Effective health service delivery depends on the ability of health care providers to provide appropriately trained staff with the knowledge, skills and attitude to deliver effective care. Competency based training is to be used in nurse training supported by academic tutorials but IBD is not covered in the UK nurse curriculum. In addition IBD training and education must be suited to the specific areas of practice, as identified in the individual job description. There can be huge variation in the roles of nurses and health care professionals caring for people with IBD. The difficulty is that, 'one size does not fit all' because nurses in an IBD role may have a different emphasis from hospital to hospital and from country to country, and roles may vary as described below:

43.1.2 Differing Roles of IBD Nurses

- The primary communicator facilitating and coordinating the patient interface
- Administration of biologic therapies in isolation of other roles
- Delivering telephone and email flare up clinics but not face to face clinics.
- Conduct face to face follow-up or flare up clinics but may or may not have responsibility for in-patients.
- Immunosuppression monitoring
- Education and counselling
- Nurse endoscopist
- Ward nurse
- IBD dietician
- IBD pharmacist
- IBD service delivery role (lead IBD nurse).

The role of the IBD nurse has been considered in the RCN IBD Role Descriptive for IBD specialist Nurses (RCN Role Descriptive 2007) but falls short of a competency framework. It does however go some way in identifying the behaviours and the holistic qualities such as complex combinations of knowledge, performance, skills and attitudes that are necessary in the specialty.

43.1.3 Developing a Competency Framework

There are no national or international standards of competency for IBD nurses. Utilizing a tailored competency framework can be the most appropriate way of initially developing an IBD nurse/healthcare practitioner role. It has to be specifically tailored to meet the need of the service/job description. In order to address the holistic component, competency based training is best supported by the use of a role model or clinical lead that will have a person centred approach to support the practitioner throughout the journey. Examples of this model can be likened to the non-medical prescribing training, where nurses are only able to take the academic course if they are assigned a mentor to support the clinical practice. On the job competency training often lacks the formal academic input but is a practical way of self-development if an individual practitioner is not supported by formal academic training.

A competency based framework is based upon outcomes and is a useful tool in developing and commissioning the workforce. The first step to developing a competency framework is tied into writing the job description and person specification for the particular role. It should be individualized to the particular needs of the service avoiding a generic copy. A well-considered job description and person specification will enable the employer to focus firstly on what they expect

from the role and so select the most appropriate candidate based upon the knowledge and skills that they can bring, highlighting to the post-holder the expectations of the levels of competency for the post. There is a need to place emphasis on meeting the needs of service users (IBD Standards 2013), and so the strategist who develops the job description, person specification should make their expectations pivotal. The RCN Roles Descriptive (RCN Role Descriptive 2007) document is a useful tool to support the job description and person specification. Some aspects of competence such as leadership, attitude and critical thinking can be identified in this selection criterion in order to select competence as a quality rather than a behaviouristic task. This approach identifies potential to perform not actual performance.

In house competency framework development can be supported by utilizing both the RCN Roles Descriptive document and the Knowledge and Skills Framework (KSF) (Department of Health 2004) which applies to all health care professionals employed by NHS in UK. It is useful in identifying the knowledge, skills, learning and development that staff need to do their job well. The KSF is a broad framework but may be useful in identifying what level a practitioner is operating at and what support may be needed to aid their development in their specific role. KSF sets out 'indicators', with level 4 being the highest and level 1 being the lowest.

Most competencies are behaviour approached and assessed by direct observation of tasks, but more holistic skills may be overlooked. Direct observation of tasks can be too concerned with what people can do rather than what they know.

Assessment is an important aspect of competency as the trainee has to be ultimately assessed as competent to undertake the role for which they have been employed without supervision. It is not always so straightforward as a yes/no assessment. It may need to be tailored to establishing if a trainee has a level where competence is judged on a scale rather than a tick box. An individual could also apply a self-assessment.

The following competency framework has been developed to include qualitative measures as well as behaviouristic tasks. These competencies include direct observation of care, which relates to many abstract skills such as

- Attitude, behaviour and empathy
- Knowledge and understanding
- Performance criteria

Ideally this framework should be supported by clinical supervision. Supervised practice enables the supervisor to observe not only a specific task but also the attitude and communication skills of the trainee. It is a good example of a framework which can be adapted by an individual to suit their service needs. It is acknowledged that not all individuals working in IBD roles spend all their time in this role—it may be tagged onto endoscopy or an infusion clinic and so it can be tailored to the individual. See Table 43.1 for competency example pro forma.

Table 43.1 Example competency Framework developed by Aileen Fraser, Bristol

Aim: Inflammatory Bowel Disease Nurse Competencies

- Support practice and increase the quality of patient centred care
- Provide a framework for competency and assessment
- Encourage evidence-based practice.

Entry Criteria: Registered Nurse working with patients with inflammatory bowel disease and their carers

Standard: To include understanding of the requirements outlined in the competency template. Band 7 CNS to achieve level 5 rating, Band 6 CNS to achieve at least level 4 rating.

Training Requirements: Experiential training shadowing clinical nurse specialist, gastroenterologists, dietician and administrator

Assessment: Competences will be assessed by the clinical nurse specialist and/or gastroenterologists

Reference Standard: Set with reference to the RCN guidelines 'Role descriptive for IBD Nurse specialists'

Knowledge and Understanding Requirements

By the end of the assessment the IBD nurse should demonstrate knowledge and understanding and be able to apply the following:

1.1 Knowledge and understanding of IBD and its treatments	Level of achievement	Evidence to support practice	Mentor
The Practitioner will demonstrate a working knowledge of:			
1. The gastrointestinal tract in health and disease			
2. The aetiology and pathogenesis of IBD and associated conditions			
3. The relevant pharmacology related to the drugs used in IBD, including methods of administration, mode of action and possible side effects			
4. Nutrition and its role in IBD as a treatment and to provide supplementation advice			
5. The complexity of the disease and treatments available to formulate and negotiate treatment plans with patients			
6. Extra-intestinal manifestations of the disease and their management			
7. Frequently used blood and stool tests, their normal parameters, when to use these tests and what to do with abnormal results			
8. Frequently used radiological tests, when to use these tests and what to do with abnormal results			
9. Frequently used endoscopic tests, when to use these tests and what to do with abnormal results			

Performance Criteria

By the end of the assessment the IBD nurse should demonstrate performance and be able to undertake the following:

Table 43.1 (continued)

Communication, decision making and documentation	Level of achievement	Evidence to support practice	Mentor
The Practitioner will demonstrate the following:			
1. Ability to discuss with the patient/carer their diagnosis, management options, possible investigations/surgery, diet, treatments and their potential side effects			
2. Ability to provide clear, easy to understand information in an appropriate format and at a level accessible to the patient/carer to reinforce the above points			
3. An insight and experience of the effect of chronic illness on the individual with IBD, e.g. loss of independence, loss of control, adherence and uncertainty and also the effect on family members and carers			
4. Ability to review all patient information to ascertain if it is appropriate, current, in a format that is patient friendly, i.e. jargon free, and be responsible for updating this as per clinical advancement or as per patient needs			
5. That patients are involved and treated as equal participants in care, ability to act as patient advocate as necessary			
6. The ability to present patients for review to medical/senior IBD nurse colleagues in a clear and coherent manner			
7. An ability to make complex decisions (including timely referral) where patients do not follow conventional approaches to care			
8. An ability to draw on knowledge and attempt to resolve complex issues with patients, e.g. sexuality, pregnancy, altered body image, financial issues and employment			
9. A high level of interpersonal skills and the ability to work well within the multidisciplinary team, e.g. presenting and discussing patients at MDT			
10. Ability to see patients on the ward, providing information and support			
11. Ability to manage the IBD Advice Line, with an awareness of own limitations and when to seek advice from senior colleagues			
12. Ability to use the current technology to dictate and approve own dictation in a timely fashion			
13. Ability to check and sign off own blood results in a timely fashion with a knowledge of what to do with abnormal results			
14. Ability to use the current technology to refer patients to the histology or radiology meetings for review			
15. Ability to review patients in outpatient clinic, using the protocols, guidelines and pro formas associated with this service			
16. Ability to review and sign off immunosuppression monitoring blood results, with a knowledge of what to do with abnormal results			
17. Ability to review screening pro forma, assess and commence patients on biologics at request of senior colleagues			
18. Knowledge of the protocols, guidelines associated with the UHB trust IBD Service			
19. Ability to see where changes to the IBD service in the Trust can be made to develop the service and to be able to make those changes as part of the MDT			

43.2 Methods to Evidence Competency

1	*Direct observation by Mentor* The mentor directly observes the learner demonstrating a competency in the practice area and records the level of achievement
2	*Direct observation by an Expert Witness/Work based Assessor Statement* An Expert Witness or qualified work based assessor, who directly observes the learner demonstrating a competency in the practice area and records the level of achievement
3	*Interview* Their mentor interviews the learner in order to assess understanding. The mentor/coach will record the level of achievement
4	*Written reflection* Learners are required to complete a written reflective account in order to demonstrate their understanding of principles and practice
5	*Simulation* The learner could demonstrate their ability to perform clinical skills in a simulated situation, e.g. a skills laboratory if appropriate

Within the competency there must be at least 2 examples of evidence from the list above.

(NB; Patient Confidentiality must be maintained at all times. References to patient identification must not be used when formulating records of evidence)

Assessment Strategies:

Assessment should be carried out in three parts:

Self-assessment—by the learner with support from the mentor shortly after the commencement of the competency

Formative assessment—by the learner and mentor during the process of collecting evidence

Summative assessment—by the learner and mentor to determine the level of achievement

You will need to state who is eligible to undertake the role of the mentor and how they are equipped to undertake this role

The mentor will verify the assessment of practice, act as a support and guide

Completion of the competencies is expected to be a collaborative process between the learner and the mentor

43.3 Direct Observation of Practice Record

43.3.1 Core Competency/Skill Observed

Date	Practitioner name	Mentor name
Standards description		
Comments—in-depth knowledge and understanding displayed and ability to perform role		
Further learning objectives identified		

Level	Description
1	Knows nothing about the skill
2	Doubts knowledge and ability to perform the skill safely, without supervision
3	Could perform the skill safely with supervision
4	Confident of knowledge and ability to perform the skill safely
5	Could teach knowledge and skills to others and can demonstrate initiative and adaptability to special problem situations

Rating (please circle as appropriate)

1	2	3	4	5

Signatures:

Practitioner	Mentor
Please print	Please print

43.3.2 Self-Learning Box: What Can I Do to Develop My Competencies in IBD Nursing?

The role of the IBD nurse can be so varied. Some nurses may work in modern dedicated IBD centres with considerable development and support from clinical colleagues

and management infrastructure, whilst others may only dip into IBD and have multifunction roles split with endoscopy or hepatology. Whatever the role is a development and education programme can be developed to support that individual role. Using the competency model as a guide you can work through and adapt the headings that are relevant to your area of practice to develop your knowledge and skills. Keep notes on your learning and document how the knowledge has impacted upon your practice. You can work through this in your own time and keep a portfolio of your learning which will demonstrate that you have the knowledge and also how this knowledge has impacted upon your practice

- It is important to start at the beginning with anatomy, physiology and pathophysiology of IBD. If you find reading a chore, there are many videos that you can explore particularly on YouTube. Many key opinion leaders in IBD, physicians, nurses and scientists upload their power points to YouTube. You can find many presentations on the aetiology and patho-physiology of IBD. Find out if your hospital has access to a virtual anatomy and physiology resource such as Visible body or Acland's Atlas, which is excellent for gaining understanding about not only the gross anatomy and physiology but understanding relationship with surrounding tissues. Examples of useful e-lectures include Therapeutic Management of IBD: The Paradigm Shift to Personalized Care (IBD Pathogenesis 2015), Mucosal Immunity Overview (Hasundagan 2013) and *Immunology in the GUT Mucosa* (Nature Immunology 2013)
- Then move on to the assessment process. Find out about the objective assessment tools available for both CD and UC. Look at scoring tools used at endoscopy. Consider all the adjuncts used in the assessment process-haematology, biochemistry, bio-markers, radiology. It is a very large area to explore but worth investing your time into. The ECCO guidelines are an excellent resource which fairly comprehensively covers the assessment and management of IBD, including special considerations such as pregnancy, transition, iron deficiency and opportunistic infections
- You can work through the categories of drugs used to treat IBD, by reading ECCO guidelines or the manufacturer's Summary of Product Characteristics
- Explore patient education and counselling. Patient support groups are excellent resources for exploration of the patient perspective
- Consider joining the nurse section of ECCO to enable access to all the learning materials on their platform
- Try to secure placements with mentors so that you can observe their practice. Record the time spent in observation and keep notes in your portfolio of the observations that you have made
- Nominate yourself to attend courses relevant to your practice

43.3.3 Formal Education and Formal Accredited Post Graduate Learning in IBD

The first UK national audit of IBD nursing roles revealed some major concerns with regard to the gap between theory and practice (RCN 2007). The audit revealed that 25.8% of IBD nurses are not educated to degree level and only 9.1% have a master's degree. Furthermore, 66.7% of nurses included in the audit had not completed an IBD module at degree level. It is concerning that IBD nurses may be operating with high levels of autonomy and have been unable to access a formal qualification in the specialty.

Formal accredited post graduate e-learning in IBD is now available in a single module at both bachelor's and master's level available from the University of Salford, UK and is accessible for professionals involved in IBD care worldwide. Demand for this accredited training has increased from originally being at bachelor's level and delivered from September to January—it is now at both bachelor's and master's level running through three semesters. From February 2018 there will be two additional modules available—a gastrointestinal module and a liver module. Students who successfully complete 2 of the 3 modules will be awarded a Master's level Post Graduate Certificate in Gastroenterology from the University of Salford, UK.

The authors of the course recognize that the emergence, adaption and adoption of digital technologies have transformed most sectors around the world. The e-learning experience has to be a happy experience in order for it to be successful and as such it is supported through a structured developmental process. The University of Salford IBD module has been developed by a leading academic, Dr Karen Staniland and two clinical IBD nurse consultants, Veronica Hall and Catherine Stansfield, utilizing the Gilly Salmon five-stage Carpe Diem Model. The aim of the module is to develop the advanced knowledge, understanding and skills necessary to care for a patient with inflammatory bowel disease based upon an extensive evidence base in order to equip the learner with a formal accredited qualification in IBD.

E-learning is an innovative efficient and cost-effective way of educating and developing health professionals involved in IBD. E-learning has to be easily accessible and negotiable for the user otherwise they may give up. The e-student needs to be self-motivated and disciplined in order to switch on their computer and engage with the e-sessions.

The module mentioned above, for example, runs over a semester at the university but has the advantage that the individual learner can access the material at a time to suit themselves with the release dates of the module which is divided into four units and is time released. The content consists of videos and PowerPoint presentations of formal lectures delivered by experts in the field as well as hyperlinks to reading material, quizzes and e-activities to demonstrate learning as well as virtually engaging with other students on the course

- Unit 1 An introduction to Inflammatory Bowel Disease including anatomy, patho-physiology
- Unit 2 Assessment of a Patient with Inflammatory Bowel Disease
- Unit 3 Treating Inflammatory Bowel Disease
- Unit 4 Approaches to Education and Counselling

Social media is an important aspect of the learning module and consists of the use of:

- Wikis.
- Voice boards—which are excellent for student feedback, with the advantage of being asynchronous. The moderators can video record feedback which can be viewed by the student at a time convenient to that student.
- Blogs, which are good for reflection and revision.
- Text messaging
- Synchronous virtual classroom.
- Social networking such as closed Facebook.

Assessment of learning and obtaining the academic qualification is by ongoing involvement with the module, overseen by the e-moderators with a final 20 min PowerPoint presentation for bachelor's level and 30 min presentation for master's level followed by 10 min of questions. This activity is via the university Collaborate or Skype or similar communication.

43.3.4 Educational Opportunities that Can Be Accessed by Individual Self- directed E-Learning

The European Crohn's and Colitis e-CCO Learning Platform is available for ECCO Members for which there is an annual charge.

The e-Library now includes around 280 presentations and 100 video recorded webcasts as well as all the scientific sessions presented at conference in the Plenary Hall as well as four of the educational courses recorded including:

- IBD Intensive Advanced Course
- N-ECCO School, 4
- P-ECCO Educational
- There is a series of Talking Heads videos. Each video brings together two or three key opinion leaders in IBD who debate a specific topic. Nurses can register to attend the N-ECCO school which runs annually alongside the ECCO conference
- The United European Gastroenterology (UEG) also has an e-learning platform which includes tutorials available for registered individuals and is also free to register.
- The Royal Society of Medicine (RSM) has free registration and access to lectures and learning material.
- Corporate sponsorship learning opportunities. The pharmaceutical industry has several clinical and non-clinical training days and programs available for IBD nurses to attend and are usually free of charge. These are often led by clinical key opinion leaders and can be very useful sources of education.
- Portfolio Development. Keeping a portfolio is an effective way of demonstrating learning and making explicit an individual's experience and capabilities within a role. If all educational opportunities and on the job developments are reflected upon using a formal model of reflection, where the IBD nurse can identify how new learning has impacted upon her practice this can be included into a portfolio of development, thus demonstrating knowledge skills and experience in an IBD role. There are many self-assessment tests which are available through the channels already discussed such as the ECCO learning platform as well as professional journals with Continual Professional Development (CPD) available.

43.4 Conclusion

It is important to remember that there is a European mandate for education and training in inflammatory bowel disease and no reason this should not apply internationally. There is also a mandate for professional development and revalidation within the nurse's role in individual countries (NMC 2017 for the UK). There is not a single solution or approach which will be suitable for all IBD services or indeed all IBD healthcare professionals. We have a responsibility to ensure that our service and our practice is fit for purpose. The approaches detailed in this chapter allow for a combined and possible gradual approach to development of a practitioner within an IBD role utilizing some or all of the strategies that have been discussed. It is not always what tasks a person can undertake or what courses they have attended that makes the right person for the role that your individual service needs. When searching for a new recruit the IBD lead needs to understand exactly what their individual service needs and to apply the correct selection criterion in order to capture the most appropriate person for the job by select competence also as a quality rather than a behaviouristic task—this approach identifies potential to perform not actual performance. After this, an appropriate development plan can be implemented.

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e-Health

44

Palle Bager

Abstract

Electronic health (e-Health) has a great variety and is developing rapidly. This is also the case in IBD. This chapter will focus on general issues and questions to be asked when considering introducing e-Health initiatives in IBD. The chapter will outline aspects about:

(a) Aims of e-Health: Why, who and when?
(b) Data issues: Who enters data in e-Health? What kind of data? How is it used?
(c) The technology of e-Health: Who develops the systems?
(d) Research based on e-Health data.
(e) Economic aspects of e-Health.

Finally the chapter will offer a few examples within inflammatory bowel disease (IBD) practice.

44.1 Introduction

Electronic health (e-Health) has a great variety and is developing rapidly. So this chapter could be outdated a few days after it has been written! The focus then will be to frame the concept of e-Health rather than describing actual e-Health initiatives in IBD because regardless of specific e-Health initiatives, some general issues and questions will arise.

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e-Health includes web-based health measurements and communication, virtual clinics, smartphone app's and other telemedicine services being used to remotely support and manage patients. According to WHO, e-Health is the use of information and communication technologies (ICT) for health (World Health Organization 2017). A subcategory of e-Health is m-Health. Mobile health (m-Health) is the term for health communication via mobile communication devices.

The aims for using e-Health applications can vary, but overall the aim is to improve the patient's health status. They can focus on health information to patients or to citizens, or they can be used to measure different patient-reported outcomes (PROs) or clinical measurements. Also, e-Health can aim to let the patient interact with a health-care professional. Health information is available from many e-sources. The quality varies, and patients need to watch out for the more unprofessional segment of the industry. Poor quality of apps and web pages could seriously jeopardise the safety of patients. Health-care professionals could play a key role in evaluation of the quality and in educating the users to become critical.

Applications to monitor and measure different physical and mental conditions are widely used both by patients and any person looking to monitor or support their own health. However for patients specifically telemedical systems have been developed, allowing the patients to monitor their condition at home or on the road. For patients, most e-Health tools allow an interaction

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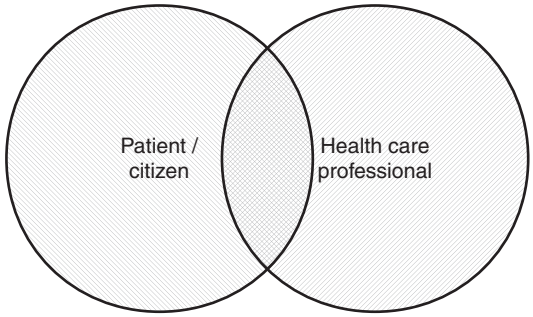

Fig. 44.1 Illustration of data distribution. A patient is also a citizen and will have non-health data. A health-care professional will have a pool of health data, and only a subset of data will be shared. An intersection between the two sets of data will have to be defined

between the patient and the health-care system. The tool could include electronic appointment booking or online pharmacy orders. It could also include interaction based on patient-reported outcome (PRO) data generated by the patient.

A frequent limitation of the interaction, however, includes the integration between e-Health data and other data from the health-care system. As illustrated in Fig. 44.1, a patient is both a patient and a civilian. Not all data recorded by the patient will be important for the health-care professional in the care planning and decision-making. On the other hand, the health-care professional may also have data that is not so important for the patient. These data are probably generated in other systems. It could be x-rays, results of blood samples or endoscopies. This means that only a subset of information will be shared between the patient and the health-care professional. If patients are motivated to use e-Health tools, the purpose should be clear for them. This might include user involvement in the development phase of the tool.

Reviews of published studies on e-Health interventions in IBD found studies heterogeneous in regard to both the interventions and the outcomes (Huang et al. 2014; Aguas Peris et al. 2015; Jackson et al. 2016). The patients enrolled were mainly patients with IBD in remission. Although it is not always clearly described, nurses seem to play a key role in reviewing the PRO data and taking follow-up action. Patients are in general positive towards e-Health and self-management approaches as long as they are well. However rapid and easy access to both gastroenterologists and IBD nurses is of importance as a supplement to e-Health (Kemp et al. 2013; Bager et al. 2013).

44.2 e-Health in IBD

44.2.1 Questions to Be Asked Prior to the Introduction of e-Health in IBD

e-Health will naturally be requested by the different players in IBD. There is no doubt that e-Health is here to stay and will be developed further in the years to come. However, before introducing e-Health solutions in IBD, a number of questions need to be addressed:

- Why use e-Health?
- Are there unmet needs that e-Health can solve?
- Who should use e-Health?
- When should e-Health be used?
- Will e-Health be acceptable by both patients and health-care professionals?
- Who will enter data?
- Who will review data in e-Health?
- Shall the e-Health program include decision tools?
- Who decides what data to register in e-Health?
- Who shall educate the e-Health users?
- Who provides the devices/programs?
- Who develops e-Health further?
- Who will have access to the data?
- Can data be used for research?
- How will the cost of e-Health be handled?

44.3 Why, Who and When

For e-Health initiatives to become successful, the aims need to be clear and logical to all involved. Furthermore, the technology needs to be accepted by all users. The aims of introducing e-Health in IBD can vary depending on the perspective.

Patients might want to be less dependent of appointments at the IBD clinic, for example, they might want to register data and communicate any time of the day. The health-care professionals, also, might see e-Health as a way to reduce the number of patients in the clinic. From managers' and societies' perspective, e-Health solutions might reduce the health-care costs. In addition, e-Health might be considered in IBD because the technology is there and is already used in other areas.

IBD is a chronic condition with periods of disease activity and periods with the disease in a stable condition. Rapid identification of markers for disease flares and rapid onset of treatment are crucial for the course of flare. A broad group of patients with IBD are young and active. Therefore any remote consultation regarding disease issues should be welcomed by the patients. Furthermore, a vast majority of patients will have access to the Internet and will have smartphones.

If the goal is to monitor the disease regardless of disease activity, patients need to be motivated for using the e-Health tool and enter data on a regularly basis. But if the goal is to be able to react fast to symptoms of a disease flare, patients need to enter data as soon as symptoms are changing: maybe even before a change and maybe the patients will need to have other assessment tools in the house in case of a flare, e.g. stool sample sets. Will this be realistic, and what will motivate the patients to do this?

For the health-care professionals, e-Health measurements will be a supplement to the medical records. An ongoing challenge is to get e-Health data into the existing health-care data systems in a safe way. Therefore e-Health might increase the number of data sources when patients with IBD need assessment and evaluation by health-care professionals. If the data reported by the patients are not used by the professionals, the motivation among patients to use e-Health will decrease.

Some e-Health systems are designed to include decision algorithms that allow the patient to change IBD medication. In such cases, further precaution is needed. The scales used need to be validated, legal issues need to be investigated, and responsibilities for the treatment given need to be clearly described.

44.4 Data Issues

Data is the key element in e-Health and needs to be accurate and relevant. However, several questions can be asked regarding data.

- What kind of data shall be added to the e-Health system?

The health-care system will probably contain more health data than requested by the patient. On the other hand, the patients will probably like to record other and more data on health than requested by the health-care professional. When designing and introducing an e-Health solution in IBD, it is advised to include the users in the development phase.

Figure 44.1 is a simple illustration of how data on health issues can vary greatly between the user and the health professional, and an intersection needs to be found and agreed on.

Patients with IBD might want to register symptoms that worry them (fatigue, urgency, anxiety, depression, pain and diet) (Stjernman et al. 2010).

- But is it acceptable for the patient to register the data if they are not used by the health-care professionals?

The health-care professional will probably ask for disease activity markers such as CDAI, SCCAI or IBDQ (Harvey and Bradshaw 1980; Walmsley et al. 1998; Irvine 1993).

- But will patients with IBD provide these data on a regular basis if the disease is in remission?

When data is entered in the e-Health system, some kind of response is needed.

- Who will response to the data entered and how?

Some systems have a decision tool included. Often the system responds with a simple colour code (red, yellow or green) (Elkjaer et al. 2010). If the system contains a decision tool, the product

needs a Conformité Européenne (CE) marking in Europe. If patients are expected to react on the data entered, they need to be educated in the specific tool and the organisation related to the tool. Furthermore, they might need to be educated and empowered in IBD diseases. Nurses will play a key role in educating patients to acknowledge disease symptoms and to describe the symptoms in a systematic way. In addition, nurses can assist the patients to become empowered in managing their IBD disease.

If nurses are expected to review the incoming data, further education of nurses may be needed. There needs to be standards for response, documentation and follow-up. Furthermore, nurses need to have access to backup by gastroenterologists when reviewing e-Health data.

- Is it acceptable to use data for other purposes than disease monitoring?

Patient data reported to an e-Health system are unique and very valuable. It will be possible to generate 'quality of care data' for quality development at hospital level. Data might also be useful when conducting research within IBD (see below). Finally, the industry will probably find the data interesting in both research and marketing. Therefore, it is absolutely essential to consider who owns the data entered and also to secure the data and ensure the anonymity of data if used externally.

44.5 Technical Issues

The technologies behind e-Health are developing rapidly. The professional segment of the e-Health industry can in many ways be valuable to patients as well as to the society. Knowledge from other areas of the tech industry can be used in e-Health solutions as well as e-Health knowledge, and experience from one disease can be used in others. Furthermore, patients' can have more than one disease; therefore it is worth considering whether to use a generic e-Health solution versus a disease-specific solution.

To date, only a few e-Health systems have been developed in the public sector or by non-commercial organisations. Most systems have some kind of commercial connection. Regardless of the setting, development and maintenance of e-Health systems, the activity will cost both knowhow and resources. When introducing an e-Health service, it is of importance to consider if the provider is robust enough to deliver and maintain the system. Furthermore, dependency on one provider might be a problem, especially if the provider is a private company.

44.6 Research Issues

Data reported to an e-Health system can be used for research. Therefore it is obvious to consider research issues already when introducing any e-Health initiative in IBD.

First, consider who owns the data entered and whether the patients need to give informed consent to research use of the data already prior to data entry. If data is merged with data from the health-care system, specific issues might arise.

Second, consider who will be in a position to apply for data and if a research purpose is valid. The purposes could have a commercial character or it could be more research orientated.

Third, consider who will decide if a research request shall be approved and if there will be a cost of the data request.

Finally, all data protection and ethical issues should be respected at any time.

44.7 Economy

Development and implementation of e-Health solutions require investment from both human and economic resources. Regardless of the type of investors, investments are supposed to give a return.

If the e-Health solution is commercially based, the investment is expected to give an economic profit. This could be linked directly to the e-Health product or to additional sales of other products.

If the e-Health solution is publicly based, improved health is expected as an outcome and/or a decrease in health-care expenses. An e-Health

solution can also aim to save health-care staff. These potential benefits need to be balanced with the initial costs plus the addition of running costs and costs related to maintenance a further development of the solution.

These basic economic issues underpin the benefit of evaluating any e-Health solutions prior to implementation. This can be done by using the principles of health technology assessment (HTA) or model for assessment of telemedicine (MAST) (The International Network of Agencies for Health Technology Assessment 2017; Kidholm et al. 2012).

44.8 Examples in IBD

e-Health and m-Health solutions in IBD have been developed over the last decade along with the technological development. There might be more examples in practice, but only a few results have been published in scientific journals to date. Currently, two e-Health systems have been developed in co-creation with the public health-care system, and several countries continue to develop m-Health.

In Denmark, a web-based solution (Constant Care) was developed for patients with mild to moderate UC. Later it was extended to patients with CD. The patients were scored on a traffic light reflecting their disease activity status (Elkjaer et al. 2010; Pedersen et al. 2012). Patients who scored green light did not need to contact the IBD clinic. While those who scored yellow or red light would need a contact to the clinic.

'Swibreg' is a quality patient register that covers a majority of patients with IBD in Sweden. The program allows patients to report both disease and health-related quality of life data into the database. The data can be merged with data from the clinics, and health-care professionals can evaluate the data and correct the treatment of patients (Jakobsson et al. 2017).

In a number of countries, several m-Health programs in IBD have been developed. Some of them were developed in co-creation with patient associations and health authorities, some together with commercial partners. In a randomized controlled trial, 'My IBD coach' (The Netherlands) was tested. The system was safe, and users had less contact to hospital when compared to the control group (de Jong et al. 2017). Other examples are 'GI BodyGuard' (Canada), 'AnswersIn Crohn's disease' (United Kingdom), 'GI Monitor' (USA) and 'IBDoc' (Switzerland).

44.9 Summary

This chapter has raised a handful of questions to be considered before introducing e-Health solutions in IBD.

- Why, who and when?
  - It is essential to have clear aims for the e-Health solution.
  - The pool of patients included need to be defined. Furthermore, solutions for the remains need to be placed.
  - The frequency of data entry and response to the data needs to be clear so all involved know what to expect.
- What are the data and how are they handled?
  - Data is the key element in e-Health and needs to be accurate and relevant. It is necessary to clarify what kind of data that must be entered in the system: both from the patient and from the health-care system.
  - In most systems, monitoring of the disease is the primary aim. Therefore, a clear plan for response to the captured data is needed. If the technology includes some kind of automatic decision tool, approval may be needed.
  - The ownership of data will be of importance both in daily monitoring and if data shall be available for research or quality improvement issues.
- How is the technology?
  - The technology develops rapidly which can be challenging.
  - It is worth to consider whether to use a disease-specific or a generic tool. Some patients may have co-morbidity and can use the tool in other settings.
  - The provider of the technology must be robust and able to update the technology when needed.

- Can data be used for research?
  - On group level, the data entered will of interest for both researchers and for commercial purposes. Before introducing e-Health solutions, it is important to consider how data can be used in these purposes and, furthermore, to consider who owns the data.
- What are the costs?
  - Development and implementation of e-Health solutions are costly. So are the running costs. The costs include both human and economic resources.
  - Included in the cost calculations, the possible benefit must be clear before the introduction of e-Health solutions.

A systematic analysis before introduction of an e-Health solution will be beneficial. The elements included in the HTA or MAST approach will cover most of aspects mentioned above (The International Network of Agencies for Health Technology Assessment 2017; Kidholm et al. 2012).

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Inpatient Care

45

Lydia White and Malcolm Tan

Abstract

The therapeutic relationship between patient and clinician is particularly important during an admission to hospital given the physical and psychological stressors involved. Clinicians must be aware of hospitalisation as a potentially tender time including, of course, the IBD nurse who often has a pre-existing relationship with the patient. However, heavy workloads in outpatient roles, uncertainty around value of visits, a lack of renumeration and activity capture for inpatient activity are all reasons why IBD nurses may find that supporting the inpatient becomes the least priority for a busy day. This chapter seeks to re-address the balance by looking first at the role of the IBD nurse when engaging with the IBD inpatient and secondly at an important clinical scenario from which to extrapolate principles for other acute admissions:

- The IBD nurse in:
  - Trust/therapeutic relationship
  - Translation and teaching
  - Teamwork and trials
- Medical considerations for the IBD inpatient
  - General and specific management
  - Salvage therapy
  - Timely colectomy
  - Discharge

45.1 Introduction

The UK IBD standards (IBD Standards 2013) recommend that all patients admitted into hospital be seen by the IBD nurse though they are not explicit as to how or for what. Anecdotal discussion and experience suggest that IBD nurses are often unsure what contribution they can make while the patient is in hospital and under regular review by the inpatient team. There is certainly a lack of specific literature on nursing the IBD inpatient, and work describing specialist roles focuses largely on outpatient management, skilled and timely assessment and treatment aimed to facilitate a person's life outside of hospital (Dudley-Brown 2006; Nightingale et al. 2000). These outpatient-focused skills are, of course, key to facilitating care for people with IBD and helping them continue with everyday life. However, IBD nurses must also recognise the importance of their knowledge and skills in supporting those who need to come in to hospital. This chapter looks at that role in generalised aspects and then specifically details the manage-

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ment of acute severe colitis, given it is one common reason for IBD admissions.

45.2 The IBD Nurse In

45.2.1 Trust and Therapeutic Relationships

> "I don't know why but I just feel desperately alone and vulnerable" (inpatient 2017 – used with permission)

It may seem an obvious point, but admission to hospital is a key moment in the patient's experience of life with inflammatory bowel disease. Their expectations and plans have been disrupted and disappointed. They are likely to be in physical pain and psychological disarray, and those factors will make it additionally difficult to process the activity around them. So increasing anxiety and possible confusion run alongside the loneliness, loss of control, isolation, boredom, fear and many more feelings that are well recognised with hospitalised people (Rokach and Parvini 2011; Holloway et al. 1998). This key time could make or break relationship with the clinical team. It has, in fact, been noted that recent hospitalisation is one of the factors associated with IBD patients choosing to change their physician for negative reasons (van Langenberg and Andrews 2012).

The IBD nurse is in a unique position. Firstly there is often a level of pre-existing relationship through, for example, clinic contacts or Advice Line contact. Also, (in most models of IBD nursing), the IBD nurse is rarely giving hands-on care while the patient is in hospital. As such they are a step removed from the ward team allowing a different perspective and support for the patient to confide to.

However, as noted in the introduction, there may be barriers to meaningful inpatient contact, particularly, lack of time. To maximise the therapeutic relationship in minimal time, then, it is worth recalling the strikingly small things which have been noted to make a large difference, such as making eye contact, using the patient's name when addressing them, the importance of appropriate touch (of course with caution/permission) and getting to know something about the patient (Rokach and Parvini 2011; Holloway et al. 1998; McCabe 2004). Box 45.1 lists a few things the IBD nurse (and any clinician) could bear in mind during interactions.

Box 45.1 The Small Things

- Look me in the eye
- Use my name
- Hear my question
- Recognise my feelings
- Ask me!
- Care

Essentially this list reads as a cry for notice and involvement. Thereby it fits with the emphasis for keeping the person at the centre, the well-worn phrase being 'patient-centred' care. There is a large amount of literature and theory exploring how to do this well, but these small points act as a helpful practical start (see also Chaps. 36 and 37—Psychological Support and Communication).

The last point above, however, is more ambiguous: to 'care'. Indeed words such as 'caring', 'empathy' and 'compassion' are certainly raised regularly in the studies or commentaries on the clinician-patient relationship (McCabe 2004). This emphasis may cause anxiety (or even irritation) to busy clinical teams who have obligations in responding to immediate health needs for their patient. Clinicians may feel they are being asked for involvement to a level of personal relationship that is not possible or appropriate—which is not the intended message. However it must be recognised that where two people interact there simply *is* relationship. For patients, this may even be a more intuitively important fact than the care itself (Guler 2017; Locock et al. 2017). It is therefore essential for IBD nurses to effectively utilise their part within the multi-disciplinary team, continuing their involvement through inpatient episodes and, with even small considerations and brief interactions, to enhance the therapeutic relationship which forms the foundation for overall care.

45.2.2 Translation and Teaching

So it is important to *be* present for the patient, i.e. to recognise and respond to them as an individual. Without something to *do*, however, this may feel an awkward request. Patients do often take note of the time pressures faced by nurses, and, ironically for them, time is one of their main challenges—but for different reasons. An excess of time in hospital has been noted to lead to boredom and loneliness, and/or the loss of time out of their usual life leads to anxiety (Holloway et al. 1998). For the sake of the IBD nurse as well as the patient, then, it's helpful to recognise that there can be important and useful functions to an interaction. In effect, *do*-ing something may help both parties acknowledge a purpose to *be* present.

One very essential role is that of the translator and educator. As an educator the IBD nurse role is well recognised.

As a 'translator' this refers to translation for medical meaning and the current situation. Given the specialist knowledge and experience, as well as familiarity with medical discussions and jargon, the IBD nurse role is perfectly placed to ensure the patient is up to date, understanding and meaningfully involved in their care.

For the hospitalised person, there are further challenges to taking information on board given the level of physical and psychological distress likely (as above). Additionally, things may change rapidly with a changing clinical condition, and there is a likely transition point during an inpatient stay, such as a move from medical to surgical care or between different therapies. The importance of 'translating' or clarifying discussions (such as from ward rounds or results) should not be underestimated. Anecdote and experience suggests that time taken to ensure understanding is more often needed than not. It is also an important factor in patients remaining engaged, involved and (most importantly) at the centre of decisions about their care (Lehman 2017; Maskrey and Gordon 2017; Tulskey et al. 2017). Very simple questions can open up discussion with the patient such as:

- How are you feeling about the plan for today?
- Do you feel you understand your care at the moment?
- Did any questions come to mind after you saw the team this morning?
- What is *your* biggest concern at the moment?

Of course communication beyond these initial introductions needs to be effective and tailored to the individual (Linn 2013; Manning 2004). Basic steps and considerations can be considered in Table 45.1.

The 'light bulb' is a colloquialism referring to the moment of understanding which is often obvious from a person's facial or verbal expression when they have grasped the understanding of something. In the likely ad hoc interactions of ward environments, these moments may be all the 'evaluation' possible or needed.

It may also be helpful to be aware of the different learning styles that patients may have. Due to different learning styles, people are likely to come at their concerns and questions from different angles: some wanting facts and information while others find the experience of hands-on learning (by doing and trying) is more important for them (Dobson et al. 2011).

There is a great deal in teaching and learning theory about types of learners, types of teachers, steps to effective communication and over-arching paradigms within which a particular approach might fall. The interested reader may wish to look into learning styles from a different theory to enhance their creativity when approaching IBD patients:

Box 45.2 N-ECCO Statement 3D

The Advanced Nurse assesses understanding and, informed by current evidence, provides education to patients with IBD and their relatives based on individual needs, preferences and coping ability. The aim is to enable and empower the patient to live with IBD [EL 3]. (O'Connor et al. 2013)

Table 45.1 Steps towards supportive education

	Steps	Consider
1.	Assess learning needs	Start with the person: what they understand so far, what they want to know, what they are worried about (questions above) Ask the clinical team, ward doctors and nurses who are regularly with the patient
2.	Identify barriers to learning	Address and mitigate physical challenges where possible, e.g. hearing impairment, language differences Recognise and seek to understand cultural or religious beliefs—these may be contrary to medical course or goals The unmotivated or unreceptive patient may need to have emotional concerns addressed prior to being able to have meaningful discussion about treatments
3.	Plan education	Time: overall schedules may need discussion to carve out inpatient support time. Utilise pre-existing aspects of a service, e.g. join regular medical wards to gain up-to-date knowledge of the patient and see the patient with the team. Use time-efficient approaches, e.g. leave written information and return later to discuss Involve key family or friends, likely to be usual to paediatric teams, but also consider in adults Use materials, e.g. written information on medications, pictures, booklets Increase specialist knowledge: go and learn/get more information as needed and consider involving other members of the team, e.g. dietician or pharmacist
4.	Implement the education	Follow through plans as above Follow the person's own conversation, and use their frame of reference if able, e.g. relate a process to something in their life or work Use pictures, drawings, diagrams (consider the visual learner) Utilise the time dilemma to advantage, i.e. the patient feels an *excess* of time, so leave materials for the person to read and consider, and then a return visit can be more succinctly about assessing understanding and clarifying questions
5.	Evaluate the education	Look for the 'light bulb' (see below) Ask people to reflect back what they understand Consider asking for feedback on written materials—useful to ensure patients read to understand and useful for service improvement Always ensure the person knows how to contact or ask in future (e.g. advice line)

Developed from Manning (2004)

Resource

Kolb D, Chapman A. (2006) *Kolb Learning Styles. David Kolb's Learning Model and Experiential Learning Theory (ELT).* http://www.businessballs.com/kolblearningstyles.htm

However, the reality of 'teaching' in this context is that even the simplified table above may seem daunting. In a ward environment, it is likely to happen in small moments of interaction. In effect, the steps can be distilled to:

- Look for areas of concern or confusion.
- Identify the information needed.
- Help a person move towards understanding.

Most important, perhaps, is to remember that teaching is an interaction of two individuals, so attention to rapport (as explored in the previous section) remains essential (Manning 2004; Kaufman 2003).

45.2.3 Teamwork and Trials

Not only are the IBD nurses well placed for the patient, but they are also able to support the clinical team. If they are hearing the patient's perspective and concerns, they can work with the ward team helping to ensure that the patient's priorities remain central to discussion. They may also be able to facilitate understanding and resolution where illness behaviour may seem challenging, or be misunderstood by staff less familiar with the clinical area. The things elaborated in the previous sections, hoped to convince the reader that involvement with the inpatient environment is critical, but re-engaging with a ward environment may also be challenging and require some intentionality. Simple acts such as answering the ward phone while at a desk or taking a set of observations on a patient while visiting might be conducive to establishing good

Box 45.3 N-ECCO Statement 2A

Nurses in contact with patients with IBD working in any setting, need to have basic knowledge of the diseases, know the difference between Crohn's disease and ulcerative colitis, and appreciate the importance of establishing timely therapeutic interventions. Awareness of the key diagnostic strategies and of the main medical and surgical options available in the management of IBD is recommended. [EL3] (O'Connor et al. 2013)

relationship with ward colleagues. More specific actions might be:

- Schedule time alongside the pre-existing ward schedule, e.g. join a key ward round each week with medical and/or nursing teams.
- Resource the ward team, e.g. ensure patient education is available and up to date and ensure contact details of key clinicians (including the IBD nurse) are visible and accessible (see also Table 45.4 with Tips for ward nurses).
- Agree and action referrals between other members of the multidisciplinary team, e.g. stoma therapy team prior to a likely colectomy, ensuring a patient is put forward for formal MDT discussion.
- Arrange direct education, e.g. offer teaching sessions for ward nurses when time is suitable to them, such as during group handovers or study days. This is particularly important when considering the overall aim of IBD care which includes an expectation that all nurses in contact with IBD patients have knowledge of the area:

Keep up to date with trials available and ensure that information is regularly (or at least strategically) communicated to ward teams.

To emphasise the point again, the IBD nurse is part of the wider clinical team in a way that the ward nurse or junior doctor may not be. Utilising knowledge of the wider service and different specialist individuals can provide valuable and timely input for someone with IBD when they are at the critical point of hospitalisation. Particularly, the IBD nurse link with current research may even highlight additional options otherwise not available.

45.3 Medical Considerations for the IBD Patient

It is, of course, important that the IBD nurse has an adequate understanding of what is going on with the patient in the hospital. To be an effective educator in the clinical context, it has been stated that being a competent clinician is the first step (Manning 2004). As a patient advocate, the IBD nurse needs to understand the complexities of medical care and the principles of medical (and surgical) therapy and weigh them with the concerns of the patient. There are multiple possible reasons for admission such as:

- Acute severe ulcerative colitis
- Flare of IBD
- Infection
- Intestinal obstruction or perforation
- Malnutrition
- Non-IBD-related reasons (e.g. pneumonia)

The following section looks specifically at managing an admission for acute severe ulcerative colitis (ASUC). In ASUC there are clear parameters for decision-making that the IBD nurse should know and be able to discuss with patients as well as the wider team. Principles drawn from this setting can then be applied in other acute IBD admissions also.

45.3.1 Acute Severe Ulcerative Colitis (ASUC)

ASUC is a medical emergency that can affect patients with UC. An estimated 20% of patients with UC will experience a severe flare somewhere along the course of their illness. There is a material risk of mortality and morbidity; thus, the patient would require an admission with close monitoring and aggressive treatment to reduce the risk of death and colectomy. Although rates of poor outcomes have been reduced over the years, the urgency of care delivery and involvement of various stakeholders cannot be understated.

Patients with ASUC present with six or more bloody bowel movements a day, with either a

body temperature of more than 37.8 °C, a pulse rate of more than 90 bpm, a haemoglobin level of less than 10.5 g/dl or an erythrocyte sedimentation rate (ESR) of more than 30 mm/h (Table 45.2) (Lotte et al. 2010; Stange et al. 2008).

In about 10% of patients, it could be their first presentation of a disease that they were not diagnosed with prior, which adds further to the mental strain these patients will experience during the inpatient stay. The tangible threat of colectomy is a constant fear that would loom over the patient throughout his inpatient stay. The short-term colectomy rate is about 29%, with a mortality rate of 1% (Stange et al. 2008). Even if the patient avoids a colectomy during an admission, there still exists a future risk of colectomy in the following years after the index admission as can be seen in Table 45.2. This can be important information requiring skilful discussion with the patient.

45.3.2 General Management

As part of the management, patients would require tests to assess the severity of disease and exclude concomitant infection (Table 45.3). Where possible, the patient should be placed in a gastroenterology ward where specialised care can be provided. The scenario highlights the importance of multidisciplinary working: a colorectal surgeon (who is ideally experienced in IBD surgery) should be involved as soon as is feasible, together with a stoma therapist to provide counselling should colectomy be the outcome. Assessment for nutritional status can be performed by a dietitian with the aim of improving the preoperative state. A clinical psychologist might also prove useful for patients who are having difficulties coping with the stress of the clinical condition.

An abdominal radiograph is useful in predicting poorer outcomes. A colonic diameter of >5.5 cm or the presence of mucosal islands confers a 75% risk of failure treatment with steroids (Lennard-Jones et al. 1975).

Antidiarrhoea and anticholingeric medications must be stopped as these can potentially exacerbate the severity of disease.

Given the multiple bowel movements and poor appetite, it is not surprising that patients can present with electrolyte abnormalities. Taking into account co-morbidities like chronic kidney disease or congestive cardiac failure, fluid and electrolytes should be adequately replaced. Attention should be given to magnesium and potassium levels as hypomagnesaemia and hypokalaemia can precipitate dilatation of the colon.

Screening for *Clostridium difficile* infection is a routine as the prevalence of *C. difficile* is higher in patients with active IBD than patients without. Moreover, it contributes to worse outcomes to infected patients, and treatment is with antibiotic therapy (vancomycin/metronidazole), rather than intense immunosuppression which is required in severe IBD exacerbation (Ananthakrishnan et al. 2008).

Prophylaxis for venous thromboembolism is recommended as these patients are at a higher risk of developing thromboembolic events such as lower limb deep venous thrombosis or pulmonary embolism. It may seem counterintuitive to provide anticoagulation for such patients, but the

Table 45.2 Truelove and Witts risk factors with colectomy rate (Sobrado and Sobrado 2016)

Truelove and Witts criteria	Colectomy rate
Bloody diarrhoea >6 episodes a day with – Heart rate > 90 bpm – Temperature > 37.8 °C – Haemoglobin <10.5 g/dl – ESR >30 mm/h	
+1	9%
+2	31%
+3	48%
+4	45%

Table 45.3 Key management points

Severity assessment	Markers for infection	Healthcare professionals
– Bowel movements – Temperature – Pulse rate – CRP – Haemoglobin – Abdominal X-ray – Flexible sigmoidoscopy	– Stool cultures and sensitivity – *Clostridium difficile* PCR – Staining for cytomegalovirus on histology	– IBD nurse – IBD doctor – IBD surgeon – Stoma therapist – Dietitian – Psychologist

benefits do outweigh the risks, and rectal bleeding is not worsened (Grainge et al. 2010).

45.3.3 Specific Management

Intravenous corticosteroid is the cornerstone of treatment. Prior to its use, the mortality in ASUC ranged from 30 to 60%, and its advent has brought mortality rates down to about 1%. Either hydrocortisone or methylprednisolone can be administered for about 7–10 days. The response rate to steroids is about 67% (Stange et al. 2008).

Flexible sigmoidoscopy should be arranged and undertaken by a gastroenterologist as soon as possible to facilitate endoscopic assessment of severity. Ulcerative colitis endoscopic index of severity (UCEIS) is a validated scale with excellent interobserver variability and is strongly recommended for use in assessment (Travis et al. 2012). Biopsies should also be taken to exclude cytomegalovirus (CMV) colitis, which is a commonly seen superimposed infection in IBD patients on immunosuppression. CMV colitis should be treated promptly with ganciclovir as it accounts for up to 10% of patients who fail to respond to steroids.

After 48 h of intravenous corticosteroids, it is mandatory to perform an assessment to determine if salvage therapy with infliximab or cyclosporine is necessary. The Oxford index is a simple composite score which predicts a colectomy rate of 85% should the patient have a stool frequency of >8 or a CRP level of >45 mg/l (Travis et al. 1996). Should a patient meet either threshold, then the high risk of colectomy would warrant salvage therapy with infliximab or cyclosporine. Otherwise, the patient would be deemed to have good response to IV corticosteroids and be continued on it for up to 7 days.

45.3.4 Salvage Therapy

When there is inadequate response to 48 h (or the third day of admission) of intravenous corticosteroids, salvage therapy should be instituted in a decisive fashion. The choice between cyclosporine and infliximab is a nuanced one, as data has shown both to be equivalent in outcomes (Williams et al. 2016). The choice is usually made on factors such as physician preference and familiarity with handling the drugs. As a rule of thumb, patients who are naïve to immunomodulators (e.g. thiopurines) can be started on cyclosporine as salvage treatment as they can be transitioned to immunomodulators. On the other hand, patients who are existing users of immunomodulators should be started on infliximab and subsequently be continued on combination therapy.

45.3.5 Timely Colectomy

Even with prompt and aggressive medical therapy, some patients will eventually require a colectomy to treat fulminant disease. The involvement of the colorectal surgeon and stoma therapist on the first day of admission would hopefully have prepared the patient for such an eventuality. Ideally, the colectomy should be performed in a semi-elective setting, with the patient adequately nourished and hydrated and having optimum electrolyte levels.

A three-step approach is preferred to minimise technical and anaesthetic complications, especially so in a patient who is unwell. The first step involves a subtotal colectomy and fashioning an ileostomy, leaving the rectum in situ. The next step can be performed about 4–6 months later when the patient is clinically in a better state. This would entail the construction of an ileal pouch and a defunctioning loop ileostomy. The loop ileostomy can then be closed in the third and final stage.

45.3.6 Discharge

On discharge, strict instructions on medication use and clear plans for follow-up must be adhered to as these patients would need to be on long-term immunosuppression. An IBD nurse engaged with the inpatient process is well placed to ensure there is good understanding here and that access to the IBD Advice service is available and clear. This is particularly important given that re-hospitalisation is not an uncommon situation. An early outpatient appointment at 1 week would allow for assessing the need of escalation of treatment.

Figures 45.1 and 45.2 summarise the information above.

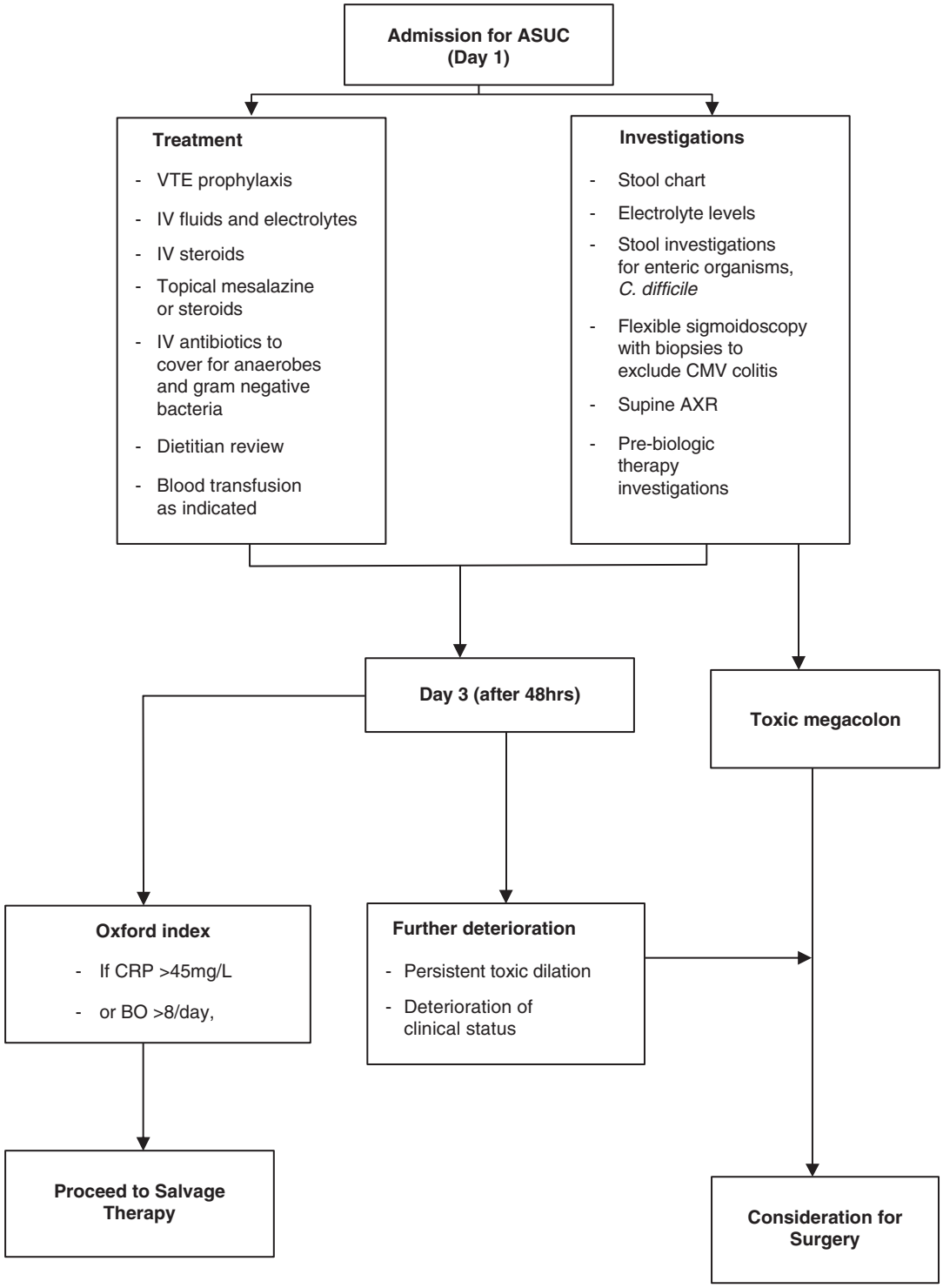

Fig. 45.1 Algorithm for management of ASUC (adapted from ECCO guidelines)

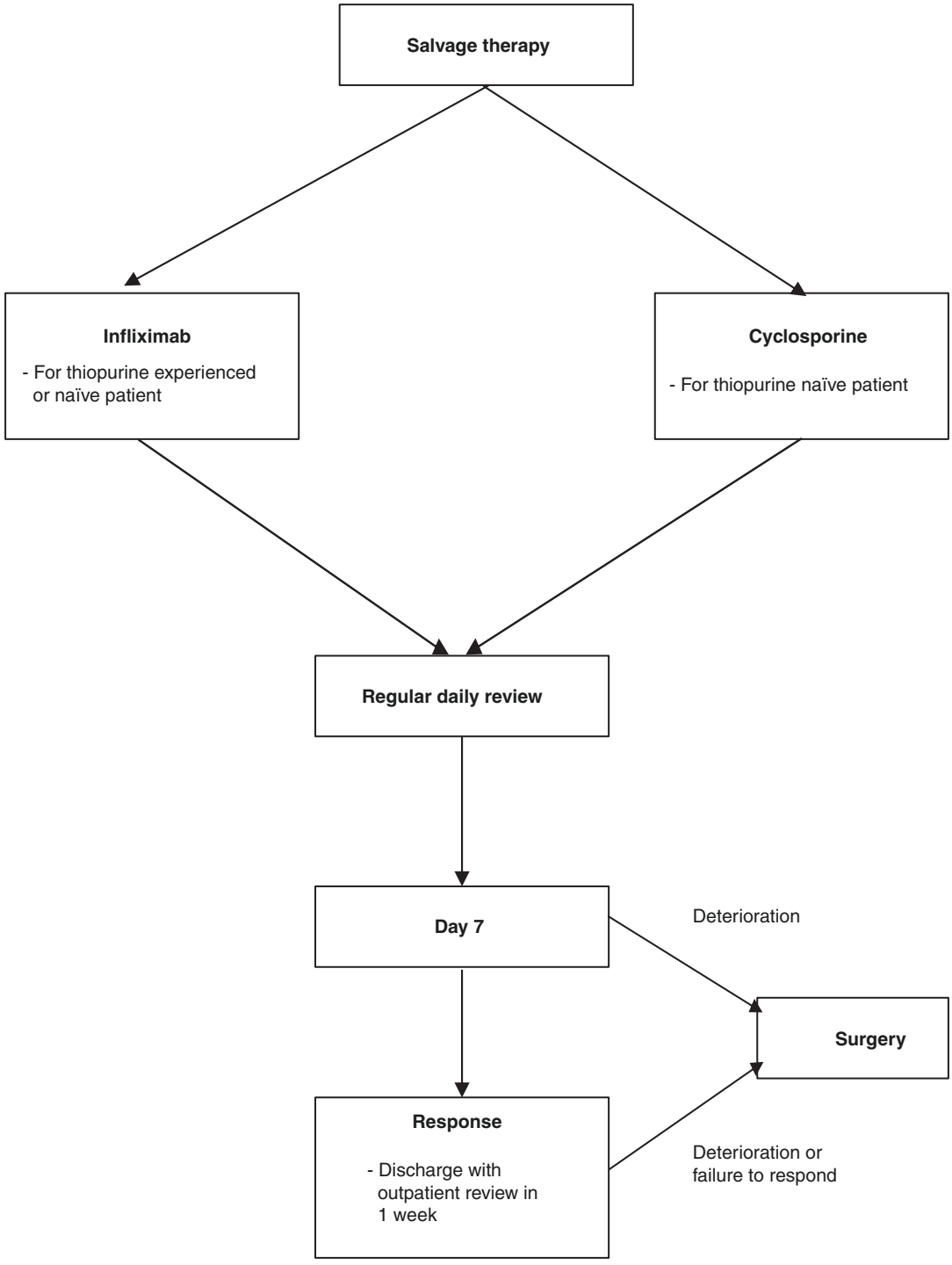

Fig. 45.2 Algorithm for salvage therapy (adapted from ECCO). ECCO Resource: http://www.e-guide.ecco-ibd.eu/algorithm/acute-severe-colitis

45.3.7 Application for Ward Nurses

As noted previously the IBD nurse could, and should, support the ward team caring for the patient. In knowing what information is needed for accurate assessment, diagnosis and decision-making, even simple tips to share with ward teams can be helpful. Table 45.4 notes key points in caring for the IBD inpatient.

Resource
Malnutrition Universal nutrition Screening Tool (MUST) via Bapen website (www.bapen.org.uk): http://www.bapen.org.uk/pdfs/must/must_full.pdf

45.3.8 Take-Home Messages

The admission for an acute IBD exacerbation is a trying time for the patient, IBD nurse and other healthcare professionals. The patient will invariably be anxious while facing the prospect of a possible change in treatment, such as colectomy, and emotional support will go a long way. In terms of medical management with ASUC particularly, key decision-making points occur at admission, Day 3 (after 48 h) and Days 6–7. Even after discharge, the patient should be aware that they are at a slightly increased risk of colectomy in the coming months and years.

45.4 Conclusion

A patient with IBD who is admitted for acute inpatient care presents a challenging scenario for medical professionals and the patient themselves. There are fewer instances where the relationship between the clinical team and the person with IBD would be more tested. So although there may be some barriers to the IBD nurse engaging with the inpatient care (time, outpatient pressures, hos-

Table 45.4 Seven tips for ward nurses looking after IBD patients

	Action	Rationale
1.	Daily **stool chart**	Accurate daily stool charts enable critical decision-making (as with ASUC above): – Frequency – Blood (present or not) Patients can often record themselves if given a chart (involves and empowers) (N.B. Bristol stool chart was developed for IBS, not IBD. Not indicated here)
2.	**Temperature** chart	Trends facilitate key decision-making, for example, in defining ASUC criteria and colectomy risk. Documentation needs to be accurate, linear and clear
3.	**Ileostomy volume**	Accurate measurement indicates fluid needs and patient capability at home: Volume = weight – For example, if volume > 1500 ml per day, IV fluids are needed So *do not* discharge a patient with volumes above 1500 ml
4.	**Weight**	Weight should be recorded every admission and sometimes more (e.g. on total parenteral nutrition, this should be daily) It helps assess the balances between adequate nutrition, energy utilised and gut function overall
5.	**Nutritional assessment**	Good nutrition is, of course, essential for energy, healing, growth, function and more. It can be compromised by many aspects of IBD, so it needs to be assessed at every admission. Tools such as the MUST tool offer ways more objective and comparable methods for such assessment (see resource below)
6.	Talk **with** the **patient**	The diarrhoea, urgency and incontinence (and more) are far more than 'inconvenient' and need to be viewed with empathy. Listening and understanding the priorities and concerns of the patient and their family enable good care and advocacy
7.	Engage with the **MDT**	Contribute to medical (and other) conversations on ward rounds, desk discussions and bedsides. Be involved, ensuring medical teams communicate their plans to the nursing team, have feedback and vice versa Communication needs to be a two-way traffic

Oxford University Hospitals NHS Trust. And References (Lotte et al. 2010; Travis et al. 1996)

pital geography, perceived lack of value or appreciation), there are important therapeutic benefits for the patient either directly (such as through advocacy, translation, emotional support) or indirectly (such as through clinical guidance, resourcing ward teams and directing to appropriate research options). Even if one perceives little practical role in a particular situation, the attributes and behaviours of IBD nurses most appreciated by patients have been cited to be that the IBD nurse is 'always there' (Belling et al. 2008). As an IBD nurse community, let us opt in and *be there* at this most critical moment.

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Nursing Support and IBD Networking

46

Karen Murdoch

Abstract

IBD nursing services can be enhanced with teamwork and collaboration from a wide range of professionals. By networking with other nurse specialists, much knowledge, protocols, and standards can be shared that can help support a new nurse in the role as well as experienced experts. This chapter will show the importance of networking and how it can help nurses support each other in their local workplace, nationally and internationally. Forging links with managers and beyond can lead to a system of improved service by providing leadership and organizational know-how. Using different methods of communicating nurses can share their ideas and knowledge easily and effectively, leading to improved clinical practices, standards, and a shared sense of a common goal. This can help improve job satisfaction, reduce stress levels, and lead to a nurse that is productive and confident of providing a high-quality evidence-based service.

46.1 Introduction

The specialty of inflammatory bowel disease nursing has been recognized for many years and impacts monitoring, clinical management, by providing advice and support to patients with this chronic disease. As the incidence of IBD increases, so does the workload of these nurses leading to the risk of becoming overwhelmed in their workplace: the need for support (within this group) has never been greater. Although IBD nurses work as part of an MDT, they might also be a lone post holder which can cause a certain degree of isolation.

46.2 Nursing Support

All nurses must be made aware of the support available to them in their field. However, communication has always been an integral part of nursing. How one communicates with patients, colleagues, and peers has a direct impact on job satisfaction and feelings of belonging (Kounenoua et al. 2011).

1. Collegial support—Other clinical nurse specialists in your immediate workplace are a useful resource when starting out. They already know the hospital system and can advise who are the key people to meet with as in senior management, information technology personnel, endoscopy staff, and inpatient

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ward managers. Collaboration through regular meetings or contact with key personnel can promote awareness of the service and help develop a partnership that supports the nurse to promote the service by implementing education sessions.

2. Clinical supervision—According to Davys (2007), support from a skilled and qualified clinical supervisor is crucial; this ideally should be a consultant from the gastroenterology team who specialize or has an interest in IBD. Asking an experienced colleague to teach and help develop this advanced nursing practice within that team could be helpful. This would then enable professional growth and allow safe and supported reflective clinical practice. By using evaluation and observation and providing feedback, the supervisor can discuss issues in a professional structured way. This can empower the nurse, enabling him/her to take responsibility for and enhance his/her practice. This partnership also promotes a healthy attitude to learning by encouraging teamwork and enhancement of the service using the skills developed in previous work environments from their different perspectives.

46.3 Management Support

The N-ECCO consensus guidelines (2013) state that advanced IBD nurses should have some knowledge about the wider strategic planning of health resources so that they can help direct their service to suit their patient population needs. Building up a trusting relationship with management is important, as they have the means and know-how to support the nurse by giving advice and guidance in setting goals and developing strategies and standards. Whayman et al. (2011) state that they believe that the educational and developmental needs of IBD nurses will need to change as the multimedia and online learning opportunities become common place. Working together with management to secure funding for education and development of the service for the future is crucial. It is suggested by Parand et al. (2014) that managers who do this can influence quality and safety, clinical outcomes, processes, and performance.

1. Nursing governance support—All countries have a nursing regulatory body who oversee nursing registration and set standards for education, training, conduct, and performance. They ensure all nurses keep their skills and knowledge up to date and abide by the council's code of conduct. All nurses must revalidate their registration either yearly or three yearly depending on which country you are in. Information can be found in their respective websites. Some examples are found below:

- Nursing Council of New Zealand
- The Nursing and Midwifery Council of UK
- Nursing and Midwifery Board of Australia
- Most countries also have a nurse's union or organization that offers professional and legal support should it be required.
- All information and fees are available on the appropriate websites.

Here are some examples below:

- New Zealand Nurses Organisation (NZNO)
- American Nurses Association
- The Royal College of Nursing

2. IBD nurses—IBD nursing practice has advanced over a short period of time in response to ever increasing needs. Even established IBD teams must navigate through the regulatory rules of their nursing bodies to ensure that nurses got the support and educational development that is required to work at an advanced level (Whayman et al. 2011). A current example of progress is this author's local example: In New Zealand we are at the stage of completing a knowledge and skills framework that will help support the IBD nurse through the stages of Professional Development and Recognition Programme (PDRP). This was introduced in New Zealand in 2004 and supported by the Nursing Council. PDRP was developed by employers and professional organizations to recognize

the clinical expertise of nurses by summiting a practice portfolio that can be assessed at a local level. Once approved this can make them exempt from going through the Nursing Council continuing competency audit. There is provision and remuneration in this agreement that awards the approved level of practice.

46.4 IBD Networking

A definition of networking according to *Merriam-Webster* (2016) is the exchange of information or services among individuals, groups, or institutions. In IBD nursing this can provide opportunities to share information and knowledge which encourages professional support among nurses who have the same common interest. It keeps nurses up to date with any new health developments and available resources. Sharing knowledge in this way helps nurses who are new or lone post holders have a sense of belonging and feel supported as part of a larger group.

Some nursing support groups were discussed in the previous section. Networks exist at many levels and are shown below, with the national level solely based on this author's experiences.

46.4.1 Local

Local support groups: It is useful to find out where the local Crohn's and Colitis organization is based as they might have local patient support groups that can be contacted to start the conversation about the service and increase its visibility. As stated by N-ECCO (2013) "It is advisable for nursing staff to be actively engaged in the creation and activity of support groups."

46.4.2 Pharmaceutical Representatives

Drug company representatives provide resources and information about products which makes building up a working relationship with them useful. However, caution is advised because this substantial educational support can also be seen as unethical (Jutel and Menkes 2008). These relationships are mostly positive, but nurses, particularly those who can prescribe medication, must be aware of being targeted to provide the commercial promotion of a (specific) product.

46.4.3 National

46.4.3.1 New Zealand Society of Gastroenterology/ Associates

Society members are physicians, surgeons, and scientists who diagnose and treat disorders or the gastrointestinal tract. They are responsible for and involved in organizing all gastroenterology registrar training and research. They hold a yearly conference for all gastroenterology departments in New Zealand, so everyone can come together and share their knowledge. The society also has regional "gut clubs" that nurses can join and receive newsletters which is a great way to meet like-minded people, increase knowledge, and widen the network field.

46.4.3.2 NZNO Gastroenterology Nurses' College

The New Zealand Nurses Organisation has various nurse's sections and colleges that focus on their specific field of nursing. The registered gastroenterology nurses come together and share and encourage excellence in nursing and college keeps members informed by newsletters or other publications they also participate in the development of evidence-based guidelines and specialty competencies. The college works closely with the gastroenterology society and is also involved in the yearly gastroenterology conference. Any nurse can apply to become part of the college and can also put themselves forward to be part of the college committee. This again is a great way to network and get involved in the wider gastroenterology community.

Below are some examples:

American Gastroenterological Association (AGA): www.gastro.org

British Society of Gastroenterology: www.bsg.org.uk

British Society of Gastroenterology Nurses Association (BSGNA)

This is a section of the British Society of Gastroenterology whose stated aim is to promote education, research, and the best clinical practice. There is a section on IBD on this site which has some great information, articles, and guidelines on care and management of IBD. There is also information on events on IBD throughout the world.

http://www.bsg.org.uk/sections/ibd-general/inflammatory-bowel-disease.html

46.4.4 International

The following organizations can be found online and provide substantial information on their respective websites. Nurses can join these organizations and apply for funding to attend international conferences. Many nurses involved are already leading the way as driving forces of change. Below are some examples:

46.4.4.1 European: European Crohn's and Colitis Organisation (ECCO)

This is a nonprofit medical association founded in 2001 and is the largest forum for specialists in IBD in the world. Their aim is to improve the management and care of IBD patients through the development of international guidelines for practice, research, and education. IBD nurses can apply to be a member for a modest annual fee. See contact details:

www.ecco-ibd.eu

46.4.4.2 Nursing European Crohn's and Colitis Organisation N-ECCO)

They have been active members of ECCO since 2007. Their aim is to provide nurse education and the opportunity for nurses to network internationally. This sharing of education enables practice development and promotes the nurse's knowledge in IBD, ultimately improving the care given to patients. Some nurses are very active in these networks and attend events all over the world. In 2012 they published a series of statements identifying the functions of IBD nurses from the most fundamental role to advanced roles; these sections are worth reading as the information could be used to give guidelines on progressing within. There are also educational programs available yearly. All information can be accessed through various sites.

46.4.4.3 World Gastroenterology Organisation (WGO)

This is a global organization whose mission statement is to promote the worldwide prevalence and optimal care of digestive disorders. They have wealth of information and IBD publications that can be accessed and downloaded online.

http://www.worldgastroenterology.org/

46.5 Where and How to Network

Howard, the director of educational resources in the Honor Society of Nursing Sigma Theta Tau International (which is one of the largest nursing organizations in the world) wrote that "Networking gives you the chance to become part of the nursing profession and not just a bystander"; "Meeting like-minded people who have the same struggles and ambition can give a sense of how nursing is changing, and how we need to be a part of it to be able to engage and get involved."

Below are some places where you can network:

- National conferences or meetings
- LinkedIn
- Professional organizations
- Become a board member or committee member
- Facebook
- Twitter
- YouTube
- Instagram

Khanum et al. (2016) discussed the role of the abovementioned social networks as useful tools that nurses can use to collaborate and share their knowledge findings which can improve the quality of healthcare. Patients use various apps and websites to gain insight and further knowledge of their health. Nurses must be able to use these systems as well so that they are able to discuss them with their patients and peers. Obviously if nurses are using social media, they must do this carefully and safely. As discussed previously in this chapter, most countries have a professional nursing body that have a nurse's code of conduct. One new area increasingly covered is the use of social media and electronic communications. The code advises nurses and informs the public what they can expect of a nurse in terms of their professional role in this new area (NCNZ 2017).

According to Sherman (2012) opportunities to network exist not only at work but in a social setting; networking is about the establishment of relationships which cannot occur if one is not in the position to meet new people. Networking is an active behavior in which some may feel uncomfortable in this situation, so below are some simple ideas/tips that may help:

- Arrive early to meetings or conferences
- Invite a colleague for support
- Become a member of a relevant committee
- Bring business cards that include an email address and phone number

46.6 Conclusion

As the use of communication and information technologies is growing throughout the world, both networking by attending events and conferences and computer networking provide an even greater platform for rapid interaction and collaboration within the nursing profession. Networking is crucial and can help with the development of a successful career by encouraging professional support through accessibility of colleagues and peers (Nicholl and Tracey 2007). Through these applications, IBD nurses have the potential to share their knowledge, expertise, and resources locally, nationally, and internationally. This will ultimately keep the specialty interconnected and moving forward in this ever-expanding profession.

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Advice Lines

47

Lydia White

Abstract

A fundamental aspect in the management of unpredictable, remitting and relapsing disease should be to assist patients to lead independent lives, to go to school, work, have families and much more. Appropriate advice and access to care is key to this goal, and achieving it is considered part of best practice in IBD services (O'Connor et al. J Crohns Colitis 7:744–764, 2013; IBD Standards Group 2013; Younge and Norton. Br J Nurs 16:208–212, 2007; van der Eijk et al. Eur J Intern Med 15:113–120, 2004). IBD nurses are key, consistent members of the multidisciplinary team and well placed (Kemp et al. J Crohns Colitis 7:e386–e395, 2013; Nightingale et al. Eur J Gastroenterol Hepatol 12:967–973, 2000). The patient perspective, most importantly, views the nurse as 'always there' and so is highly valued for direct expertise and timely access to further care when needed (Belling et al. 2008 and Woods et al. 2006).

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For many centres it is the 'Advice Line' or 'Help Line' that best utilises the advantage of the IBD nursing post and enables the link between the patient and specialist care when needed, facilitating the need for access often recommended (Pearson. Gastroenterology 7:15–19, 2005; Torjesen. Br Med J 344:e2675, 2012; Carter et al. Gut 53:V1–V6, 2004). The literature cited ranges from consensus opinion to audit and questionnaire, and it has been suggested that individual centre studies in particular lack the design, methodology and detail to support adequate statistical analysis (Hernandez-Sampelayo et al. J Crohns Colitis 4:611–622, 2010). However the body of literature continues to grow and Advice Lines have become a basic expectation for IBD services. This chapter offers a practical approach with recognition of safety and quality issues:

- The safety of remote assessment
- Setting up an Advice Line (with protocol excerpts)
- Nursing assessment of IBD
- The Advice Line for:
  - General advice and support
  - Investigation and treatments
- Documentation
- Monitoring quality via audit and survey

A. Sturm, L. White (eds.), *Inflammatory Bowel Disease Nursing Manual*,
https://doi.org/10.1007/978-3-319-75022-4_47

47.1 Introduction: The Advice Line

Essentially an 'Advice Line' for IBD patients is the point of contact that patients can use to get advice. Most centres use telephone and email advice primarily, but there is increasing use of other tools such as texting, websites, telehealth, apps and more (see Chap. 44. e-health). Due to its commonality with most services, the role of the telephone as the Advice Line is used as the main example in this chapter, but the principles can be adapted to other forms of connection.

Clinically the role of the Advice Line in IBD is to provide triage, early intervention and rapid access to patients (O'Connor et al. 2013). To start, each service should be clear on the remit of that interaction. The Royal College of Nursing (UK) document on setting up such a service recommends the term 'Advice Line' rather than 'Helpline' or 'Hotline' to avoid misunderstanding the availability of the service, i.e. this gets away from the 'immediate' response implicit using the word 'help' (RCN 2006). This particular nuance is in the English language, but each country or language should be mindful when setting up a point of contact service for IBD patients. This, and further considerations (below), should be carefully considered and agreed to ensure that patients, IBD nurses and supporting medical and other MDT colleagues have clarity.

47.2 Safe and Appropriate Remote Assessment

Use of remote assessment in health care has been debated through the years due to concerns about the loss of many non-verbal and para-verbal aspects of communication. In 2002 Peter Toon suggested that an undercurrent of suspicion regarding use of the telephone existed especially when used in routine practice as a replacement for face-to-face contact rather than as an adjunct to usual patient care. More than a decade later, this attitude may be shifting as technology becomes increasingly embedded in everyday life.

Remote contact with patients has certainly now been used for at least two decades in a variety of formats. A Cochrane review in 2008 looking at the use of interactive media concluded that more research is needed to demonstrate safety and efficacy where the telephone is used for clinical care (Currell et al. 2008). Since then, literature continues to accumulate examples of use supporting people with chronic conditions through expert advice, measures to improve disease control and for disease-related education (Lindberg et al. 2013). Entire journals and associations, such as the *Journal of Telemedicine and Telecare* and the Association of Telehealth Service Providers, continue to review and explore possibilities. However it is still important and relevant to balance the limitations of remote assessment with its practicality.

Clinicians also need to be appropriately skilled. There is a skill set inherent to a nurse using remote methods of assessing and advising patients. For example, the ability to use the technology at hand is an obvious start, and knowing when to use clinical judgement to ascertain what needs visualisation or physical examination such as with skin rashes (Rheumatology Forum 2006). However to maximise the safety of remote assessment, it is primarily essential that IBD nurses are skilled in advanced communication skills (O'Connor et al. 2013; Bulik 2007; Miller et al. 2002). Chapter 37 (communication skills) goes into further detail, but also individual centres should consider any local recommendations which may exist in their centre or via their governing bodies. For example, in the UK there are specific points about assessment and prescribing remotely (discussed below). These offer an essential starting point to UK practitioners highlighting the importance of working within competence as well as considering practical points such as establishing a current history in the context of the past (see Table 47.5) (General Medical Council 2006).

In summary it must be appropriately trained, competent, experienced and specialist clinicians who should remotely assess IBD patients.

47.3 Setting up an Advice Line

Details of an Advice Line service will vary between countries, health-care systems and even different local hospitals depending on local policy and guidelines. However, consideration of the following eight points (Table 47.1) will help ensure a comprehensive setup.

Point 6, above, recommends establishing a 'protocol'. Essentially this is the guidance, or agreement, that can be used so that clinical teams, and patients, have clear expectations of an Advice Line service (van der Eijk et al. 2004). Local protocols will reflect local practicalities and legalities and should outline the aims, lines of responsibility and the remit agreed for those involved in running and Advice Line (Coleman 1997; O'Connor 2011). They need not be overly complex. Tables 47.2, 47.3 and 47.4 and Fig. 47.1 are examples of key elements which could be included in an Advice Line protocol.

Individual hospitals are likely to have specific requirements on what needs to be included in a protocol, but it is recommended to try and keep these clear and succinct to ensure complexity doesn't outweigh usefulness.

47.4 Nursing Assessment

Having established the Advice Line plan, the IBD nurse will need to assess each call. Assessment of the unwell patient should follow a systematic approach and take into account the individual context. There is little nursing literature structuring IBD assessment though this is growing (Duncan 2011, pp. 81–94; Whayman et al. 2011). See also Chap. 4, Clinical

Table 47.1 Eight considerations when setting up an Advice Line service

1.The patient	• Is the clientele of a service able and likely to engage in remote assessment (see inclusion/exclusion criteria Table 47.4) • How will they be informed of the option? Patient information booklets, website announcements, face to face in clinic
2. IBD nurse	• Experience, knowledge and competence as well as specific qualifications (e.g. prescribing) • Availability of the nurse/s to agree cover. Some centres may only have part-time or single staff. This will dictate how the service can run and its sustainability
3. Support personnel	• Medical support for the nurses regards queries and situations outside of knowledge and experience. This will always be needed but to a lesser extent over time • Multidisciplinary support; links to other teams such as dietetics, pharmacy, care in the community as needed • Administrative support; may be needed for filtering clinical vs nonclinical calls, providing access to notes, inputting data to ensure cost recuperation and more
4. Access to resources	• Medical notes are essential for the whole context to deliver safe assessment and advice • Investigations and treatments (see below on prescribing) • Urgent clinic slots or hospital bed-space as needed • Complementary written or web resources • Adjunctive support services such as patient support groups
5. The practical environment	• Quiet uninterrupted environment for contact • Computer with links to hospital systems and data • Telephone with headset to allow hands-free work • Documentation (e.g. paper, electronic database communication)
6. Protocol	• Agree a protocol to reflect local policies and legalities • Include aims, responsibilities and remit (see below)
7. Quality control	• Audit; continuous and/or intermittent and detailed • Patient experience, e.g. by survey
8. Money flow	• Is there an appropriate mechanism for the remuneration of Advice Line support? For example, consider who would have provided this previously. If the patient would have had to come to an outpatient clinic, can this revenue be reassigned to contribute in principle/support or actual funds to the IBD nurse service

Table 47.2 Advice Line aims

Primary
a. Review and respond to patient's condition at time of contact
b. Improve access for acutely unwell patients
c. Improve safety of ad hoc contact with a thorough and contextual assessment
Secondary
d. Improve patient quality of life through the reassurance of a skilled accessible contact when needed
e. Improve appropriate use of clinic slots
f. Improve skill use as problems are triaged and more acute or complex patients can be discussed or seen by senior medical staff in clinic
g. Reduce cost for *hospital trust*, the *primary/community care* and the patient
h. Generate income for the *hospital trust* through appropriate charging (this is still less than a clinic cost so remains a cost saving for *primary/community care*)

Oxford University Hospitals Advice Line protocol v2017

Table 47.3 Advice Line responsibilities

Patient responsibility
1. Accurate and truthful communication
2. Polite and respectful at all times to staff
3. Responsive/consider advice or redirection
4. Use of Advice Line appropriately (more details can be given in local IBD service information booklet)
Advice Line team
1. First response attempt within 24 h of working days and total 3× attempts
2. Careful listening and comprehensive assessment of problem
3. Accurate and comprehensive documentation
4. Completion of agreed plan

Oxford University Hospitals Advice Line protocol v2017

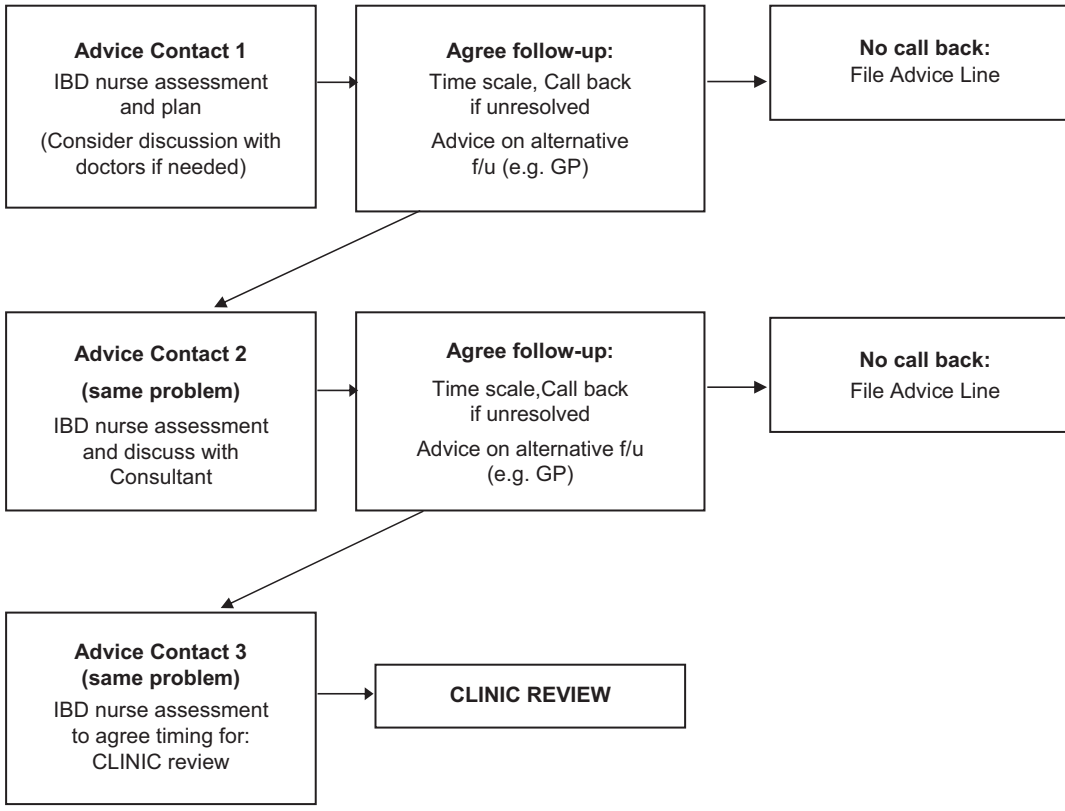

Fig. 47.1 Advice Line escalation policy

Table 47.4 Inclusion/exclusion criteria

Inclusion	Exclusion
1. Diagnosis of Crohn's disease, ulcerative colitis, yet-to-be determined, indeterminate 2. Patient records available to team 3. Patient (or carer) is able to communicate comprehensively and safely remotely	1. IBD diagnosis not yet made, microscopic colitis, coeliac disease 2. Patient records unavailable 3. Patient is unable to communicate comprehensively and safely remotely 4. Requests for results (bloods, biopsies, etc.) unless directed by IBD nurse

Oxford University Hospitals Advice Line protocol v2017

Assessment. To summarise, the important areas for assessment to consider in IBD are:

- Context
  - Diagnosis
  - Duration of diagnosis
  - Disease location
  - Disease pattern and behaviour
  - Additional factors: extra intestinal manifestations
  - Smoking and alcohol status
  - Past medical, surgical and psychosocial history
- Current assessment
  - Current medication
  - Presenting problem
  - Symptom profile
  - Disease activity (can use an index/tool)

When assessing the unwell patient, the current situation is of primary importance although the context must also be considered. As with any specialty, the nurse will need to gather both subjective and objective data to build an accurate history. It is good practice to advise a comprehensive approach initially to ensure important detail is not missed. However, with practice, experience and knowledge of individual patients, a more focused history taking approach becomes realistic (Rushforth 2009). It should also be noted that nurses managing an Advice Line should be sufficiently experienced and competent to identify and redirect as appropriate. Enquiries or concerns may not all be IBD related.

For the assistance of newer clinicians, particularly, an assessment aid (which could be included as a protocol appendix; Textbox 1) may help establish good initial technique:

Text Box 1 Assessment Aid for Telephone Advice Line

Before calling the patient, note the context:
Diagnosis and history

- Age/occupation (if available)
- IBD diagnosis, date, distribution, behaviour
- Previous surgery
- Key or recent investigations/bloods
- Previous medication and intolerances
- Others, e.g. EIMs, key social history, other key medical history, smoker/non-smoker

Current medication

- Prescribed medication (but then clarify with patient directly)

Call to the patient:

- Confirm details above
- Confirm medication and over the counter (OTC), herbal, recreational drugs

Assessment
PC (Presenting Complaint)

- Main or first concern of the patient: *important for appreciating the patient priorities - recognise main complaint or query, general well-being, off work, etc.*
- Symptoms
- Bowels: *frequency (day and night, time of day), consistency and odour (watery, explosive, variable), blood (colour, mixed, on wiping), mucous, wind, urgency (hurry, incontinence), compare to what's normal for the patient?*

(Text Box 1 Continued)

Text Box 1 Continued

- Pain in the abdomen or elsewhere: *location, frequency, duration, severity, constancy, characteristics, precipitating factor, bloating*
- Diet: *eating normally? appetite, weight loss*
- EIMS: *skin, eyes, joints, also fatigue, fevers, mouth ulcers*

HPC (history of presenting complaint)
How long have symptoms been going on, any correlation with treatment efforts/events…

Impression and plan

- Differentials (and indicate why)
- Discussion and choices offered
- Plan agreed (and indicate actioned)

Follow-up

- Always agree a backup plan: call if not settled, emergency GP if needed, escalate if… *After* call file or book records appropriately

Oxford University Hospitals Advice Line Protocol Appendix 1 2017

47.5 General Advice and Support

There are many aspects in a patient's life beyond the changes in their condition which can be addressed or supported via an Advice Line. Material on the patient's perspective note a wide range of subjects such as those discussed on the website of the main UK charity: https://www.crohnsandcolitis.org.uk. Just some examples are:

- Schooling and employment
- Smoking
- Diet
- Pain
- Fertility and pregnancy
- Travel
- Sexual and other relationships
- Medical compliance
- Stigma
- Transition from childhood to adulthood
- Fatigue

Literature corroborates the indissoluble relationship between managing IBD and these multiple aspects of life (Beaulieu and Kane 2011; Gassull and Fernandez-Banares 2007; Joachim and Acorn 2000; Kane et al. 2003; Nightingale 2007). It will not be possible for IBD nurses to know the correct advice in every given situation on such a vast array of topics so it is important to have access to appropriate information and to be embedded within the wider multidisciplinary team.

Finally, it is essential to recognise the limitations of an Advice Line. General support and advice does not replace the need for, for example, professional counselling in certain situations. IBD nursing services should be aware of how and where to refer patients within their local area.

47.6 Investigation and Treatment

Following a remote assessment and diagnosis of what may be causing particular symptoms, it may be appropriate to organise investigations such as blood tests, stool tests and radiological investigations (such as abdominal X-rays). This allows the accumulation of objective data to help guide practice but will, of course, be subject to the limitations of individual practitioner experience and agreed access to these tests.

Given that there is an infinite range of possible clinical scenarios which may present via an Advice Line contact, it is difficult to provide guidance for IBD nurses. Knowledge of current

guidelines, such as national or international guidelines on the management of IBD, are essential (ECCO guidelines: https://www.ecco-ibd.eu/publications/ecco-guidelines-science/published-ecco-guidelines.html).

To guide their nursing teams, individual services may wish to consider specific treatments and what they feel is appropriately done via remote assessment. For example, brief notes on key medications can help guide nursing teams.

- Mesalazine, sulphasalazine or balsalazide
  - These medications are appropriate in the use of ulcerative colitis but not Crohn's disease.
  - Dose adjustment may be appropriate to treat disease exacerbations.
  - Prescription of rectal products may be appropriate to treat disease exacerbations.
  - These medications may be stopped where there is concern of adverse reactions or side effects.
  - Caution should be used in the presence of renal impairment or other potential nephrotoxic drugs or disease.
  - General discussion and queries regarding the medication are appropriate via the Advice Line, and directing patients to written sources of information is advised.
- Thiopurines
  - Azathioprine and mercaptopurine are thought to be effective in the maintenance of Crohn's disease and ulcerative colitis. There is no place for their use in the main treatment for disease exacerbations.
  - Signs of disease toxicity or adverse reactions should be considered, and doses may be adjusted or medication stopped where appropriate. Outpatient review should follow.
  - Advice Line review is not appropriate for commencing these medications although preliminary discussion may be appropriate in the context of a second course of steroids within a year.
  - General discussion and queries regarding the medication are appropriate via the Advice Line, and directing patients to written sources of information is advised.
- Steroids
  - Have no place in the maintenance of Crohn's disease or ulcerative colitis and management and support may be appropriate via the Advice Line to reduce and discontinue this.
  - It may be appropriate to commence steroids via the Advice Line.
  - Discussion with medical colleagues is advised depending on experience.
  - Clinic review is advised during a reducing course so that maintenance therapy can be reviewed.
  - General discussion and queries regarding the medication are appropriate via the Advice Line, and directing patients to written sources of information is advised.

This list is clearly not exhaustive, and it is key to recognise that different levels of autonomy will accompany differing experience, competency and qualification. Services must also consider local policy, training and legal confines as well as update this information as practice changes with knowledge and research in the field.

47.7 Prescribing Remotely

Different countries and nursing governance issues will dictate whether, and how, prescribing remotely can be achieved and individual services need to consider these. Essentially, patients should have timely access to medicines from the professional most qualified to deliver care. For IBD, as with other complex chronic

Table 47.5 Applying safe principles to remote prescribing

GMC requirement	Application
1. Patient history including the concurrent treatment and non-prescription medicines	Review with patient notes for context, including medication intolerances and non-prescription medications
2. Assessment to identify the likely cause of condition	Use of qualified ANP assessment and diagnostic skills
3. Justification to prescribe and where appropriate discuss other options	Assess, discuss and document options and agreed plan of care
4. Treatment is not contraindicated for the patient	Review with notes for context including intolerances and concomitant conditions
5. Clear, accurate and legible records of prescribed treatment	All conversations and emails for file and follow process above. Pharmacy fax
6. Appropriate arrangements to follow the patient and monitor progress	Plan clearly documented to including follow-up and escalation plan
7. Inform the GP	Summary letter to GP but more detailed letter to be written if needed

conditions, this is considered to be within a specialist centre or via that centre. Despite challenges, therefore, remote prescribing can be appropriate for qualified and experienced clinicians (GMC 2013, NMC 2008). Advice Line protocols need to agree the specific processes which adhere to local and national requirements ensuring comprehensive communication and safe remote prescribing (GMC 2013, NMC 2006, 2008). For example, Table 47.5 shows simple practical steps that can sit alongside the General Medical Council (GMC, UK) recommendations.

47.8 Documentation

Advice Line contact should be documented clearly and communicated where relevant beyond the direct multidisciplinary team. Aside from the principles of accurate and comprehensive documentation (assumed here), it is important to ensure that documentation is recorded in a way, and place, that is accessible to all relevant members of the multidisciplinary team (van der Eijk et al. 2004; O'Connor 2011). A standard documentation form may be a logical approach. This example offers a simple telephone call back record with space to link with the wider service and to document actions taken:

Document 1

Oxford University Hospitals
NHS Foundation Trust

IBD Telephone Advice Line

Date:
Time:

Caller: ☐ Patient ☐ Relative ☐ GP/DN/PN
☐ other: _____

Call to: ☐ Advice Line ☐ Secretary ☐ Direct to CNS
☐ other: _____

Patient: Name
D.O.B
M.R.N

Phone numbers for return call:
1.
2.

Message:

Return calls and attempts:
1.
2.
3.

Diagnosis and History:

Current Medication:

Assessment:

Trial Discussion:
☐ Yes → Research Nurses
☐ No → Not suitable: _____
Patient choice: _____

Discussion with:
☐ Consultant: _____
☐ Clinical Fellow / SpR: _____
☐ Other: _____

Impression and Plan:

Follow-up:

Practitioner:
Sign and print

Date and Time:
of completion

Audit:

Query is chargeable to GP: Yes / NO
Total time taken to deal with query: _____ minutes

CONTENT	Clartfication	Query	Unwell
RESPONSE	Admin	Advice	Treat
FOLLOW-UP	Not urgent	Urgent Appt.	Admin

V4 AUDIT April. 2016. Lydia White

If you did't have the Advice Line would you have considered:
a. A&E admission Yes☐ / No☐ b. Urgent GP Yes☐ / No☐

Additionally, communication may need to be extended to other teams where care is shared, such as to GPs/primary care. Secure methods of communication must be utilised in line with local guidelines. It should also be noted that accurate documentation forms part of the safety of an Advice Line and support should liability of a case be in question (O'Connor 2011).

47.9 Monitoring via Audit and Survey

The final important consideration when setting up any service is to demonstrate its worth, its effectiveness, safety and quality as a whole. Both quantitative and qualitative outcomes are relevant to assess different angles of the service such as the:

1. Patient impact
2. Service delivery and organisational impact
3. Nursing impact

If set up well, it should be possible to regularly collect certain data for collation at appropriate intervals. For example, in the document for telephone Advice Lines offered above, it can be seen at the bottom that simple summaries can be built in about whether calls are charged, how long they took, what the calls were about and what the outcome was. This information can be used in many ways. At the least call number collation can demonstrate growth of a service and income generated (if relevant depending on the health system). This information can be key to justifying and growing nursing personnel needed for IBD nursing care (Fig. 47.2).

Quality review is not limited to audit, however. Patient survey at agreed intervals into Advice Line experience will give valuable feedback to a service or even internal service discussions of particular cases.

Below are some different applications of quality monitoring that could be applied to the service angles identified:

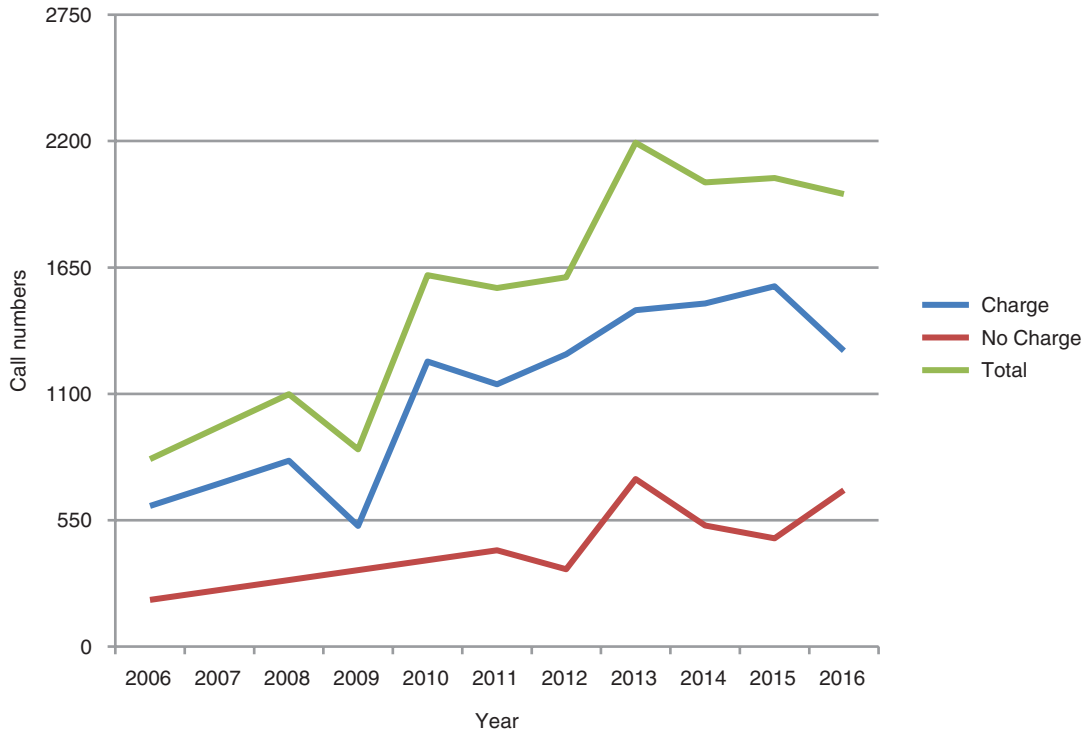

Fig. 47.2 Advice Line call growth in hospital nursing service ('Charge' is made when clinical care is given)

1. Patient impact
   a. Patient survey
   b. Additional audit to establish
      - Avoidance of primary or secondary care attendance
      - Effectiveness of clinical advice
      - Treatments remotely prescribed
   c. Detailed team review of any patient complaints
2. Service delivery and organisational impact
   a. Continuous audit of numbers of contact and
      - Main content or reason to call
      - Response category
      - Follow-up category
   b. Additional audit every few years to establish
      - Impact on resources and clinics, waiting times, clinic slots
      - Avoidance of clinic or GP visits
      - Time to call back and length of consultations
3. Nursing impact
   a. Discussion within the team, at nurse management meetings and at bimonthly IBD consultant team meetings
      - Training needs of post-holder
      - Impact of numbers on other role functions

Finally it should be noted that audit, survey and other quality measures or discussion need to be reported, actioned and evaluated. This ensures that the wider hospital team including key stakeholders and managers remain aware and invested in the service. Information gained will then help to inform future developments of the service and the evidence base for Advice Lines and nurse-led clinics in general.

47.10 Summary and Conclusion

This chapter has explored the role of the Advice Line in IBD service delivery. IBD nurses are understood to be a key point of contact for patients, and an Advice Line a key part of any IBD service ensuring timely advice, treatment and urgent access to care. When thoughtfully and appropriately set up, Advice Lines can safely assess, support and manage many aspects of IBD care. To achieve this, patients should be assessed by an effectively trained and supported IBD nurse using a systematic approach that takes into account the individuals' context. Finally, documentation of Advice Lines is important both in protocol and in individual assessment. Such an approach can then facilitate audit, survey and other quality indicators to continually assess the service.

The details of every Advice Line service are unlikely to follow all the details offered in this chapter. However the principles should be reflected in any service such that patients with this unpredictable and challenging condition are effectively advised and cared for in the timely and skilled way they need.

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Clinics

48

Usha Chauhan

Abstract

Inflammatory bowel disease is a lifelong, chronic condition consisting of two main subtypes: ulcerative colitis (UC) and Crohn's disease (CD). It is often characterized by an unpredictable disease course with fluctuating periods of quiescence and flares despite optimal therapy. As a result, the clinical management of patients with IBD requires flexibility. The majority of patients are managed in an outpatient setting. An outpatient clinic schedule aims to accommodate prompt access appointments for those patients who are experiencing exacerbation of their disease and for those who are experiencing side effects to medical therapy.

Nurses play a key role within the multidisciplinary team by providing clinical support and education and serving as a patient advocate. In a traditional clinic setting where face-to-face follow-up appointments are scheduled at the time of the clinic visit, there is a shortage of available clinic time for urgent, frequent, or prompt medical appointments. As a result, many specialist IBD nurses are filling in the required gap by setting up nurse-led follow-up clinics for prompt access or frequent follow-up appointments within the chronic disease model of care for IBD patients.

The onset of IBD is usually during teen years or young adult life, requiring frequent follow-up clinic visits which can disrupt family members' daily life to facilitate the scheduled clinic appointment. As a consequence, creative ways of conducting follow-up appointment are being considered through virtual clinic follow-up visits, telephone follow-up visits, or distance self-management. This chapter will cover face-to-face and virtual clinic appointment; however, telephone review and distance management will be discussed more in the e-health (44) and advice line (47) chapters.

48.1 Introduction

Sometimes, the diagnosis of IBD is delayed due to the presentation of mild or nonspecific symptoms or because extraintestinal manifestations are prevalent and supersede the gastrointestinal disease. Inflammatory bowel disease activity varies over time with episodes of quiescent disease followed by acute exacerbation of disease and follows an unpredictable disease course. This may be due to multiple factors such as disease progression, delay in access to medical therapy, and poor medication compliance (Sack et al. 2012). Medical treatment can be complex to

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induce remission or to maintain remission, and, as a result, patients with IBD may have to take multiple drugs for variable lengths of time ranging from a few weeks to a lifetime. All chronic diseases present with common challenges to the sufferers and their families, dealing with day-to-day symptoms, disabilities, emotions, difficult medication regime, and challenging lifetime adjustments (Wagner et al. 2001). Patients with IBD may suffer in silence and often do not want to discuss their bowel habit in public with the family and friends.

Continuity of care should be assured to establish a trusting relationship between the clinician and the patient. Providing effective, efficient, timely patient-centered care, which is responsive to individual needs of the patient, is paramount. The patients should be given the information about the disease and treatment necessary to achieve remission. They need to participate in decision-making on the available therapeutic options by clear explanations of the therapeutic potential along with the possible side effects of the prescribed drugs (Morar et al. 2015).

Through all the modes of clinic discussed in this chapter, these principles should remain the foundational focus of care.

48.2 Face-to-Face Clinic

The current model of IBD follow-up care is based on episodic visits based on the physician and clinic availability. The actual type of visit during any given scheduled clinic is based on physician preference, such as all initial consultation visits, all follow-up visit, or the mixture of both. The time allotted for each clinic visit is also based on the physician or the healthcare provider's preference. The initial consultation visit is often scheduled for a longer time period than a follow- up visit.

Most of the IBD care is provided in the outpatient clinic where symptoms, medication, and blood tests are reviewed (van Dullemen and Kleibeuker 2016). The clinic models fluctuate based on the available resources, and the model may include:

- One gastroenterologist model.
- Gastroenterologist shared care model, where a group of gastroenterologist provide shared care within a clinic setting; this can be with or without an IBD nurse specialist.
- Shared care model with advance practice nurse (APN) such as a clinical nurse specialist (CNS) or nurse practitioner (NP) (Sack et al. 2012).

The shared care models, with IBD nurse specialist or APN, allow for access to frequent follow-up visits allowing for alternating visits between the gastroenterologist and IBD nurse or with the APN. In addition, having an IBD nurse specialist allows for access to healthcare advice for the IBD patient between scheduled clinic visits, through telephone or scheduled face-to-face clinic visits. This model maintains consistency of care for the IBD patient.

The frequency of visit varies based on resource availability and the needs of the IBD patient and disease course. Frequencies of visits occur between every 3 and 12 months. These appointments commonly occur at a time when a person is feeling well and may result in little change in management of the condition (Whear et al. 2013a). The purpose of the clinic visit is to ascertain that the patient continues to feel well and determine and schedule necessary investigations for surveillance, such as screening colonoscopy and health promotion (influence and other vaccination, cervical Pap smear for females). The downside of scheduled appointments is the risk of missed appointments, especially if the patient is feeling well, and sometimes the clinic is not notified as a result which prevents access to those patients who need an earlier follow-up.

Many gastroenterology clinics work within a reactive model of acute care, with a single practitioner typically providing care for patients with active disease rather than providing continuous care. Their services are limited by time restraints. Despite considerable resources invested into this reactive acute care model, patient outcomes are often unsatisfactory, which suggests a potential for improvement (Mikocka-Walus et al. 2013).

48.2.1 Patient-Initiated Clinic

Patient-initiated follow-up visits offer control for the patient, with an aim to be more responsive to the needs of the patient with the likelihood of minimizing missed appointments (Kemp et al. 2013; Whear et al. 2013b). Currently in practice, patients experiencing an exacerbation of their condition can call the "on the telephone" advice line, manned by a specialist nurse or an administrative assistant, and a necessary consultant appointment is arranged as soon as possible (Whear et al. 2013b). Patient-initiated clinic appointments, studied in IBD by Robinson et al. (2001), reported that the time between symptom flares and treatment was significantly reduced for patients in the patient-initiated clinic group, in comparison to the control group (m = 14.8 h vs m = 49.6 h), respectively; $p < 0.0001$. Cheung et al. (2002) report open access or patient-initiated clinic follow-up delivers the same quality of care as routine outpatient care and is preferred by patients and general practitioners. It also uses fewer resources in secondary care practice; however, the total resource utilization was similar and reports better methods of ensuring urgent access to outpatient clinics are needed (Cheung et al. 2002).

48.2.2 Prompt/Urgent Access IBD Clinic

Due to the unpredictable nature of IBD, patients may need to be seen promptly when the disease is active. Options include going to an urgent care unit or emergency department. To maintain continuity of care for the IBD patient and prevent misuse of emergency room services, many IBD outpatient clinics reserve clinic appointments for urgent or prompt access during the scheduled clinic time. Alternatively, half day prompt or urgent access clinics run as shared practice models with a gastroenterologist or advanced practice nurse are often routinely available. The appointment is scheduled within 1 week for those patients exhibiting symptoms of active disease or a new diagnosis of IBD (Paterson et al. 2006).

48.2.3 Nurse-Led Biologic Clinic

Biological therapy has made enormous impact on treatment of IBD, is costly, and has been used extensively in the past 20 years. The safe, cost-effective, and efficient delivery of biological treatment requires careful coordination and supervision. An IBD specialist nurse involved in the management and delivery of biological therapy is in a position to ensure appropriate screening before starting biological therapy with the identification and recording of any contraindications to therapy (O'Connor et al. 2013).

Decision to start biological therapy is made within multidisciplinary team (MDT) or by the primary gastroenterologist and the patient. The choice of the drug should be tailored to the individual needs of the patient, preference of the patient, route of administration, patient's lifestyle, cost of therapy based on jurisdiction and the type of medication coverage, and ability to safely deliver the medication and monitor the treatment safety (Hamlin et al. 2011). The role of the IBD nurse specialist can be crucial in counseling and educating the patient about biological treatments, coordinating pretreatment screening tests, and organizing treatment.

Once the biological therapy is commenced, it is important to monitor for medication side effects and response through validated disease scales such as the modified Mayo scale for ulcerative colitis and Harvey Bradshaw index for Crohn's disease. Within the nurse-led biological clinics, IBD nurses are well positioned to monitor, provide regular assessment of disease activity, and support information sharing, coordination, and continuity of care for the IBD patient.

There are different settings in which an IBD nurse can facilitate aspects of care for patients receiving biologic therapy.

Nurse-led biologic clinic are set up in both an academic hospital setting and in the community clinic or private practice setting. Some clinics will actually administer the infusion as well as the injection training of subcutaneous biological therapy. In order to save healthcare resource and time for patients, an IBD nurse can conduct

routine follow-up appointment that may also be scheduled based on needs of the patients every 3 months.

48.3 Virtual Clinic

The lifelong management of chronic disease faces major challenges in the current healthcare system, especially the outpatient clinic. In light of the unpredictability of IBD and pressure of conventional follow-up which occur once per year in a busy gastroenterology clinic, to maintain specialist contact can be inconvenient and expensive for both the patient and healthcare system (Hunter et al. 2012).

Virtual clinics, whereby healthcare providers monitor and make management decisions in the absence of the patient, have been utilized in chronic disease processes (Ward 2016). There are a number of different models. One model is situated within a multidisciplinary care model whereby weekly meetings are attended by gastroenterologists, surgeons, IBD nurse specialists, an ostomy nurse, dietician, pathologist, radiologist, and pharmacist (Panés et al. 2014). This model of virtual clinic allows for reviewing complex IBD cases and ensures that a consistent approach to treatment and monitoring of patients who receive biological therapy is maintained (Panés et al. 2014). The meetings are documented, and correspondence is provided to the patient and the general practitioner. The IBD nurse specialist plays a key liaison role and acts as the patient advocate within the MDT model (Panés et al. 2014).

Virtual compassionate medication access clinics have been set up to manage patients who have secondary loss of response to biological therapy, based on predefined protocols (Ward 2016). Dose intensification was provided through the compassionate access of biological therapy, once again providing a consistent approach to optimal therapeutic management.

Hunter et al. developed a virtual IBD clinic to solve long wait times. Patients were identified from a database; 2 months before a scheduled annual follow-up, a blood test was taken, and a simple disease assessment questionnaire was mailed to patients with instructions to call the IBD specialist nurse if they met any of the criteria on the questionnaire for possible active disease. The blood test was reviewed by the IBD nurse specialist, and a report was sent to the primary care physician. Surveillance tests were also scheduled based on the current practice guidelines. Between 2006 and 2009, 866 outpatient appointments were avoided, and 90% of patients were satisfied and preferred the virtual clinic.

Virtual clinics and networking may also provide models through which high-quality, expert-integrated patient care in IBD can be delivered, and outpatient clinic appointments can be avoided to reduce wait time. This model allows for the ability to schedule required appointments.

48.4 Pediatric to Adult Transition Clinic

Children and adolescents with IBD tend to have more extensive and severe disease than adults, which interferes with growth, psychosocial, and sexual development often delaying adolescent milestone development (Goodhand et al. 2011). Transition is the purposeful, planned movement of adolescents and young adults with chronic physical and medical conditions to adult-orientated healthcare systems (Goodhand et al. 2011). Pediatric healthcare is family focused, multidisciplinary, and reliant on parental involvement for consent and guidance; however, in contrast, adult gastroenterology is focused on the individual patient, is carried out by single providers, and advocates patient independence (Bollegala and Nguyen 2015). In some jurisdictions, patients cannot be admitted to a children's hospital past the age of 18. Good preparation, early education about the transition process, and the acquisition of self-management skills are crucial to fostering a smooth transition process. Readiness to transition will impact the adolescent's ability to become independent, as well as the adult provider's ability to address the adolescent's medical and psychosocial needs.

The North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN) (Baldassano et al. 2002) has pub-

lished a set of recommendations pertaining directly to the transition of patients with childhood-onset IBD from pediatric to adult care. In them they state the pediatric gastroenterologist begins the process of transition by performing the following four steps:

1. Seeing adolescent patients without their parents
2. Discussing with the patient and family the benefits of transition to an internal medicine gastroenterology practice
3. Developing a relationship with an adult gastroenterologist who is knowledgeable in caring for young adults with a history of childhood-onset IBD
4. Providing all of the necessary medical records and summaries so that the family will realize that all providers are working together to deliver excellent care

Some of the models and principles of transitional care presented in the review by Bollegala and Nguyen (2015) include:

1. Yearly combined visits with the pediatric and adult gastroenterologist starting at age 14 years.
2. Three alternating visits with a pediatric and adult gastroenterologist in the year prior to transfer of care.
3. One combined final visit with the pediatric and adult gastroenterologist, occurring at the time of transfer.
4. Choose a time that is convenient for the patient.
5. Both pediatric and adult gastroenterologists should be present in addition to other healthcare providers, including the IBD specialist nurse.
6. A medical summary should be provided to healthcare practitioners, as well as the patient and their family in advance of the transition appointment.

The transition period has been associated with poor health outcomes due to nonadherence to medical therapy and follow-up care (Kahn 2014). Adherence issues are related to multiple factors such as young age, single status, high-level disease activity, heavy pill burden, high cost of medications, medication refill inconvenience, perception of lack of therapeutic benefit, feeling of being uninformed about medication, low socioeconomic status, psychological comorbidity, and perception of social stigma (Kahn 2014).

With earlier use of biological therapy in pediatric IBD patients, the frequency of clinic follow-up appointments is every 2–3 months, with routine blood work done at the time of clinic visit to maintain compliance in conjunction with a clinical assessment. Once transitioned to the adult care, the IBD nurse specialist can closely monitor the young adult patient by maintaining the frequency of visit schedule to every 3–4 months within a shared care model or through the nurse-led biologic clinics. The IBD nurse specialist can also provide care between clinic visits through telephone or email access. Additionally, the virtual clinic model may be useful in communities where access to IBD specialists is more challenging.

48.5 Integrated Model of Care

The integrated model of care has been defined as bringing together different services required for the IBD patient to provide service related to diagnosis, treatment, care, rehabilitation, and health promotion (Mikocka-walus et al. 2013). The benefit of working in a multidisciplinary environment has been shown to improve the continuity and cost-effectiveness of care in chronic diseases, to improve health and quality of life of patients, and to contain healthcare costs for both in- and outpatient management (Morar et al. 2015). (See also Chap. 50, The IBD MDT.)

For the IBD patient, this may include engagement in the provision of care with an IBD nurse specialist, gastroenterologist, surgeon, and enterostomal therapy (ET) nurse, within a multidisciplinary team (MDT) (Panés et al. 2014). Preferably this care should be delivered within an IBD center of excellence (Panés et al. 2014). The clinical team should have access to essential supporting services with an interest in inflammatory

bowel disease, including a psychologist or counselor, psychiatrist, rheumatologist, ophthalmologist, dermatologist, obstetrician, nutrition support team, pediatric gastroenterology clinical network, and general practice based on the needs of the IBD patient at any given time during the course of the disease (Panés et al. 2014; Morar et al. 2015). It is recommended that the IBD MDT team communicates readily with the general practitioner (GP) because the GP remains the preferred source of information in 83% of IBD patients (Farraye et al. 2017).

Each member of MDTs provides a unique service to the IBD patient as described below.

48.6 Role of the Dietitian

Malnutrition is common in patients with IBD, especially in patients with Crohn's disease (Louis et al. 2015). Taking a diet history is an essential skill of a dietitian; however, nurses need an awareness of potential nutritional issues in patients with IBD, to ensure these are appropriately identified and managed (O'Connor et al. 2013). A dietary history can be completed one of three ways: by retrospective questioning of the usual dietary intake, by 24-h recall, or by a 3–7-day documented food record that is completed by the patient before the consultation (Halmos and Gibson 2015). Nutritional quality and quantity may be determined through dietary pattern, number and type of meals and snacks consumed in a typical day. Micronutrients are assessed through the variety of food consumed within the five food groups (Halmos and Gibson 2015). Therefore, obtaining a thorough diet history is vital assessment required for IBD patient.

Nutritional care in children with IBD includes promotion of optimal growth and development and prevention or treatment of nutritional deficiency and malnutrition (Louis et al. 2015). Numerous studies have supported the efficacy of enteral feeding compared to corticosteroids inducing remission in children with Crohn's disease (Richman and Rhodes 2013). Enteral feeding is a first-line therapy for pediatric IBD patients.

Malnutrition occurs in up to 85% of patients, and weight loss affects up to 80% of patients with Crohn's disease and 18–62% of patients with ulcerative colitis (Lomer 2011). Nutritional deficiencies are particularly prevalent in relationship to anemia and osteoporosis. Patients with small bowel strictures are prone to mechanical obstruction; therefore a low-residue diet or one limiting fibrous food may be helpful (Lomer 2011). Quality of life can be affected by functional symptoms such as bloating, abdominal pain, flatulence, and diarrhea. A group of poorly absorbed carbohydrates which naturally occur in diet called fermentable oligo-, di-, and monosaccharides and polyols (FODMAP) have been associated with causing rapid gas production and increased fluid delivery to the colon leading to functional symptoms (Lomer 2011; Richman and Rhodes 2013). A diet in low FODMAP can help elevate functional symptoms.

48.6.1 Role of the Psychologist and Psychiatrist

The diagnosis of IBD frequently occurs at an early age and can often result in hospitalization and surgery, leading to numerous physical and psychosocial challenges for IBD patient. There is evidence to suggest that abdominal pain perception, sleep dysfunction, increased use of psychotropic drugs, nonadherence to medication, and negative illness perceptions are likely manifestations of psychological morbidity in young people with IBD (Brooks et al. 2016). These psychological disorders can contribute to poor health-related quality of life regardless of the disease severity (Zhang et al. 2013). Stress has been reported as major contributor of development of disease and is thought to cause the flare of disease (Häuser et al. 2014). Healthcare providers in IBD need to look beyond IBD symptoms and disease severity and examine the patient's perception of functional disability, coping with IBD, and observe for symptoms of anxiety and depression by routinely screening all patients for signs of psychological morbidity, including anxiety and/or depression.

Screening may be conducted using the brief, four-item screening scale for anxiety and depression (PHQ-4) or by more elaborate interviews

such as the Luebeck semistructured Interview for Psychosocial Screening in IBD (Alarhayem et al. 2015; Bennebroek Evertsz' et al. 2012) or the Hospital Anxiety and Depression Scale (HADS) (Zigmond and Snaith 1983). Screening can also be completed using three key questions to identify those with psychological symptoms followed by three further questions to determine persistence and severity of symptoms, as described by Graff et al. (2009).

Once a diagnosis of anxiety or depression is suspected, referral to psychotherapeutic services should be made, based on the services available within the local healthcare system. Treatment within the MDT with a psychiatrist or psychologist may include specific pharmacological agents, particularly the selective serotonin reuptake inhibitors [SSRIs] such as citalopram, fluoxetine, fluvoxamine, paroxetine, and sertraline and the serotonin norepinephrine reuptake inhibitor [SNRI] venlafaxine. In addition, patients may benefit from receiving psychological interventions such as cognitive behavior therapies (Graff et al. 2009). Patient anxiety about treatment can be reduced by understanding the expected clinical benefits of medical therapy and having knowledge that medication may not begin to be effective until 2–4 weeks after commencing therapy. Patients also need information about medication side effects, especially worsening of gastrointestinal symptoms, reduced sexual function, and weight gain, which all may be transient (Graff et al. 2009). Screening for early signs of depression or anxiety and initiating pharmacological or psychological treatments when appropriate can lead to improved functioning and positively affect the course of disease.

Access to psychologists is still problematic worldwide despite all the evidence that unmanaged mental symptoms may impact disease activity, thus leading to preventable suffering and increased healthcare costs (Mikocka-Walus et al. 2014).

48.6.2 Role of the Colorectal Surgeon

Some studies report surgery rates in IBD have decreased with the availability of improved medical therapy (Balzola et al. 2013); however, the cumulative surgery remains around 15% in UC and 47% in CD (Frolkis et al. 2013). The reduction of surgery is due to access to availability of targeted medical therapy for the IBD patient and enhanced knowledge of medical therapeutic strategies through practice guidelines. There is a shift in care of the IBD patient from a surgeon to a gastroenterologist.

The UK standards group recommends that surgery should be performed by an experienced colorectal surgeon who is a core member of the IBD team (IBD Standards 2013). Postoperative complications are decreased due to the operating surgeon's volume with operative procedures and experience (Louis et al. 2015). Patients requiring ileoanal anastomosis (J-pouch) surgery or more complex CD procedures should have the operations carried out by specialist surgeons with appropriate training and experience (Louis et al. 2015). This prospective study following an ileoanal anastomosis with multidisciplinary team facilitating follow-up and management showed that this type of team provided more efficient, beneficial care, enhancing patient satisfaction.

It is important to maintain a close and structured integration of medical and surgical management to determine the right time for surgery in order to prevent postoperative complications and reoccurrence of disease (Louis et al. 2015). This can take the form of parallel or joint medical and surgical clinics or through close communication with each program (Louis et al. 2015).

48.6.3 Role of the Enterostomal Therapy Nurse

Enterostomal therapy (ET) nurses specialize in management of patients who will be undergoing colorectal surgery with formation of an ileostomy. The ET nurse plays a crucial role in preoperative stoma site marking, preoperative education, appropriate pouch/barrier fitting, and pouch maintenance (Stelton et al. 2015).

Once the stoma is created, the ET nurse provides ongoing support for any peristomal

skin-related problems, issues related to poorly fitting appliances around the stoma causing leaks and skin irritation, and problems with the stoma either with protrusion or inversion. In additional, the ET nurse can provide support with postoperative wound healing complications and any perianal skin-related problems due to perianal fistulizing disease.

48.6.4 Role of the Maternal Medicine Program

Inflammatory bowel disease is often diagnosed in the reproductive years (Molodecky et al. 2012). Therefore, managing IBD patients requires discussion regarding future pregnancy plans and is necessary in order to educate IBD patients about the importance of optimal disease control of IBD before conception and the safety of IBD therapies. The impact of IBD on pregnancy outcomes correlates with the level of disease activity at the time of conception. Overall, most women with inactive IBD experience an uneventful pregnancy (Hendy et al. 2015).

Preconception counseling should be an essential part of primary and preventive care for all women of childbearing age who present for a periodic health examination (Nguyen et al. 2016). It provides an opportunity for the healthcare provider to address IBD women's concerns regarding transmission of IBD to the offspring, to optimize control of disease activity and to avoid inappropriate discontinuation of medication. Preconceptual counseling is effective in achieving desirable behavioral modifications in IBD women in terms of folic acid intake, smoking cessation, and correct IBD medication adherence, eventually reducing disease relapse during pregnancy (de Lima et al. 2016).

In the recent Toronto guidelines, they recommend that for women who are planning a pregnancy, "an objective disease evaluation be performed before conception to optimize disease management" (Nguyen et al. 2016). Poorly controlled IBD prior to conception can lead to preterm delivery or small gestational weight infant. When activity is present at the time of conception, two thirds of women will have disease activity that persists or may worsen during the pregnancy. Women often overestimate harmful effects of medications, but underestimate the harmful effects of IBD exacerbation during pregnancy.

Throughout pregnancy, patients may be shared between a gastroenterologist and an obstetrician. The number of visits during pregnancy should be individualized based on the severity of disease, other medical factors, and the needs of the IBD patient. Regular medical visits need to be done according to the health status of the mother and the baby, allowing monitoring of disease activity, providing the opportunity for ongoing patient education, and reinforcing the importance of adherence to IBD therapy.

The IBD nurse specialist may also play an important role in counseling and following the pregnant woman with IBD, e.g., providing the female patient with information to help her accurately evaluate the pregnancy-associated risks associated with relevant IBD drugs and help prevent unnecessary avoidance of pregnancy.

Labor and delivery plans should be discussed with the treating team; IBD may affect the decision if a vaginal or cesarean delivery may be preferred.

Breastfeeding is strongly encouraged because there are a number of benefits for both women and infants. Breastfeeding is not associated with an increased risk of disease flare and may even provide a protective effect against disease flare in the postpartum year (Hendy et al. 2015).

48.7 Summary

In summary this chapter has provided an overview of various outpatient clinic models for IBD patients. This includes face-to-face clinic, single physician, to shared care model. Current outpatient clinic models of episodic follow-up visits may not be an ideal model for both the IBD patient and healthcare provider; it can cause long wait times and clinic backlog. Virtual clinic, open access, or patient-initiated clinic models can be associated with improved care provided for

patient, which in turn can lead to improved quality of life. This model can also reduce clinic wait times.

The long-term course of IBD often presents with periods of symptomatic flare-ups with periods of remission, and, as a result, outpatient clinic models need to accommodate the needs of the patient. Typically, IBD patients are managed by a gastroenterologist and an IBD specialist nurse with a shared care model; however in some cases due to the complex nature of the disease, other specialties are required within an integrated or multidisciplinary model of care. The members of the MDT provide the necessary care required for the complex IBD patient which impacts on patient quality of life. The best care is provided by a dedicated IBD unit and by a multidisciplinary team [MDT] with expertise in different aspects of the conditions.

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Maintaining an IBD Nurse Service

49

Catherine Stansfield

Abstract

The following chapter considers the development of an IBD service and strategies that can be used to capture the value of the service, including the use of patient stories and audit in capturing outcomes from the service. Then reflecting upon how this information can be used to provide the basis of business case development.

Recruitment and retention are also discussed to inspire nurses' enthusiasm for the specialty including considering student nurse placements and link nurse roles to support the expansion of specialist nurse services recognizing that process of services is often cyclical and further expansion required as the service develops.

49.1 Maintaining an IBD Service

IBD management is increasingly concentrated in units with expertise in the condition, committed to improving the outcomes of individuals with the disease. A key role in the day-to-day running of these units is that of the clinical nurse specialist. The prevalence of such roles has increased exponentially over the last decade in the UK (RCN 2012), and projects such as the NECCO consensus (O'Connor et al. 2013) reflect growth around the world as well.

One of the main challenges for nurses leading teams is to demonstrate the value and contribution of the nursing team to improve outcomes for patients and measure the impact of their role upon clinical services. The aim of this chapter is to help nursing services to consider their contribution, how value and impact can be demonstrated and how this information can be utilized to expand the service.

49.2 Demonstrating Value

It can be difficult for nurses to articulate their contribution to patient care; as a result this can make it difficult to articulate the aspect of service development that is required. Nobody will contest that specialist nurses are valued by the people who receive care, but sometimes it is difficult to express exactly what the value is. On reflection, it is easy to understand how finance and service managers fail to understand the complex nature of caring, and, as such, roles can often be undervalued (RCN 2010). It is these misperceptions that require dismantling, and nurses need to develop skills to collect evidence to clearly demonstrate their contribution and value to care. There are several approaches which can be taken, some more simple than others.

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49.2.1 Patient Stories

Capturing the patients' perception of the service is a good place to start. It helps to show what works well and how the experience can be improved and can help to inspire teams to improve care as patients should be central to service delivery and development. A number of strategies can be utilized such as patient satisfaction surveys, patient panels, and patient stories. The use of patient stories to understand the patient journey is a simple way to collate this evidence (NICE 2017). It is usually done by someone outside of the nursing team to avoid any perceived bias. The format of patient stories can be as simple as questions such as:

- Talk me through what happened to you:
  - Where was it?
  - When did it happen?
  - Who was involved?

Stories will often relay how patients felt about their experience and the particular care touchpoints and the impact of these touchpoints on them. Relating this to IBD, patient stories can help the organization understand how health care fits into the patients' wider life, for example, when a patient starts biological therapies, what happens between the episodes of care? This can illustrate the implications of how things are done, of the way clinics are organized, or of problems such as delays, poor communication, or the need to chase and complete follow-up. It is this information which often demonstrates the difference an IBD nurse makes in the patient experience.

49.2.2 Job Plans

It is also important that nurses are able to plan and evaluate their service when considering service development. Important considerations to consider as an IBD nurse are:

- Demonstrate how you spend your time.
- Describe the complexity of your work.
- Quantify your contribution to safety, quality, and efficiency.
- Articulate what is unique about your work.

The Apollo specialist nurse resource (Apollo Nursing Resource 2016) (www.apollonursingresource.com) is extremely valuable in enabling these questions to be answered. Within the resource, nurse specialists are recognized as key contributors to patient safety, articulating their activities in terms of the following domains:

- *Rescue work*—this involves the early detection of impending deterioration and taking preemptive action to prevent adverse events (e.g., managing exacerbations of IBD, managing adverse events related to DMARDs).
- *Vigilance*—active monitoring of patients (e.g., azathioprine monitoring).
- Preventing unscheduled admissions—many specialist nurses run helplines assessing disease control, advising medication changes, or signposting to other services (e.g., colorectal surgeons, GPs).
- *Using outcome measures* such as dealing with distress and symptom control.

Within the Apollo resource, the authors suggest the use of Cassandra© app (www.apollonursingresource.com). This is available within the website and provides a template to capture CNS interventions and demonstrate their value on a daily basis. Information is usually captured over a week or a month, and data is transferred to a spreadsheet to collate the information. Repeating this annually will demonstrate how a nursing service has evolved and how the demands have changed.

49.3 Developing Job Plans

Building on the Cassandra app, the use of a detailed job plan is one of the quickest and easiest ways to show how time is spent. It demonstrates what is done during the day but also the deficit for the service in the absence of the nurse. Initially, the nurse needs to consider where they

go and what they do. Then they should reflect upon these activities in terms of the domains of vigilance, admission avoidance, rescue work and outcome measures, and how these domains can be used to describe the work that nurses do.

A basic job plan would cover 10 sessions over 5 days, but in some roles which include evening and weekend work, there may be a need to be more flexible. An example job plan is shown in Fig. 49.1.

49.4 Using Audit to Capture Service Activity

Clinical audit is a proven method of quality improvement (NICE 2017); audit is important to identify certain aspects of a service there may be concerns about. For example, the amount of biologics used may have increased significantly, and compliance with ECCO guidelines and services may need to be developed. Audit enables:

- Identification and promotion of good practice
- Improvements in patient care
- Provides information about the effectiveness of a service
- Highlights problems and helps with solutions
- Improves team working and communication

The process of clinical audit is summarized in the audit cycle in Fig. 49.2 (NICE 2017).

49.4.1 Developing Audit Questions and Setting Standards

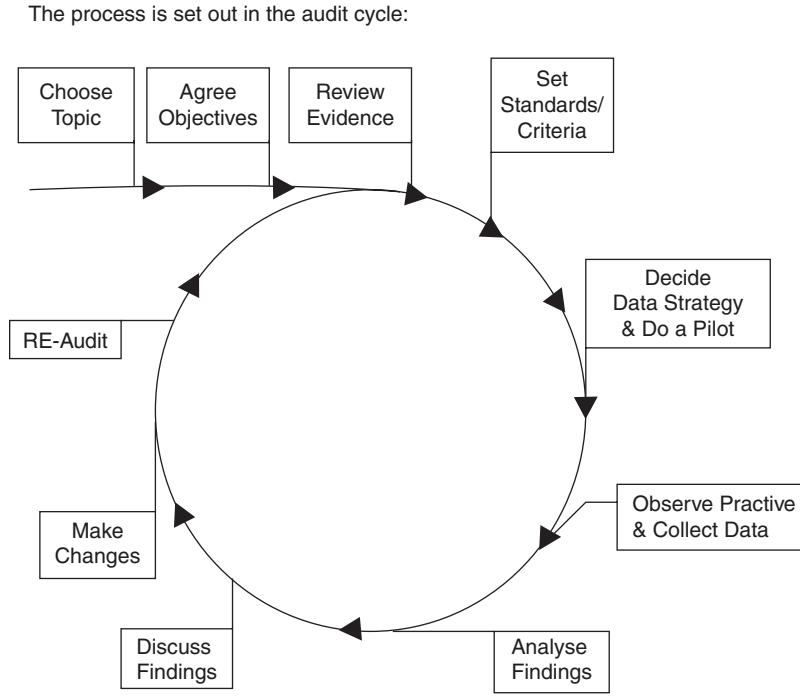
The use of audit offers a systematic way of looking at practice and making improvements. To

Fig. 49.1 Job plan

	Mon	Tues	Wed	Thurs	Fri
AM	helpline	Helpline	Helpline/ biologics	Helpline/ admin	Helpline
PM	Clinic	Biologics	Clinic	Clinic	CPD*

*Continuing Professional Development

Fig. 49.2 The audit cycle process



begin with consider appropriate areas of audit such as:

- Local concern—patient complaints
- New treatment—use of biosimilar
- Patients' concerns—response times for helpline calls
- Risk issues—opportunistic infection screening
- Wide variance—variances in care between clinicians
- Trust priorities

A good audit topic:

- Addresses a known quality issue
- Addresses an important area of practice
- Has the potential to achieve an improvement in the quality of patient care
- Addresses an area of clinical certainty and consensus
- Will use explicit audit measures
- Has clinical support
- Involves self-audit

Considering these two areas will enable the formulation of a good audit question. Once this is formulated, it is possible to think about the evidence and establish standards to audit from. Evidence can be taken from a wide range of areas, for example:

- National and international guidelines (ECCO, AGA, BSG, NICE, NSFs, Royal Colleges)
- Research findings, particularly systematic reviews
- Local policies, protocols, and procedures
- Local consensus

Box 49.1 demonstrates an example of objective and standard setting for auditing. This is developed from review of national guidelines and a wider review of evidence in journals. Books and databases such as MEDLINE should also be considered to establish best standards to audit against. Initially it is best to develop a broad audit topic which will provide objectives and then standards to develop from these objectives. Standards should be developed based upon a SMART framework:

Box 49.1

1. Topic
   Outcomes of a telephone helpline
2. Objective
   To determine the use and outcomes of a nurse led IBD helpline
3. Standards
   - 100% of patients will be given a business card with details of the IBD helpline on diagnosis referral to the service.
   - 100% of calls to the helpline will be returned in 3 working days
   - 100% of calls to the helpline will be documented in the patient notes.

- *S*pecific covers one topic only.
- *M*easurable can be measured in a practical way.
- *A*chievable is something that is reasonable for staff to achieve.
- *R*elevant is an issue that is important to patients and staff.
- *T*imescale can be measured within a reasonable period of time.

Within (Box 49.1), the standards demonstrate the target percentage of patients, cases, and/or records to meet. This is normally set to 100% to aim for the best care. However it may be influenced by previous audits to allow for comparison to show improvement or a national target.

49.4.2 Collecting Data

Once the standards have been set, it is important to consider:

- Where is the data?
  - e.g., Paper notes/prescriptions/electronic record
- *Who is going to collect it?*
  - e.g., Nurse/medical student/admin worker
- *How will it be collected?*
  - e.g., Questionnaire/pro forma
- *How much should you collect?*
  - e.g., How many patients
- *How long will it take?*
- *What resources do you need?*
  - e.g., Time, people, support

49.4.3 Analyzing the Data

It is important to use a tool the auditor is confident with in analyzing the data. This may be pencil and paper, a calculator, or a simple spreadsheet. Simple descriptive statistics, such as averages and ranges, are adequate for most audit rather than complicated statistical tests.

Following analysis it is important to carefully reflect upon the results:

- Were the standards met?
- If not, why not?
- Does the data point to ways of improving care?
- What do the results tell you?

49.4.4 Making Changes

Finally an audit report and/or presentation is an essential step to ensure that all stakeholders can see what the results of the audit are. The stakeholders are then able to discuss the results and decide if any changes are needed.

- If the audit says you're meeting the standards:
  - Share the news.
- If you haven't met some standards, think about possible solutions:
  - Which will lead to change?
  - Which are feasible and acceptable to staff and patients?

Whether an audit has met the standards or not, an action plan is needed to summarize recommendations, actions, responsibilities, and timescales for implementation. This should include identification of who, how, and when there will be review of the action plan.

49.4.5 Completing the Cycle: Reaudit

Have the changes made a difference to patient care? The next step will be to re-audit to check the changes that have made the difference expected? However, assurances will be needed to make sure that recommendations and changes have been embedded in clinical practice. When reaudit occurs (unless national practice has been changed), the reaudit should follow the same design to enable comparisons with previous audits to take place. If the reaudit shows that the standard has been met, the audit cycle is complete.

49.4.6 Business Case Development

Once a need for service development has been identified, a business case will need to be developed to articulate the need for the service and the costs associated with the service development. Developing a business case can be a daunting prospect. A starting point might be to consider sections earlier in the chapter that have highlighted particular service problems and identified areas of need to develop further. Remember that the purpose of any business case is to provide the justification for undertaking additional investment in the IBD service within a local health economy. It needs to set out the costs of investment and the anticipated benefits, offset by identified risks. The holders of investment are then enabled to review the investment priority against other investment proposals. The business case should contain all that is necessary to decide on additional investment in IBD CNS nursing.

49.4.7 Getting Started

49.4.7.1 Identify Allies

As well as building a strong evidence base for a specialist nurse role, establishing a group of allies who support the case is an important step. Without clear clinical investment in the case from a number of sectors, it will be very difficult to deliver a compelling business case. There is no prescribed group of allies, but they can include:

- Consultants
- Operational managers
- GPs
- Specialist nurses
- MDTs
- Commissioning managers
- Service users
- Service providers
- Patient groups

49.4.7.2 Identifying the Audience

As well as identifying appropriate allies for change, it is important to understand who the audience will be. Different audiences will have different priorities, and it is vital a business case aligns with those priorities, e.g., research departments, family physicians, or hospital units.

49.5 Building a Business Case

The following sections of the chapter provide an example of how to develop a business case, the language that may be required, and the format of the document.

Consider starting with an executive summary.

49.5.1 Executive Summary

This introductory section needs to be short and provide a brief outline of the business case document, including background, rationale and the benefits of implementing the business case. Figure 49.4 shows some suggested text which can be used as an introduction although it may be easiest to return to an introduction after plotting out certain details such as calculated costs and return on investment.

49.5.2 Objectives of IBD CNS Role

This section should clearly and succinctly set out the objectives of the role. The objectives can include:

- Care-related objectives (e.g., support, advice, and liaison with other local support for IBD patients)
- Outcome-related objectives (e.g., compliance with national guidelines)
- Service/finance related (e.g., assisting in referral and facilitating liaison within multidisciplinary groups)

The objectives should be tailored to align with local priorities and guidance such as ECCO guidelines.

49.5.3 Demographic Information

This section demonstrates the clear local need for a CNS. To do this it is important to provide a comprehensive snapshot of the current popu-

Fig. 49.3 Example executive summary

The implementation of the following business case for a IBD Nurse Specialist (IBD CNS) will achieve quality benefits for patients, with a potential [return on investment of x% or financial benefits of £x]. IBD patients will, as a result of this proposal, have increased access to care at the time of need, whilst simultaneously maintaining quality of care and providing value to commissioners.

This business case is proposed by a multi-disciplinary group, with [consultant name] acting as the clinical champion and [nursing name] as the nurse lead. [It is supported by [commissioner] and [patient group.]]

It is recommended that [organisation(s)] invests additional funding of £[x] in a new IBDCNS post, in support of the implementation of Option [x] [Option 2 or 3, as per Investment appraisal] by [date of service expansion and/or service change].

lation, as well as an examination of inequalities that may exist. Local information on referral patterns and diagnostic trends to demonstrate changes in local needs can be helpful. Consider:

- Local population data, e.g., number of patients at the center, number on biologic therapy, and number of patients on azathioprine
- Country-specific data from patient groups
- International data, e.g., ECCO guidelines

49.5.4 Options Appraisal

This should be the core of a business case and should demonstrate an option appraisal, setting out the range of options that will deliver the outcomes expected (Apollo Nursing resource 2016). It should include:

- The implications of "doing nothing"
- The options for delivery
- An assessment of the pros and cons for each option (benefits and disbenefits)
- The potential costs of each option and sources of funding
- A recommended option for both delivery and funding

Table 49.1 Options appraisal

Option one	Option two	Option three
Do nothing	Expand current service provision	Change to service model

49.5.5 Options

It is worth proposing a range of options to include a "do nothing" and a preferred option. Table 49.1 offers an example of how this could be displayed.

49.5.6 Expected Benefits

Table 49.2 demonstrates the potential benefits of each option appraisal for introducing a specialist nurse.

Benefits are improvements from the perspective of one or more stakeholders. These should be measurable and linked back to the reasons for the business case. If the benefit listed applies to one or more options and stakeholders, then place a tick in the corresponding column. The information in the benefits column should be concise, e.g., the benefits against Reason 1 and also for Reason 2, and put "see above" plus any additional benefits specific to Reason 2. If possible include benchmarks for access to IBD nurse specialist or another type of CNS nationally and in comparable hospitals or published data.

49.5.7 Expected Disbenefit

These are outcomes of implementing the business case which are perceived as negatives by one or more stakeholders. They arise as consequences of the proposal, rather than risks.

In this section of the business case, it would be useful to outline what the disbenefits are for each of the business case options and to compare these appropriately.

Table 49.2 Benefit summary

Option	Benefit	Reason	Stakeholder
1	• Cost saving	• Not paying for specialist nurses	• Hospital
2	• Expand capacity in clinic • Increase new to follow up ratio in clinics • Better patient experience • Less expensive than medical cover	• Additional capacity developed by appointing a nurse • Nurse relieves pressures in medical clinic by seeing more follow-up patients to enable consultants to see new patients • Patients have better access to services	• Hospital • Primary care • Patients
3	• Expand capacity in clinic • Flexibility across the whole of gastro (endoscopy, ward work)	• Appointment of locum medical staff gives flexibility across gastroenterology • Benefits as per options two	• Hospital

49.5.8 Risks

The risks presented by a business case need to be locally determined, assessed, and mitigated, depending on the scale and type of the proposed developments and the local context. The table below is a template which could be used to identify, rate, and potentially mitigate these risks. It is advised to prioritize these in order of risk and highlight the top three to five risks at the top end of the table.

It may be appropriate to consider submission of risk registers of what has been developed.

49.5.9 Business Case Development and Implementation

The text below outlines a method of summarizing an approach to how the business case has been developed and how implementation will take place. Each case will be different, so this is likely to differ depending on the methods and arguments for a case.

> This business case has been developed following a series of [x] workshops, between [start date] and [end date], attended by [specialist nurse, consultant, service manager, commissioning manager, GP, and service user]. This business case is proposed by a multidisciplinary group, with [consultant name] acting as the senior clinical champion and [nursing name] as the nurse lead.

> [Name] has undertaken the role of business case sponsor. The business case sponsor will ensure appropriate governance arrangements in order to support implementation of proposals, risk mitigation within acceptable timescales, and report back to [the committee or board receiving the business case] as agreed.

49.5.10 Costs

A comprehensive approach to outlining projected costs will be crucial in ensuring a business case is taken further. Linking costs—and returns on investment—to local and/or national policies and frameworks will show a wider understanding of the financial and political landscape. If the costs are not apparent, it is important to discuss with a senior nursing colleague or local specialist nurse champions who are likely to be experienced in finding and presenting this information (Table 49.3).

49.5.11 Investment Appraisal

Once benefits, disbenefits, savings, costs, and risks for each proposed option have been calculated, appraising and comparing these will enable the completion of a business case and support of final recommendations. The tables below are examples of a simple layout and how costs may be proposed (Table 49.4).

Table 49.3 The costs of each proposal are set out

Cost	Option one	Option two	Option three
For example, additional future cost to provider	No cost	£35,000	£50,000
For example, additional future nursing income to provider		£43,000	£43,000

Table 49.4 Layout suggestion

Factor	Option one	Option two	Option three
Relative benefits	*For example, none*	*For example, medium*	*For example, high*
Relative disbenefits			
Relative saving			
Relative cost			
Risk			

49.5.11.1 Recommendation Timings

Recommendation Statement
It is recommended that [organization(s)] invest[s] additional funding of £x in IBD specialist nurse, in support of implementation of Option x by [date of service expansion/service change].

A section should set out the predicted timelines for delivery if the business case is accepted. It should include milestones, such as recruitment, commencement of changed services, and the period of time over which there will be return on investment.

Time to recruitment is variable. In the UK, a typical recruitment process may take a minimum of 5 months from business case approval, with the following timescales representing relatively quick turnaround:

1. Funding formally confirmed—1 month
2. Job description updated and internal approval to recruit—1 month
3. Post-advertised, applications received—1 month
4. Shortlisting and interviewing—1 month
5. Employment checks and notice period before commencement—1 month

49.5.12 Other Sections

There may be additional requirements for business cases as defined in a local area such as:

- A quality and safety impact assessment
- An equality impact assessment
- Information on patient and public involvement in the implementation of the business case
- An assessment of the impact on physical assets (i.e., estates)

Not every area will need this information, but it is important to explore local requirements when planning and submitting a business case.

49.6 Recruitment and Retention

Following a successful outcome, it should be possible to appoint additional team members. Throughout service development there are likely to have been individuals who have shown interest in looking after people with IBD. These may be individuals who:

- Have worked in areas that care for patients with IBD, e.g., outpatients, infusion units, colorectal surgery, medical gastroenterology, or endoscopy
- Completed IBD courses or projects around caring for patients with IBD
- Work at more junior levels in other hospitals

When considering developing a service, it is worth identifying people who may be interested in becoming specialist nurses; such individuals should be nurtured and developed through:

1. Link nurse roles
   (a) Invest time in training ward staff and educating them regarding IBD and their role in managing patients with IBD.
   (b) Encourage link nurses to educate other staff members regarding how to care for patients with IBD.
   (c) Share information regarding national study days and nurse network groups, and encourage them to attend.

Investing time early inspires nurses to take the specialist nurse career path. This enables people to be identified who can be appointed when successful business cases have been approved. Otherwise there may be difficulties appointing appropriate candidates.

49.6.1 Developing Specialist Nurses

Once appointed the nurses must be trained and developed. This can be through the following approaches:

- *Induction program.*
  - Key considerations include:
    - What you need your nurse to do and know.
    - Spending time with MDT members, dietician, psychologist, and pharmacist.
    - Identifying a consultant supervisor to provide one to one mentorship and training.
    - Spending time with other nurses not based in your hospital.
    - Access to academic courses.
    - *Competency frameworks*
  - Competency frameworks have developed in response to nurses expanding their practice into new. Role descriptors (NICE 2017) provide a good starting point (https://www2.rcn.org.uk/__data/assets/pdf_file/0008/433736/004197.pdf).
  - The competencies may reflect:
    - Key skills—examination and drug administration
    - Knowledge—able to demonstrate sound knowledge of IBD, the drugs used, and the potential complications of the disease
    - Scope of practice—education and assessment
  - Usually competency frameworks are endorsed by the local hospital, and they should be ratified with hospital executive teams.

49.6.2 Staff Well-Being

1. Caring for patients with IBD can be challenging and difficult at times; this combined with heavy workloads can affect staff well-being. This can be managed with:
   (a) Regular 1:1s with managers
   (b) Support from occupational health
   (c) Regular clinical supervision for the nurse
   (d) Flexible working patterns
   (e) Ensuring annual leave is taken
   (f) If working in a team, rotation through different roles in the team

49.6.3 Career Progression

2. Regular appraisals and development of a personal development plan.
3. Support the nurse with aspirations, recognizing that junior team members may aspire to senior posts and ensuring that they are given the appropriate access to training to meet their expectations.
4. Access to academic courses:
   (a) IBD modules
   (b) Master's pathways

49.7 Summary and Conclusion

This chapter has reflected upon maintaining an IBD service, considering the use of audit to inform practice and provide the basis of business case development. It has recognized the process is not straightforward and the development and approval process for recruitment are complex. Usually the lack of predefined working standards affects the process of audit and consequentially the articulation of the problem. Clear definition of what specialist nursing practice involves gives way to well-developed services which subsequently develops enthusiasm for the specialty including considering student nurse placements and link nurse roles.

Expanding services was explored. The use of audit supported the clarification of the problem and the development of a business case enabling service leads to consider the implications of service expansion and reflect upon questions which may be raised during its presentation.

Finally, it is worth remembering that this process is cyclical, and often within a couple of years from recruitment, further business case planning is required to manage growth of the service and accommodate the increasing demands upon the IBD service; therefore the cycle of audit will be required again.

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IBD Nurse Within the MDT

50

Idan Goren, Revital Barkan, and Iris Dotan

Abstract

Inflammatory bowel diseases (IBD) are chronic diseases with a highly variable clinical course. A subset of patients with IBD may develop disease complications, both gastrointestinal and extraintestinal. Delay in treatment may lead to potentially preventable complications and result in worse clinical outcomes. Driven by the aforementioned complexity, specialized IBD units consisting of a multidisciplinary team (MDT) have been established worldwide. The role of the IBD nurse within the multidisciplinary team is discussed in this chapter.

50.1 Introduction

Along with the global increase in the incidence of IBD over the past two decades, the number of patients with IBD complications is rising. In patients with Crohn's disease (CD) over 10 years of follow-up, about half of the patients develop stricturing or penetrating disease, and in patients with ulcerative colitis (UC), between 10 and 15% require colectomy over the disease course (Burisch et al. 2013).

In addition to surgical complications, IBDs are characterized by development of systemic extraintestinal manifestations (EIM), phenomena that increase in prevalence over the disease's clinical course.

The clinical course of IBD is characterized by periods of exacerbations, which are diverse in their presentation and management and often require treatment escalation, surgical intervention, and frequent follow-ups.

Dealing with the physical manifestations of IBD can be challenging even to an experienced healthcare provider; however, IBD is associated with many psychological manifestations such as anxiety disorder and depressive disorder. Both psychological manifestations are associated with the severity of disease (Hauser et al. 2011).

Social interference is an additional facet of IBD. Disease burden includes absence from work and studies due to frequent bowel movements, pain, fatigue, therapy, and hospitalizations. The inability to plan ahead due to the unpredictable disease course, combined with the need to maintain close proximity to toilets, can lead to behavioral patterns like abstaining from social activities and isolation (Devlen et al. 2014).

The wide spectrum of disease manifestations, the multiple organs that may be involved in the disease, and the complexity of the medical, surgical, psychological, and social effects of IBD

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require collaboration between multiple medical and nonmedical disciplines in the form of a MDT in substantial number of cases.

50.2 MDT Structure and Operating Procedures

In the past decade, there has been a trend toward favoring outpatient treatment of IBD cases. In areas where multidisciplinary outpatient IBD services are available, a decline in the frequency and costs of inpatient services has been reported. Therefore inpatient care can nowadays be reserved for those patients with a severe disease course and for those without regular access to MDT care (Connell et al. 2015).

From a medical point of view, teamwork in IBD ensures that both interdependent actions and joint recommendations are synchronized and fully committed to a single result. One major benefit of such teamwork stems from the fact that most members are experienced personnel dedicated to the treatment of patients with IBD. MDT members usually have complementary diagnostic and therapeutic skills (Ricci et al. 2008). The broader expertise and better resources, available to an IBD center with MDT as compared to a single physician practice, allow specialized care for patients with IBD and can improve outcomes.

The ideal MDT should work closely with the IBD unit and includes IBD-oriented gastroenterologists and colorectal surgeons, IBD-specialized nurses, stoma-specialized nurses, radiologists experienced in IBD, dieticians with IBD orientation, medical pathologists with expertise in gastroenterology, medical psychologists, social workers, and administrators (IBD Standards Group 2009; Calvet et al. 2014) (Fig. 50.1).

Moreover, MDTs should have contact with ancillary services from additional medical disciplines. These include rheumatologists, dermatologists, and ophthalmologists with knowledge in the management of IBD-related complications. Likewise, MDTs should have an affiliated obstetrician/gynecologist (obs/gyn) preferably one that can consult and follow preconception and pregnant IBD patients in conjugation with a gastroenterologist. Another aspect of an MDT is to ensure continuity in the transition of pediatric IBD patients to the adult clinic. It is therefore recommended that a pediatric gastroenterologist

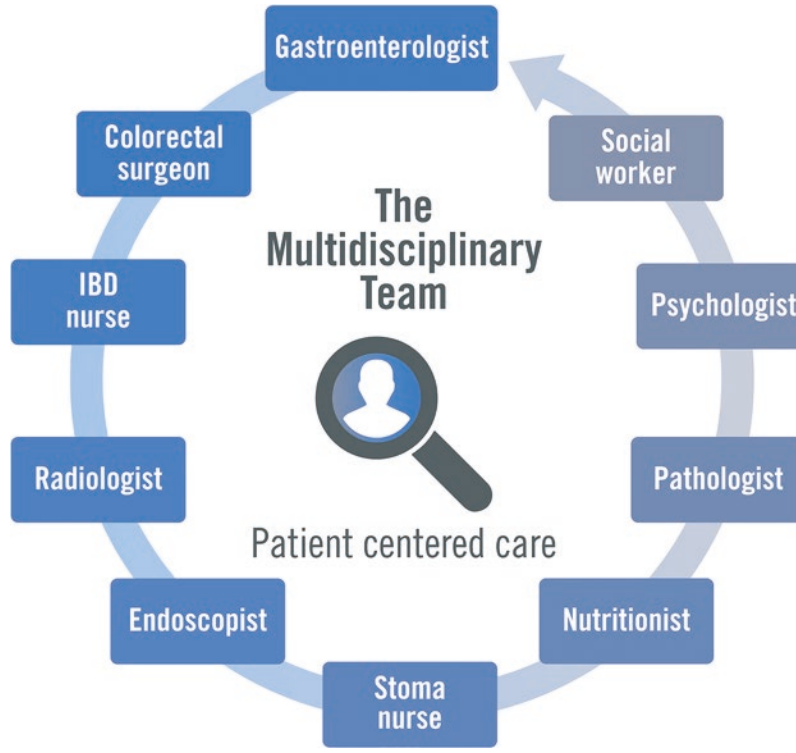

Fig. 50.1 Structure of multidisciplinary IBD team

from the transition clinic would be affiliated to an IBD MDT (Mowat et al. 2011; Tursi et al. 2013; Elkjaer et al. 2008; Louis et al. 2015).

50.2.1 Proposed Operating Procedure of MDT

- The MDT should have regular scheduled weekly meetings to discuss complex IBD cases.
- Urgent cases should be discussed in an ad hoc MDT meeting.
- Recommendations made during the meeting should be documented in the patient's medical records.
- MDT conclusions should be reported and discussed to provide the patient with complete information, treatment options, and strategies.

50.3 The Role of an IBD Nurse Within MDT

Assignment of nurses into MDTs has proved beneficial in different medical fields. Vazirani et al. showed that the addition of a nurse practitioner to MDTs resulted in improved communication and collaboration among the participants (Vazirani et al. 2005). In Canada, the integration of a nurse practitioner into MDTs had improved communication among the newly formed teams. Quinlan et al. have found that nurses in these teams were able to mobilize their holistic training and practice, to exploit their medical and nursing knowledge and skills, and thus were able to contribute more than other members to the synergy and knowledge exchange within the MDT (Quinlan and Robertson 2013).

Specifically in IBD, several groups showed the advantages of an IBD nurse implementation into MDT for the treatment of patients with IBD. In Australia, for instance, IBD nurse service added into MDTs has been shown to improve clinical outcomes by virtue of reduced number of IBD-related hospital admissions (Leach et al. 2014). Similarly, Sack et al. found that the introduction of proactive IBD nurse to the MDT/IBD service decreased number of IBD-related admissions and disease burden (Sack et al. 2012). Kemp et al. reported that IBD patients in the United Kingdom appreciated the central role of an IBD nurse within the IBD team and proposed an IBD nurse as an interface between primary and secondary care systems (Kemp et al. 2013).

With the increased workload of IBD around the world, the role of IBD nurses becomes critical. IBD nurses are involved in patient care from the time of diagnosis throughout the treatment plan, treatment administration and monitoring, clinical follow-up, and management of complications. The valuable role of IBD nurses within the MDT is becoming widely recognized both as a key link between the MDT members and also in the communication between patients and MDT members (Fig. 50.2). The main roles of an IBD nurse within the MDT are as follows:

- *IBD nurse as patient spokesman at MDT meetings*: as nurses are more commonly involved with patient's personal life, IBD nurses ensure that the discussion is focused on managing IBD in the context of the patient's life, rather than concentrating on disease activity (Hernández-Sampelayo et al. 2010).
- *IBD nurse as coordinator of MDT members*: effective synchronization is crucial for the success of MDT. The IBD nurse is an active member who, on one hand, recognizes the health professional's roles and responsibilities and, on the other hand, knows the patient's needs. The IBD nurse is the prime link in the communication network within the multidisciplinary team and between specialists and primary care. The IBD nurse ensures that the synergy of the knowledge and skills of the various professions involved is directed to the patient's well-being.
- *Deliver MDT recommendations to the patient*: the IBD nurse should have effective communication skills and good rapport with patients and their families. As such, the IBD nurse can discuss MDT recommendations with the patient.
- *Management and implementation of team decisions*: it is now recognized that specialized nurses contribute to the long-term management of MDT tasks which are often complex and may include more than a one-step procedure (Greveson and Woodward

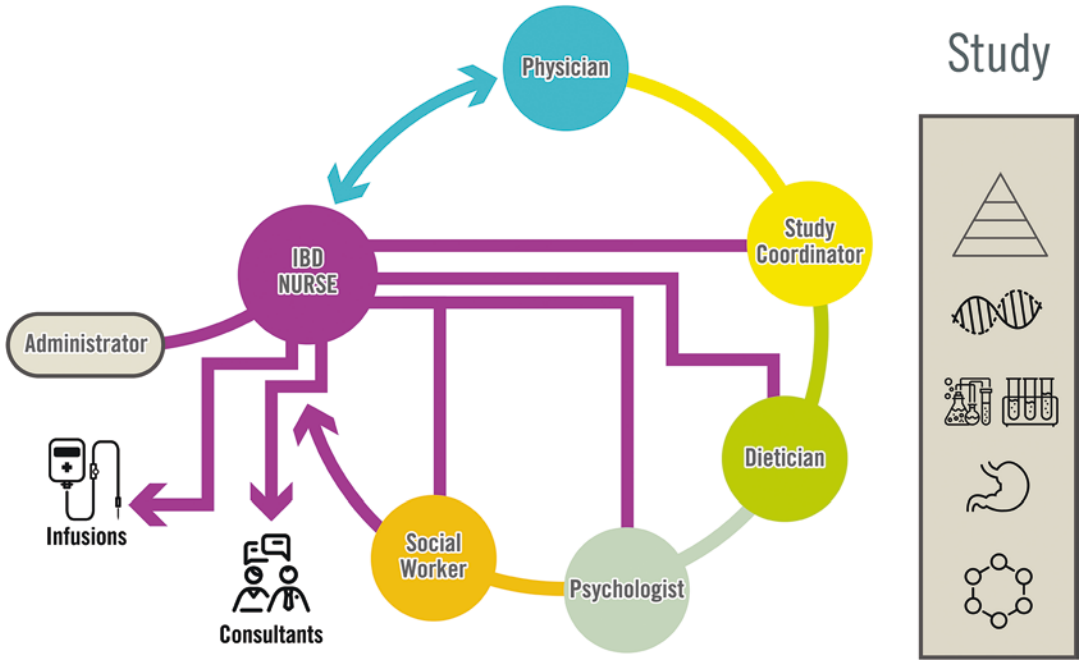

Fig. 50.2 The central role of the IBD nurse in the crossroad between the patient and the MDT and among the MDT members

2013). The IBD nurse serves as an access point for patients and often is the guide for the perplexed. Moreover, IBD nurses play an active role in the administration of care and in the continued monitoring of treatment effect on the patient well-being.

- *Extended roles*: in countries where nurse practitioner is employed, IBD nurses with extended authorizations can independently provide follow-up visits for stable patients, prescribe medication, and monitor their effects and adverse effects supported as needed within the MDT (see examples in Chaps. 47 and 48).

50.4 Daily Practice of IBD Nurse in MDT

A standard workday of an IBD nurse within MDT is diverse and dependent on factors such as the local health system regulations, workload, and medical environment of the MDT, ranging from *hospital setting* to *outpatient*-based MDTs. Therefore, it is difficult to define universal roles. Nevertheless, some examples of how IBD nurses integrate within the MDT model are described below:

50.4.1 Preparation Prior to a New Patient Visit

New patient's arrival for the first time to the clinic includes those with suspected IBD or IBD patients who were diagnosed elsewhere and are new in the clinic. When a patient schedules the first visit to the clinic, the IBD nurse verifies that patient's medical history including medical referral letter, endoscopy reports, histopathologic reports, and relevant laboratory analysis will be submitted if possible prior to the first visit to the clinic.

50.4.2 Joint Care Appointment with Newly Diagnosed Patient

The nursing role at the beginning of a patient visit should include recording of relevant history,

vital signs, weight and height, BMI calculation, and documentation of parameters such as number and consistency of daily bowel movement, incontinence, and bleeding.

Then, following the physician's medical checkup and its summary report, a team consisting of an IBD nurse and MDT members such as dietician, psychologist, and social worker can meet with the patient and introduce the MDT and the services available. The initial meeting should include collection of demographic data, inquiry regarding disease impact upon daily life, evaluation of family and social support, assessment of patient's knowledge regarding the disease, etc. A standard "first visit questionnaire" can ensure that all aspects are covered which is especially helpful for less experienced IBD nurses. Based on the new patient's needs, an IBD nurse can assist with the specific follow-up strategy and guide further interventions.

50.4.3 Treatment Continuity in Cases of Multiple Caregivers Within MDT and Primary Care

In cases where multiple healthcare providers are involved in the treatment of an IBD patient, the IBD nurse coordinates the delivery of care. IBD nurses should be able to contact medical and non-medical members of the MDT and others that include services, which might not be provided by MDT such as the primary care physician, ambulatory therapeutic infusion centers for biologic therapy, and *pre- and postoperative care*.

Here the IBD nurse role can be more complex when caring for a patient with multiple caregivers as is the case of IBD patients that undergo surgical intervention.

Prior to elective surgery, the IBD nurse could be well placed to provide an overview regarding the entire process including general outline of the procedure, the recovery process, and the expected medical course before and after the surgery. If ileostomy, jejunostomy, or colostomy is planned, IBD nurse will arrange a meeting with a psychologist prior to the operation if available in a center. When possible, a meeting between the patients undergoing surgery and postsurgery patients can be arranged by the IBD nurse. The IBD nurse schedules a postoperative follow-up meeting as well.

Postoperative intervention is a critical period in IBD nurse-patient interaction. The IBD nurse receives daily updates during the first week and on weekly basis in the following month. Using phone calls and Internet-based communications, the IBD nurse can identify postoperative complications that require further investigation while giving support and reassurance that address concerns raised by the patients, which do not necessitate change in the postoperative medical management. If ileostomy, jejunostomy, or colostomy was done, a meeting with a stoma-specialized nurse should be scheduled prior to hospital discharge and later on if required. Introduction to a support group is highly recommended.

50.4.4 Nurse-Based Referral

IBD nurse-based diagnosis and referrals are major contributions of the IBD nurse. Patient with EIM should be referred to the relevant specialist. In cases of malnutrition patient should be referred to a dietician. In cases of anxiety and depression or when the disease negatively affects body image and self-esteem, the patient should be referred to a psychologist.

Patients who are eligible to participate in a clinical study will receive explanation, guidance, and contact information of the study coordinators.

50.4.5 The Pregnant Patient

Ideally, IBD patient who plans to become pregnant is referred to a specialized joint gastroenterologist-obstetrician/gynecologist (GI-obs/gyn) clinic for counseling and adaptation of treatment strategies. In cases when patient is already pregnant, basic counseling and relevant educational information should be offered by the IBD nurse and physician alongside the referral to the joint GI-obs/gyn clinic.

50.4.6 Urgent Medical Care

Diagnostic delay may be associated with disease complications. An emergency IBD service aims to improve the availability of IBD-oriented personnel when urgent medical intervention is essential. In such cases, the IBD nurse is usually the "point of contact" as most advice lines are managed by IBD nurses (see also Chap. 47; advice lines). What an IBD nurse is able to offer over an advice line depends on experience and level of autonomy. For example, where a nurse has a prescribing qualification, it is likely that treatment can be adjusted or started via this assessment and avoids the necessity of appointments or admission. Whatever the level of autonomy, however, an ideal team consists of IBD nurses and an IBD-oriented physician working well together. This can ensure comprehensive services to both patients and their community physicians in urgent cases. When applicable, such patients should be assessed clinically as soon as possible (such as same-day appointment) and referred as needed. When same-day appointment is not available, a suggested approach includes contact with either primary care physician or emergency department physician who examined the patient. If required, the team will recommend further investigation.

50.5 Benefits for the IBD Nurse Who Takes Part in MDT

Similar to other members of the MDT, attendance in the MDT meetings allows the IBD nurse to have an up-to-date knowledge regarding IBD and broader perception on its management. As such, an IBD nurse who is part of the MDT can provide patients with expert advice about their IBD and has sufficient knowledge to give guidance in key areas of concern for patients. Specifically, regular interaction and personal acquaintance with MDT members improve IBD nurses' understanding of common symptoms and complications of IBD, medical and surgical therapies, medication and related potential side effects, and social support options (Bernstein et al. 2011). Based on the collaboration, IBD nurse can develop and implement new protocols to improve surveillance and follow-up of IBD patients, monitoring of clinical parameters and patient-reported outcomes along disease course and regarding therapeutic interventions.

Improving knowledge has been shown to improve nurse professional satisfaction at work. Based on a Spanish survey of 133 gastroenterologists and 69 nurses of which two thirds treat all kinds of GIT diseases and one third exclusively treated IBD patients, the latter reported higher level of satisfaction in treating patients with IBD (Casellas et al. 2013).

From an academic point of view, the interaction between IBD nurse and the MDT can serve as a platform for multidisciplinary basic science and clinical research group in IBD. Amo et al. showed that the incorporation of a specialized IBD nurse into MDT had a major research benefit in addition to the medical and economic advantages (Amo et al. 2016).

50.6 Conclusion

With the increase in incidence of IBD, healthcare systems worldwide pursue an improved IBD care. The holistic model consisting of specialized IBD units with a multidisciplinary team (MDT) is considered the mainstay approach to treating patients with IBD specifically complicated IBD cases. Current data shows that MDT in IBD enhances the IBD practice and subsequently improves patient satisfaction and clinical outcomes. The IBD nurse has a crucial role in the work of MDT. The IBD nurse is recognized as the key link both among the MDT members and also in the communication between patients and members of the MDT. Professionally and personally, there are positive outcomes for the IBD nurse as a result of a role demanding advanced knowledge and clinical responsibilities. Lastly, the IBD nurses, working as part of MDT, can utilize their unique placement and skill set to contribute to work, such as research, that benefits the larger IBD community and any future patients.

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