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## Diverticular disease of the colon

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Despite being one the most common diseases of the colon, diverticular disease remains an area of interest to the gastroenterologist and colorectal surgeon. Remarkable strides have been made regarding pathogenesis and possible management strategies. The clinical problems remain a challenge, from diagnosis to management, reflecting a wide spectrum of clinical manifestations, an extensive differential diagnosis and the need for more local evidence to provide suitable guidelines.

### Definition

A diverticulum of the colon is a sac-like outpouching of the mucosa and submucosa through the muscular layer and is thus in reality a pseudodiverticulum because all the layers of the colon are not represented. However, unless otherwise specified most specialists will refer to colonic pseudodiverticular disease without the 'pseudo-' prefix, which is well understood by all.

Diverticulosis refers to the condition without symptoms and diverticular disease (DD) is the term used when associated symptoms are present. DD is further subdivided into uncomplicated DD ('diverticulitis', i.e. local inflammation only) or complicated DD when perforation, fistula, abscess, obstruction and/or bleeding are present.

### Epidemiology

Most of the epidemiological information about this disease comes from the developed world, but a few local studies have provided interesting revelations while simultaneously dispelling the myth that DD is virtually non-existent in Africans. In black South Africans the descending colon is predominantly affected, whereas the sigmoid colon is invariably involved in Western countries and right-sided diverticulosis is more prevalent in Asian populations. Furthermore, haemorrhage is the most common presentation among South Africans.

DD has become more frequent during the course of the past couple of hundred years and this is related to an ageing population. In developed countries diverticulosis may be found in approximately 30% of those over 50 years and in 50% of those over 70 years. There is no established difference in the prevalence of the disease in men and women.

In younger patients diverticulosis may be associated with Marfan's syndrome, Ehlers-Danlos syndrome and polycystic kidney disease (conditions associated with abnormalities of collagen). In addition, steroid use and obesity are also risk factors for earlier development of diverticular disease.

The relatively rapid emergence of this 20th-century disease is probably related to an ageing population and dietary fibre deficiency common to the Western lifestyle.

**The development of diverticulosis appears to be multifactorial, and theories of how it develops are controversial.**

### Pathophysiology

The development of diverticulosis appears to be multifactorial, and theories of how it develops are controversial. Ageing appears to play a role, although past studies in the elderly African population who did not eat a Western diet showed that the condition was extremely rare. Low dietary fibre is strongly associated with this condition. The theory is that low fibre reduces colonic transit time, allowing for increased water absorption and thus the production of smaller, firmer stools. This could lead to excessive colonic segmentation and increased intra-luminal pressure, facilitating the outpouching of diverticula through natural points of weakness in the colonic wall, i.e. where colonic nutrient vessels penetrate the mucosa. While an attractive theory, the link to pressure change has not been conclusively demonstrated. Other factors that are thought to be involved in the pathogenesis of diverticulosis include genetic factors and alterations in collagen.

Obstruction of a diverticulum by faeces or hardened mucus leads to inflammation, i.e. diverticulitis. However, this theory for the cause of the inflammation remains speculative and is currently not widely accepted. Chronic inflammation has been shown to precede clinical diverticulitis. A fibre-deficient diet leading to alteration in the colonic microflora and subsequent changes in the intestinal immune response may represent the actual mechanism causing diverticulitis.

### Course of the disease

Diverticulitis may resolve, perforate and remain localised or there may be free perforation with peritonitis or fistulisation (colovesical fistula are commonest). Other sequelae are abscess formation and stricture causing intestinal obstruction. Pyogenic liver abscess from portal pyaemia may be secondary to an episode of diverticulitis.

### Clinical evaluation

The clinical spectrum ranges from no symptoms to life-threatening disease. Approximately 75% of patients with diverticulosis will remain asymptomatic. In the symptomatic group, 25% will present with haemorrhage and 75% with diverticulitis which may be uncomplicated (75%) or complicated (25%).

The clinical features of specific complications such as peritonitis or intestinal obstruction from stricture, fistulisation etc. are common to all intestinal disease and warrant immediate resuscitation and appropriate referral.

The classic presentation is of left lower abdominal pain and fever. The segment of colon involved and where it lies (e.g. redundant sigmoid loops on the right side of the abdomen) dictates the site of pain. Nonspecific features of gastrointestinal disturbance such as nausea, vomiting, anorexia and changes in bowel habit (constipation with or without bouts of diarrhoea) are common in diverticulitis.

A sympathetic cystitis due to the close proximity of the inflamed sigmoid colon to the bladder may cause urinary symptoms. Abdominal examination may

show tenderness and guarding around the site of disease. A palpable, tender mass may be present. A neutrophil leucocytosis is usually found but its absence does not exclude diverticulitis.

It's important to bear in mind that clinical features may be subtle in the immunocompromised and the elderly, emphasising the need for a high index of suspicion. Furthermore, the clinical presentation coincides with that of many other conditions. Diverticulitis affects mainly the elderly in whom the second peak of inflammatory bowel disease also occurs, ischaemic colitis is prevalent and colon cancer is often a consideration.

The differential diagnosis of acute diverticulitis includes:

- colorectal carcinoma
- Crohn's disease
- ulcerative colitis
- ischaemic colitis
- infectious colitis including pseudomembranous colitis
- tuberculosis
- pancreatitis
- pyelonephritis
- pelvic inflammatory disease
- ovarian cyst or torsion
- acute appendicitis
- leaking aortic aneurysm.

The implication of such a wide clinical spectrum and differential diagnosis is that careful clinical evaluation is mandatory, inclusive of observation over a few days in certain cases, especially in those with minimal or masked symptoms. The final diagnosis is often made at surgery.

If the patient is known to have diverticulosis then a presumptive clinical diagnosis can usually be made. In the acute stage a high-quality CT scan is the initial investigation of choice, with a sensitivity of up to 97%. It is non-invasive, can quantify the extent of disease, delineate complications and help in excluding other diagnoses. Due to its availability ultrasound is usually employed as the initial investigation but is highly operator dependent and overlying bowel gas may obscure collections.

The distribution and severity of DD is best demonstrated by barium enema. In symptomatic patients a barium enema is relatively contraindicated due to the risk of perforation. Intraperitoneal barium is toxic. In acute situations where the diagnosis is uncertain, urgent surgery should be contemplated and if CT scan is not readily available an unprepared single-contrast water-soluble study is useful. Colonoscopy about 4 weeks after successful conservative management (not during the acute episode) should be performed to aid in confirming the diagnosis and exclude differential diagnoses. Colonoscopy in patients with extensive diverticulosis can be a technical nightmare and is best left to well-trained, experienced colonoscopists.

**Asymptomatic patients incidentally diagnosed with diverticulosis should be advised on adequate fibre and fluid intake and made aware of the symptoms of diverticulitis to allow for early presentation.**

## Issues in management

Asymptomatic patients incidentally diagnosed with diverticulosis should be advised on adequate fibre and fluid intake and made aware of the symptoms of diverticulitis to allow for early presentation. Insoluble fibre from fruit and vegetables seem to be more protective. Irrespective of the state of one's colon, adequate fibre intake forms part a prudent diet that is central to good health.

## Uncomplicated diverticular disease

Patients without systemic upset, minimal symptoms and who are able to self-hydrate can be managed as outpatients. An antibiotic regimen and a bland liquid diet (low fibre) along with paracetamol as required should suffice. Usually a quinolone and metronidazole are prescribed for a week. Acceptable alternatives include amoxicillin and clavulanic acid or sulphamethoxazole-trimethoprim and metronidazole. Symptomatic improvement should be expected within 2 - 3 days. This is crucial, as failure to improve warrants re-evaluation along with admission. In those patients who have difficulty accessing health care one should have a low threshold for admission. To decrease the chance of future attacks dietary fibre is introduced but not during or immediately after an acute episode.

Promising strategies to prevent recurrent attacks, and possibly in the treatment of symptomatic uncomplicated diverticular disease, include mesalazine, the poorly absorbed antibiotic rifaximin and pre-/probiotics. The presence of chronic inflammation in the bowel wall, even between attacks, has lead to the evaluation of mesalazine (a mainstay of ulcerative colitis therapy) with or without antibiotics in this condition. Mesalazine may ameliorate the course of diverticulitis when used with antibiotics and reduce the incidence of recurrent attacks. Further study is justified before a strong recommendation regarding the place of mesalazine in DD can be made.

Patients requiring hospitalisation for acute uncomplicated diverticulitis should be managed with bowel rest, intravenous fluid replacement, appropriate antibiotics (e.g. metronidazole and cefotaxime/cefuroxime IVI) and close monitoring. Most patients will settle within 3 days and the decision to intervene in this period should be taken by an experienced surgeon. Ideally these patients should be jointly managed with a gastroenterologist.

Surgery takes a prominent role in complicated diverticular disease.

## Abscess

Small abscesses identified on CT scan or ultrasound can be successfully managed with antibiotics without drainage. Peridiverticular abscesses more than 5 cm in diameter should preferably be drained percutaneously (CT or ultrasound guided) along with antibiotic cover. This allows for stabilisation of the patient without the need for general anaesthesia before any surgical intervention. Abscesses that are anatomically inaccessible to percutaneous drainage, multiloculated ones and those not responding to percutaneous drainage will require surgery.

## Bleeding

Most cases of bleeding from colonic diverticula are self-limiting. Acute severe bleeding, or more often recurrent bleeding, from DD usually requires surgery. Identifying a diverticulum as the bleeding source can be difficult in the acute setting and evaluation takes place after adequate resuscitation, usually when the bleed has subsided. Investigation is directed at excluding other causes of gastrointestinal bleeding. In selected cases of severe bleeding a rapid bowel preparation can be given and urgent colonoscopy undertaken (6 - 12 hours after admission), which may establish a firm diagnosis of bleeding from diverticula. Endoscopic therapy may be performed to stem the bleeding. Successful endoscopic management reduces blood transfusion requirements, recurrent bleeding and need for surgery. This requires the expertise of a skilled and determined colonoscopist as the procedure in this situation can be particularly frustrating and hazardous.

## Perforation and bowel obstruction

These complications will need aggressive resuscitation and surgical management.

## Elective surgery

This remains an area of controversy regarding the value of colectomy in preventing recurrent disease and complications. Traditionally surgery is recommended in the young patient after one episode of documented diverticulitis (complicated or uncomplicated). In the elderly, one episode of diverticulitis does not justify the risks of surgery given the low recurrence. Recommending surgery in elderly patients with recurrent attacks of uncomplicated diverticulitis should be made on a case-by-case basis.

**Further reading**


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# Advances in hepatitis B


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Hepatitis B virus (HBV) remains an important public health issue in South Africa. Prior to the incorporation of HBV vaccination into the Expanded Programme of Immunisation (EPI) more than a decade ago, prevalence rates of HBV were estimated at between 0.3% and 15%.[1] However, the potential benefits of introducing the vaccine have not yet been accurately assessed and may not be fully realised without complete vaccination coverage. A further potentially negative factor in HBV control is the burgeoning HIV/AIDS epidemic as the natural history of HBV is altered in those who are co-infected.[2] The long-term risks of chronic HBV infection include chronic hepatitis, which may evolve to cirrhosis and the risk of hepatocellular carcinoma is significantly increased, irrespective of the presence of cirrhosis.

**Knowledge and understanding of both the natural history of HBV and therapeutic advances have significantly increased over the last decade.**

Highlighting the advances in the understanding of HBV is that in the past 2 years four major groups, viz. the American Association for the Study of Liver Diseases (AASLD), the European Association for Study of the Liver (EASL), the Asia-Pacific Association for the Study of the Liver (APASL) and the World Gastroenterology Organisation (WGO), have updated their guidelines on the management of HBV infection.[3-6]

Knowledge and understanding of both the natural history of HBV and therapeutic advances have significantly increased over the last decade. Key among several factors that explain the predilection of HBV to persist has been the understanding that the virus remains within the nucleus of infected hepatocytes. It achieves this through covalently closed circular DNA (cccDNA) that forms the template upon which viral particles can be replicated. During transcription, cccDNA is replenished by returning to the hepatocyte nucleus. An insight in the virus' ability to persist is that patients who have cleared HBV surface antigen continue to harbour cccDNA. This may allow for so-called occult HBV infection that is clinically defined as detectable HBV DNA in the serum of those previously exposed to HBV, i.e. HBsAg negative and HBcore antibody (IgG) positive. To date no discernable liver disease is associated with occult HBV infection; however, the risk of reactivated disease exists in those who are immunocompromised.

## Natural history

Intrinsic to defining an appropriate management strategy for patients with chronic HBV infection is determining in which phase of the natural history of chronic infection they are in. In those with chronic infection, an initial immune tolerant phase is characterised by the presence of HBeAg, high HBV DNA levels while transaminase levels are normal. Histologically there is minimal or no necroinflammation or fibrosis.

It is followed by a phase of immune clearance that is similar to the immune tolerant phase. However, transaminases are now elevated and histologically there is increased necroinflammatory activity. This phase may last for several weeks to years and if successful, HBeAg seroconversion will occur with the development of sustained HBe-antibody titres.

The next phase of HBV latency (also called inactive HBV carrier state) is characterised by loss of HBeAg, normal transaminases and low or undetectable HBV DNA levels. HBsAg loss during this phase may occur spontaneously but does so in <1% of individuals.

The HBV latent phase may persist lifelong, but in about 5 - 15% of patients HBeAg-negative chronic HBV hepatitis can occur. This phase, more common in older men, is due to patients harbouring HBV variants with nucleotide substitutions in the precore and/or basal core promoter regions of the HBV genome, resulting in the inability to express HBeAg while being able to avidly replicate. The phase is thus characterised by undetectable HBeAg, fluctuating transaminases and HBV DNA levels. Invariably, there is significant necroinflammatory activity with progressive fibrosis. The concern with this particular phase is the propensity to develop more rapidly progressive fibrosis and cirrhosis.

Data published in the last 2 years and, most notably, the REVEAL-HBV study, strongly suggest that suppressing HBV DNA levels reduces the risk of cirrhosis and/or hepatocellular carcinoma.[7] However, an important consideration in this particular study is that 85% of patients were HBeAg negative and hence findings may not be applicable to all patients with chronic HBV infection.

**Key to choosing a specific therapy for a patient with chronic HBV infection is deciding who actually warrants therapy.**

## Management strategies

Key to choosing a specific therapy for a patient with chronic HBV infection is deciding who actually warrants therapy. Firstly, as indicated, patients need to be categorised in terms of which phase of chronic infection they are in. Treatment should be considered in those in the immune clearance and HBeAg-negative phase of chronic HBV infection. Treatment should also be considered in patients with established cirrhosis, especially decompensated cirrhosis. Furthermore, a useful clinical point to remember is that HBV causes liver disease and liver biopsy remains an important adjunctive clinical tool in deciding who warrants therapy.

Goals of therapy differ depending on HBeAg status. In HBeAg-positive patients the primary goal is sustained HBeAg seroconversion, while in HBeAg-negative patients the goal is sustained HBV DNA suppression. Secondary goals in both scenarios are normalisation of transaminases that invariably follows HBeAg seroconversion in HBeAg-positive and HBV DNA suppression in HBeAg-negative patients. Improvement in liver histology is probable if these endpoints are achieved. HBsAg loss and seroconversion is the ultimate goal of HBV therapy but remains distinctly elusive with currently available therapies.

Six drugs are currently available in South Africa for the treatment of hepatitis B. These include standard and pegylated alpha interferon, lamivudine and entecavir. Not registered in SA but available for off-label use, is tenofovir (alone or in fixed combination with emtricitabine). Tenofovir was registered for chronic HBV infection by both the European regulatory authority as well as the FDA in 2008. Ordinarily, tenofovir alone, or in a fixed-dose combination with emtricitabine, is used in the treatment of HIV/AIDS.

Patient selection for a given treatment modality is vital. Ideal patients for alpha interferon include HBeAg-positive patients with elevated transaminases, an HBV DNA viral load ($<10^7$ IU/ml) and high necroinflammatory activity scores on liver biopsy. Patients also need to be motivated. Existing data suggest that HBV genotype A and B is more responsive to interferon that genotypes C and D. However, genotyping is not routinely available in South Africa and genotype alone should not singularly direct the choice of treatment. Six to 12 months of standard or 48 - 52 weeks' pegylated interferon are both effective in HBeAg-positive patients. If interferon is to be used in HBeAg-negative patients, pegylated interferon should be used, as standard alpha interferon has poor sustained efficacy in this group. While on treatment, factors such as an HBV DNA decrease to <20 000 IU/ml at 12 weeks of therapy predict for a sustained response when using interferon. Benefits of pegylated interferon over standard interferon include improved efficacy and the convenience of once-weekly dosing. However, the side-effect profile is similar with both standard and pegylated interferon. Contraindications to interferon remain decompensated cirrhosis, autoimmune disease and uncontrolled severe depression or psychosis. The overwhelming benefit of interferon-based therapy includes a finite course of treatment, immune-mediated containment of HBV infection and the absence of resistance.

**Prevention with the continued widespread implementation of HBV vaccination remains the cornerstone of management.**

Compelling indications for oral antiviral therapy are contraindications to interferon, cirrhosis or as primary therapy in HBeAg-negative patients. The major concern with antivirals remains the development of resistance. In drugs with a low genetic barrier to resistance such as lamivudine, resistance can exceed 70% after 5 years. The newer agents have greater efficacy and have higher genetic barriers to resistance. Existing data for entecavir and emerging data for tenofovir suggest a very low rate of resistance developing with sustained long-term use.[8] Preferentially agents such as lamivudine should be avoided but given the cost differentials between lamivudine and some of the newer agents this is not always possible. Fortunately tenofovir remains very affordable in South Africa. When using antivirals, in particular lamivudine, monitoring for genotypic and phenotypic resistance is required. An incomplete or failing response to an antiviral warrants an appropriate intervention that is beyond the scope of this review. Endpoints in patients on antiviral therapy differ somewhat to those using interferon. In HBeAg-positive patients antiviral therapy should continue beyond HBeAg seroconversion for approximately 1 year before considering stopping antiviral therapy. However, this should be carefully considered and dictated by the clinical scenario. HBeAg seroconversion with antivirals will occur in approximately 20% of patients after 1 year of treatment. In the absence of HBeAg seroconversion therapy should continue indefinitely. In HbeAg-negative patients the aim of therapy is prolonged HBV suppression. Therapy, therefore, once initiated, is continued indefinitely. Given the issue of resistance, combination antiviral therapy has been an attractive option. Evidence in favour of *de novo* combination therapy remains limited and current guidelines suggest *de novo* combination therapy in cirrhotics and post liver transplantation for HBV.

## Conclusion

Chronic HBV remains a public health issue in South Africa. Prevention with the continued widespread implementation of HBV vaccination remains the cornerstone of management. In those with chronic HBV infection careful evaluation of who actually warrants and would benefit from treatment is as important as tailoring a therapeutic modality to a patient. Practitioners should have a low threshold for referral of patients to specialist centres for expert opinion and advice.

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# Hepatitis C virus (HCV)

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Approximately 170 million people worldwide are chronically infected with hepatitis C. The prevalence in different countries ranges from 0.1% to >10%.[1] In South Africa it ranges from 0.1% to 1%, depending on the province. There is an expected rise in the prevalence in South Africa owing to the HIV pandemic, an increase in substance abuse, and the migration of Africans from North Africa, where approximately 20 - 30 million people are infected.[2]

Before the 1980s the main route of transmission of the hepatitis C virus (HCV) was via blood transfusions, and since then via the illicit use of injectable drugs. Other modes of transfer are less relevant and include chronic haemodialysis and perinatal transfer in co-infected patients, particularly in mothers with a high viral load.[3]

Much progress has been made in understanding the natural history of this chronic progressive liver disease. The major factors associated with fibrosis progression are older age at infection, male gender, excessive alcohol ingestion and immunocompromised patients.[4,5] Hepatic steatosis, obesity and diabetes have also been recognised to play a role in disease progression. However, the precise interaction between metabolic derangements, insulin resistance and HCV replication is not fully understood.[6] Viral load and genotype do not appear to influence disease progression.

There are no tests that reliably predict disease progression. Liver biopsy remains the gold standard. Two alternatives to liver biopsy are biomarkers for fibrosis and liver stiffness, which are both non-invasive predictors. Stiffness assessed by ultrasound (Fibroscan, Echosens, France) evaluates the velocity of propagation of a shock wave within the liver tissue, thereby examining a physical parameter for elasticity in liver tissue. Ultrasound has been shown to be valuable for the detection of cirrhosis but not for the different stages thereof, and is therefore not useful for the detection of disease progression. Biomarkers for fibrosis also have the same drawback and therefore cannot replace liver biopsy.[7] High serum alanine aminotransferase (ALT) levels are associated with a higher risk of fibrosis compared with persistently normal serum ALT levels. The current recommendation to assess the progression of fibrosis is to repeat the liver biopsy 3 - 5 years after the first one.[5]

Even though great progress has been made in the treatment of HCV infection, roughly one-half of patients do not respond to therapy. The reference therapy for HCV is a combination of pegylated interferon (PEG-IFN) and ribavirin. The aim of therapy is to achieve a sustained virological response (SVR), defined as an absence of detectable virus 6 months after cessation of therapy. SVR is considered to be a cure for HCV, as extensive studies have shown that 97 - 100% of patients retain undetectable serum HCV RNA. Further studies have shown that HCV RNA is undetectable in the liver. Recent studies have indicated that, in cases of extensive fibrosis or cirrhosis, SVR is associated with an improved outcome, an improved survival and a decreased development of hepatocellular carcinoma.[8-10]

Three categories determine response to therapy, i.e.:

- viral (genotype and viral load)
- treatment related (type, dose, duration, and compliance)
- host (presence of cirrhosis, obesity, hepatic steatosis, insulin resistance and genetic factors).[11]

HCV is classified into 11 major genotypes (designated 1 - 11), many subtypes (designated a, b, c, etc.), and about 100 different strains (numbered 1, 2, 3, etc.) based on the genomic sequence heterogeneity. Genotypes 1 - 3 have a worldwide distribution.

Types 1a and 1b are the most common, accounting for about 60% of global infections. They predominate in northern Europe and North America, and in southern and eastern Europe and Japan, respectively. Type 2 occurs less frequently than type 1. Type 3 is endemic in south-east Asia and is variably distributed in different countries. Genotype 4 is principally found in the Middle East, Egypt, and Central Africa.[12] Type 5 is almost exclusively found in South Africa; however, there are 2 reports of cases in Belgium and France of patients with genotype 5.[2] Furthermore, the South African registry demonstrates more cases of genotype 1. HCV genotype 1 is the most difficult to treat, with an SVR after 48 weeks of treatment of 34 - 52%. Genotypes 2 and 3 are easy to treat, with an SVR after 24 weeks of treatment of 80 - 100%. The treatment period of these genotypes can be reduced to 12 -16 weeks, depending on early virological response after 4 weeks.[13,14] From the 2 published studies with genotype 5, the response to treatment appears to be better than with genotype 1.[2] Because of the difficulty in treating genotype 1, novel compounds are being developed – the so-called specifically targeted antiviral therapy for HCV (STAT-C) – that hold great promise for the future.[15]

In summary, much progress has been made in the understanding of the natural history of HCV. However, huge challenges still remain in the management of patients with HCV, specifically those with genotype 1.

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