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Editorial

Dear readership

"The times they are a-changin" the lyrics of Bob Dylan's famous song are as pertinent now they were in 1964. COVID has brought the fragility of our existence to the fore. We all know colleagues who have had the illness, dodged a bullet or tragically have succumbed to the disease. We also are in the midst of coping with its physical and mental effects on the health care system and the life in general. The initial focus was on protecting the patients and healthcare workers with almost paralysis of the procedural disciplines for all but emergencies. This has brought all forms of innovation to platforms for teaching and managing patients of which ZOOM has been the "preferred provider" It has brought a new impetus to tele-consultation and brought realization that perhaps traditional outpatient clinics should be a thing of the past. The exponential growth of internet educational offerings means there is a lot to choose from including the Virtual Congress. The Wits Biennial was the first to try their hand and even experienced presenters and chairpersons exhibited they could fall down an abyss with technical factors, within and beyond their control. Next came the SAGES Virtual Congress with the professional organizers again finding their feet with an improved if not flawless performance. In this issue we have report backs on the various elements of the Virtual Congress including my own comments on the Gastro Foundation WEO partnership. A partnership that will be part of the G-ECHO (Extending Community Health Care Outcomes) to Sub Saharan Africa initiative for gastroenterology going forward from its launch on September 3rd. I am sure the feedback will provide food for thought and until travel, particularly internationally is restored we must do our own homework to "perfect" the product.

In this issue I have taken the opportunity I hope to showcase some of the efforts of the trainees that I have been involved with at various levels in the production or their masters. With both a surgical and medical bent these are reworked versions of their literature reviews. I do hope the trainees and mature medical and surgical gastroenterologists enjoy these offerings.

It is pertinent to reflect on the untimely death from colon cancer of Chadwick Boseman the "Black Panther". He died at the age of 43 from colon cancer, a demographic profile typical of the cancer in Black Africans in Africa. A phenomena that the paucity of data from the continent has provided few answers. In this issue Leo, one of several researchers trying to shed light on this deficit, makes some suggestions.

The times really are a changing and we do need to focus on how we are going to modify practice to get back to normal functioning as a gastroenterology community. I hope the journal helps with the process.

Sandie Thomson

SAGES VIRTUAL PRIZE WINNERS

First prize
Rachel Mtlotha-Mitole
Paediatric acute liver failure; A retrospective review from a South African Tertiary Centre

2nd prize
Muhammad Ismail
Demographic, Endoscopic and Histological Profile of Oesophageal Cancer in the Gastroenterology Service of the Central Hospital of Maputo from January 2016 to December 2018

Gastro Foundation : Best work by a fellow/trainee
Dirkie Claassen
Review: Ebstein-Barr Virus(EBV) status in Inflammatory Bowel Disease patients attending Out Patients at Tygerberg Hospital

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South African
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The impact of COVID-19 on blood supply: Information from the South African blood services

The COVID-19 pandemic has negatively impacted the blood supply because:

- Donors fear being exposed to the SARS COV-2.
- Many donors are deferred from donating due to exposure to Covid-19 positive people or Covid-19 illness.
- The lock down have markedly reduced the availability of collections sites e.g. corporate and residential clinics.
- Access to a large number of committed young donors were negatively impacted due to University closures and schools not allowing on-site blood donation clinics.

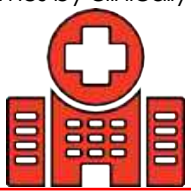
The following patients are most likely to suffer the consequences:

- Patients on chronic transfusion regimens e.g. chronic kidney disease, oncology, hematological disease, etc. whose treatment cannot be postponed or stopped.
- Patients who bleed during childbirth.
- Trauma patients.
- Patients in remote areas reliant on Group O blood in emergency fridges.

Treating doctors can implement a number of measures to help ensure a sustainable blood supply.

- Apply Patient BloodManagement (PBM) principles.
- Utilize measures to minimize the usageof allogeneic blood products.
- Prevent wastage of scarce resources.

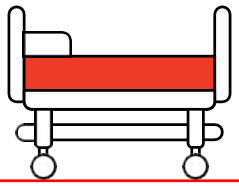
Patient Blood Management is an evidence-based bundle of care to optimise medical and surgical patient outcomes by clinically managing and preserving a patient's own blood.



28 % lower hospital mortality
Leahy MF et al. Transfusion 2017: 57:1347-1358

21 % fewer hospital acquired infections
Leahy MF et al. Transfusion 2017: 57:1347-1358

31 % fewer heart attacks and strokes
Leahy MF et al. Transfusion 2017: 57:1347-1358

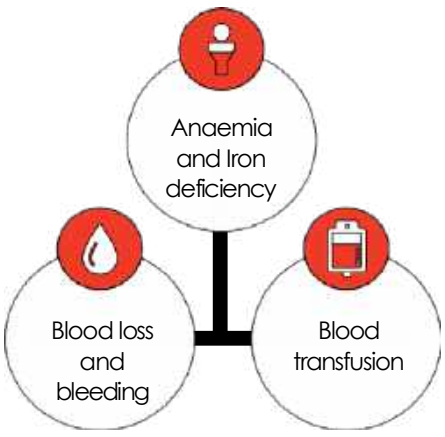


3 days shorter hospital stays
Leahy MF et al. Transfusion 2017: 57:1347-1358

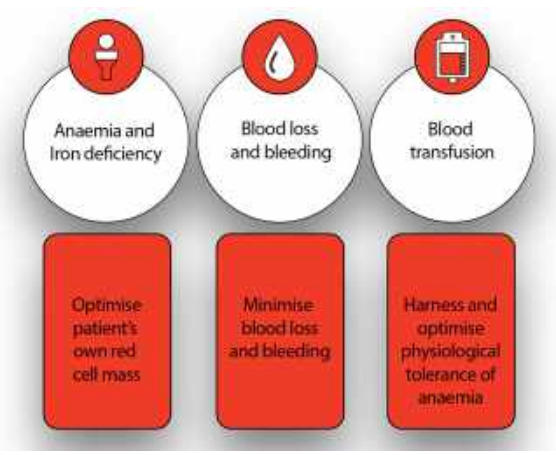
PBM aims to improve treatment results by:

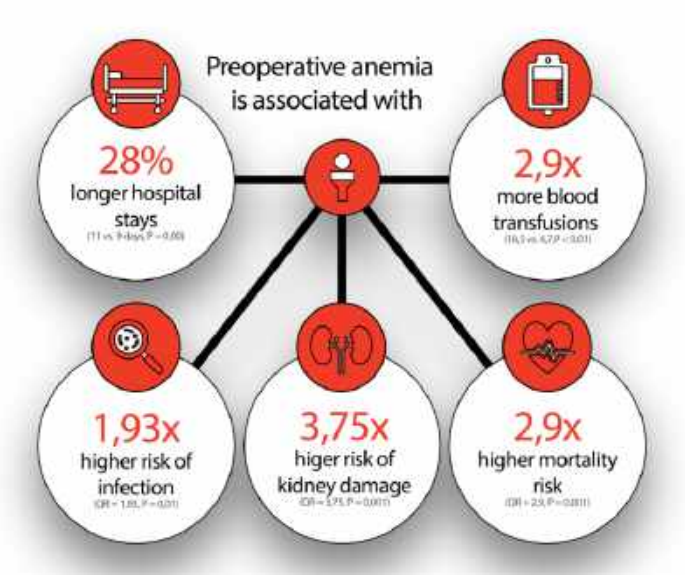
- Detection and management of anaemia
- Minimising blood loss
- Avoiding clinically inappropriate blood transfusion

Three independent risk factors that contribute to negative patient outcomes, were identified.



The 3 pillars of BPM were developed to address each of these independent risk factors





Pillar 1: Diagnose and treat anaemia prior to operations

What can doctors do?

- Screen for anaemia
- Diagnose type of anaemia
- Fully treat anaemia
- Cancel elective surgery if anaemia is untreated

Pillar 2: Minimize blood loss and bleeding

Consider preventative, diagnostic, physiological and pharmacological measures in all bleeding patients.

What can doctors do?

- Use technology and POCtesting
  - Where available, use cell saversand point-of-care (POC) testing suchas thromboelastography (TEG) and rotational thromboelastometry (ROTEM) to reduce the need for allogeneic bloodproducts
- Reduce bleeding
  - Obtain a proper history to identifybleeding risks or drugs that may cause/aggravate bleeding
  - Maintain a normal volume,temperature and acid-base status in yourpatient
  - Limit phlebotomies

Pillar 3: Optimise the patient physiologically to increase their tolerance to anaemia

What can doctors do?

- Maintain normal volume, temperature and acid-base status
- Optimise oxygenation/ventilation and acid-base status
- Minimise oxygen consumption
- Treat infections promptly
- Follow evidence-based transfusion triggers

Other measure to conserve blood

- Make use of blood on returnable basis (BRB) services where it is available.
- Implement a one-unit-at-a-time policy as a matter of urgency.
- Use Type and Screen service where clinically indicated.
- Use emergency fridge group O blood in life-threatening emergencies only.
- Limit stock in emergency fridges to a minimum.
- Consider Group O positive units for men and women of non-childbearing age.
- Consider switching to group-A plasma and group-specific, uncross-matched blood early for massive transfusions.
- Optimize temperature and acid-base balance to reduce bleeding and improve coagulation.

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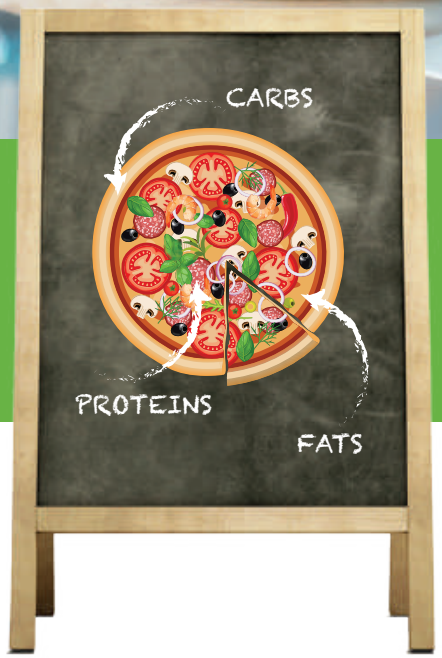

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- The work must be presented at the SAGES annual congress.
- Sponsorship of the work is to be acknowledged in all publications.
- The funds will be administered through the nominated university or the sponsor.
- The grant will only be paid once proof of ethics approval has been received. Should the study not be commenced within one year of the grant being awarded, the grant is to be returned.

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The ins and outs of percutaneous cholecystostomy

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[1] Department of Surgery, Health Sciences Faculty, University of Cape Town, Cape Town, South Africa
[2] Surgical Gastroenterology and Acute Care Surgery Units, Groote Schuur Hospital, Cape Town, South Africa
[3] Emeritus Professor, Division of Gastroenterology, University of Cape Town

Introduction

Acute calculous cholecystitis (ACC), a complication of gallstones, is a common reason for emergency surgical admission. It is usually easily diagnosed on clinical and ultrasonic grounds. Conversely, acute acalculous cholecystitis (AAC) is a less-common but well-recognised disease entity that occurs as a complication of diabetes and critical illness. ACC is usually due to stone(s) in the cystic duct causing persistent partial or complete obstruction. AAC is postulated to be related to bile stasis and gallbladder wall ischaemia. Both aetiologies predispose to bacterial colonisation from gastrointestinal tract translocation, which combined with bile stasis, triggers a release of inflammatory mediators, causing further distension and inflammation of the gallbladder. This is manifest as signs of local inflammation (Murphy's sign) and as the systemic inflammatory response syndrome (SIRS), producing a spectrum of disease severity.

The diagnosis and severity assessment and management recommendations for ACC, based on clinical, laboratory and imaging parameters, are well described in the 2018 Tokyo Guidelines.[1] According to these guidelines,[2-4] the standard of care for the management of ACC is the use of empiric antimicrobial drugs and same admission laparoscopic cholecystectomy (LC). Percutaneous transhepatic gallbladder drainage, otherwise known as percutaneous cholecystostomy (PC), is also described in the Tokyo Guidelines as an alternative to LC for sepsis control, in a small subset of patients in specific clinical settings of ACC.[2,3] These include patients who are at high risk for anaesthesia, as well as critically ill patients or patients with severe (Grade III) cholecystitis.

In contrast, the diagnosis of AAC is more difficult to make in the critical care setting where it may be only one of the multiple sources of SIRS and bacterial infection in this patient population. The diagnosis is based on a high index of suspicion and ultrasound or CT Scan findings of high-density bile, sub-serosal oedema and an increased perpendicular diameter of the gallbladder. Unlike ACC the treatment is usually PC, with cholecystectomy reserved for those patients in whom gas within the gallbladder or a lack of gallbladder wall enhancement suggest imminent perforation.

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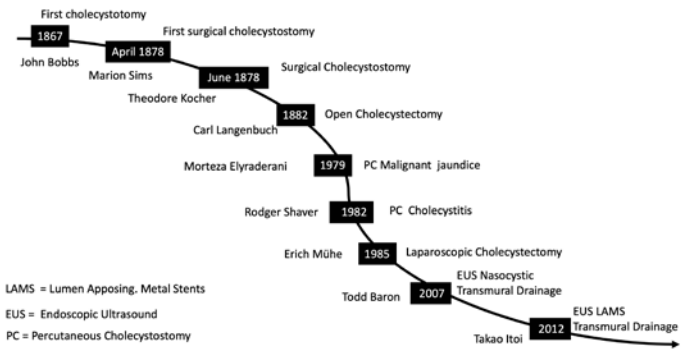
Transmural endoscopic ultrasound (EUS) drainage with the use of either naso-cystic tubes or lumen-apposing metal stents (LAMS) is increasingly being used in the management of acute cholecystitis, however experience with this expensive modality is limited in South Africa. Hence this review focuses on the history and role of PC in the management of acute cholecystitis, aiming to define its role, detail the technical options and their complication rates and finally describe post-procedure treatment options.

History

Figure 1 below outlines the landmark historical events that led to the current options for the management of cholecystitis. Dr John S. Bobbs performed the first cholecystotomy (opening of the gallbladder, as opposed to stoma) on July 15th 1867. This was the first operation on the gallbladder, done inadvertently while he was searching for an ovarian cyst in a young female patient with a four year history of biliary colic. He closed the gall bladder after extracting multiple stones and placed it under the abdominal incision. He termed the procedure 'Lithotomy of the gallbladder.' The patient recovered well and lived longer than her surgeon.[5]

Figure 1. Timeline demonstrating evolution of the management of cholecystitis



Dr Marion Sims performed the first actual surgical cholecystostomy on April 18th 1878. He sewed an open gallbladder to the corner of an abdominal incision after extracting multiple stones and bile. The patient died eight days later of massive internal haemorrhage. Dr Theodor Kocher performed the first successful cholecystostomy two months later, in June 1878. After this, cholecystostomy became the standard operation for

cholelithiasis,[5] until a few years later when Dr Carl Langenbuch performed the first cholecystectomy.

Percutaneous cholecystostomy was first performed by Dr Morteza Elyaderani, in 1979. The patient was a 72 year old female, admitted with obstructive jaundice in the setting of metastatic uterine carcinoma. She had an enlarged gallbladder with a mass in the head of pancreas. Her clinical condition was deteriorating due to cholangitis and she was too unwell for surgery. PC was then performed, with pus aspirated from the gallbladder. The procedure was uncomplicated and the patient responded well, showing clinical improvement.[6] Dr Rodger Shaver further developed the procedure, extending the indication to include acute cholecystitis in patients with underlying systemic disease that would render them high risk for surgical management. They reported their experience with 13 patients who underwent PC, five for cholecystitis and eight for biliary obstruction. Of the cholecystitis group, four patients did well with no complications, but one patient failed to respond clinically, with a subsequently dislodged drain and later died of severe sepsis.[7] PC thus became recognised as a management alternative in patients unfit for cholecystectomy.

Percutaneous Cholecystostomy

Indications

By far, the most common indication of PC is in the management of acute cholecystitis.

In AAC where the cause is the original critical illness, PC is often the first line treatment for the condition until the critical illness has resolved. In ACC the patients are critically ill from their gall bladder pathology and when this is combined with multiple comorbidities, these patients are poor candidates for general anaesthesia and LC. Some patients may never progress to a point of fitness for general anaesthesia. LC as a definitive procedure is generally recommended for ACC, once the patient stabilises and if they are able to tolerate surgery as it removes the risk of subsequent attacks cholecystitis. In AAC this risk of recurrent cholecystitis is less, so the need for LC after recovery can be individualised based on their clinical course.

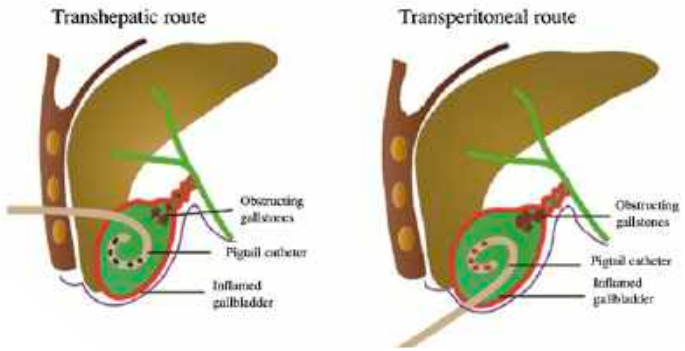
Another indication of PC is as an alternative route of access to the biliary tract, in patients with obstructive jaundice or cholangitis. This is reserved as a last option, in cases of failed endoscopic retrograde cholangio-pancreatography (ERCP) and percutaneous trans-hepatic cholangiogram (PTC) access. This route can then be used for biliary drainage, dilatation and stenting of strictures and rendezvous procedures.

Description

Modern PC involves the placement of a pigtail drainage catheter into the gallbladder via skin puncture, strictly observing aseptic precautions. The procedure is performed under ultrasound or CT-guidance under local anaesthesia with tailored procedural sedation. Fluoroscopy is used to confirm correct catheter position and technical success is defined as visualisation of the pigtail loop in the lumen of the gallbladder.[8, 9]

The gallbladder is accessed by either a trans-hepatic or trans-peritoneal route (Figure 2).[10, 11] In the trans-hepatic approach, access to the gallbladder is achieved via the bare area of the liver. This is the route recommended in the Tokyo guidelines, as it reduces the risk of intraperitoneal bile leakage, with enhanced catheter stability and faster tract maturation. However this route does carry the risk of other complications such as haemobilia and pneumothorax.[12, 13] Severe liver disease and coagulopathy are contraindications to using the trans-hepatic approach. Trans-peritoneal access may be difficult in patients with massive ascites or bowel interposed between the gallbladder and abdominal wall.[8-12]

Figure 2. Schematic illustration of the Transhepatic and Transperitoneal approaches to percutaneous cholecystostomy (modified from Katabathina et al[33])



Technique

Either the Seldinger (Figure 3) or trocar (Figure 4) techniques can be used for PC. The Seldinger technique involves needle puncture and gallbladder access, confirmed by aspiration of bile. Once position is verified by contrast opacification, guidewire placement into the gallbladder follows. Subsequently the tract is dilated and the catheter is advanced over the guidewire and locked in position.[8, 9, 12] The trocar technique involves direct puncture into the gallbladder, through a cannula with a rigid stylet. The stylet or trocar is removed from the cannula, bile aspirated and the catheter introduced directedly through the cannula.[8, 9, 12] The Turner needle shown in Figure 4 is an example of such a trocar system.

The Seldinger technique has some advantages over the trocar technique as it uses a small calibre needle for access, thereby reducing the risk of iatrogenic organ perforation or bleeding from the liver, while the trocar technique is faster due to the fewer number of manoeuvres.[8, 9, 12]

Once the diagnosis of acute cholecystitis has been made and the decision taken to perform PC, the procedure is performed, usually using the Seldinger technique described above, via the transhepatic route through the bare area of the liver. Empiric antibiotic treatment is commenced pre-procedure and is guided by local microbiology treatment protocols, bearing in mind that gram negative cover is also necessary. Upon puncture of the gallbladder, bile/pus is aspirated and a sample sent for culture. Subsequent antibiotic treatment can then be culture-directed if the clinical picture demands it.[8, 9, 12]

Figure 3. Seldinger technique of performing percutaneous cholecystostomy (modified from Katabathina et al[33])

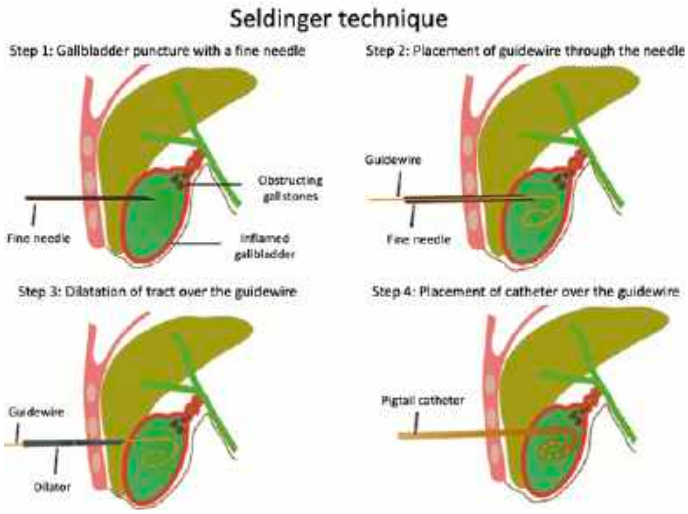
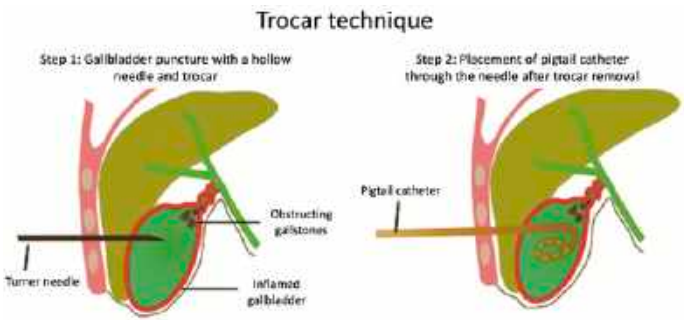


Figure 4. Trocar technique of performing percutaneous cholecystostomy (modified from Katabathina et al[33])

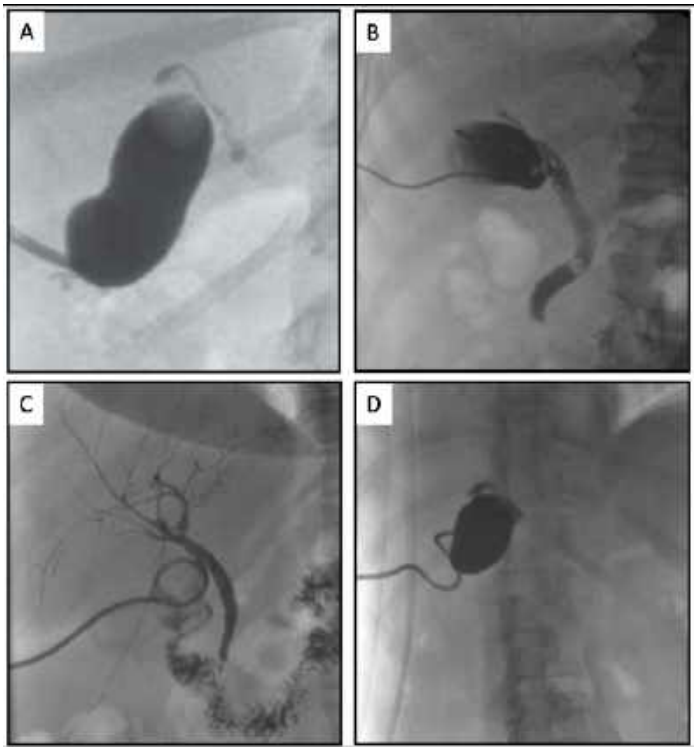


Subsequent management

When technical success has been achieved, the drainage catheter is locked in position and the patient is monitored in the radiology suite for any immediate complications. Once stable, the patient is transferred to the ward to monitor for early complications and clinical response. The drainage catheter is flushed twice a day, with 20ml of 0.9% saline, to avoid blockage. In the absence of a good clinical response within 72 hours alternative methods of treatment should be considered. In uncomplicated cases with positive clinical response, patients may be discharged with the drainage catheter in situ, after education in drain flushing to ensure patency.

Catheter removal is usually performed between 14 - 30 days due to variable rates of tract maturation as a result of factors such as diabetes, malnutrition, steroid therapy, ascites or sepsis.[8, 9, 12] Removal must be preceded by trans-catheter cholecystography (Figure 5), to assess tract maturation, absence of contrast leakage, cystic duct patency and the presence of stones in the common bile duct. Provided the cystic duct is patent and the tract matured, the drainage catheter can either be test-clamped, capped or removed. In cases of ACC, percutaneous stone extraction or lithotripsy are alternate options to LC to prevent recurrence, but they are rarely used. Recurrent attacks can be managed with repeat PC if necessary. If the patient is for permanent catheter drainage, replacement should be performed at three-monthly intervals.[8, 9, 12]

Figure 5. Check cholecystography images demonstrating various possible scenarios



A: Patent cystic duct, but persistent large stone in the gallbladder. B: Patent cystic duct with CBD stone. C: Patent cystic duct with good flow of contrast into the duodenum. D: Persistent occlusion of the cystic duct.

Outcomes

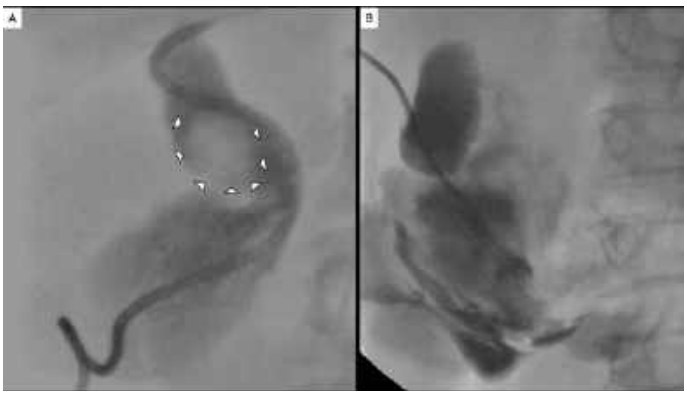
The low procedure-related complication rate and positive clinical response of PC have been described in a number of studies and attest to the safety and efficacy of this procedure.[14-20]

Table 1 shows the key variables reported on the outcomes of PC in recent studies for ACC or ACC alone or in combination. Two of the studies had more than a hundred patients. Surprisingly, technical success rates are 100% in all of the six studies, whereas overall reported technical success rates vary between 85-100%.[17, 21, 22] Technical failure may be caused by factors that make gallbladder puncture difficult, like porcelain or thick-walled gallbladder. Other factors may include a heavy stone burden, or small gallbladder which does not accommodate the pigtail. Sedation and patient co-operation issues may also contribute to technical failure.[8, 12] In cases of technical failure, other routes of gallbladder drainage including laparoscopic cholecystostomy or subtotal cholecystectomy may be feasible alternatives, but these patients are already generally unfit for anaesthesia. EUS-guided transmural drainage is a technique that is rapidly gaining momentum and popularity.[23-25]

Positive clinical response is defined as improvement in patient symptoms, reduction in temperature and reduction in white cell count over 72 hours. The positive clinical response rates to PC are reported in only three of the six studies in Table 1 and vary from 87 - 98%,. Earlier studies reported lower clinical success rates of around 60%.[8, 12] This variation is likely due to the heterogeneity of patient populations, indications and clinical condition of patients at the time of PC.

Complications associated with PC can be divided into immediate, early (within the first few days) and delayed/ late. Furthermore, subsequent cholecystectomy (when performed) may also have an associated morbidity and mortality. Immediate complications include malposition (Figure 6), technical failure, pneumothorax, bile leakage,

Figure 6. Fluoroscopy images



A: Technical success with drainage catheter in the gallbladder lumen and a large stone obstructing the cystic duct (outlined by arrows). B: Malposition of catheter, demonstrating free contrast in the peritoneal cavity

Table 1. Summary of recent studies of PC

Study	Year	Number		Technical Success		Clinical Success Number (%)	Later Cholecystectomy Number (%)		Complication rate (%)	Overall Mortality rate Number (%)
ACC and AAC										
Masrani et al[20]	2020	377		377		NS	118 (31)		4	50 (13)
Kuan et al[19]	2020	96		96		NS	24 (25)		21	16 (16.7)
Kamer et al[16]	2017	12		12		11 (92)	12 (100)		25	0 (0)
AAC										
Noh et al[21]	2017	271		271		235 (87)	127 (47)		2.2	23 (8.4)
ACC and AAC		ACC	AAC	ACC	AAC		ACC	AAC		
Aroori et al[15]	2018	41	12	41	12	NS	17 (41)	5 (42)	28	7 (13.2)
Cha et al[18]	2014	46	36	46	36	80 (98)	23 (50)	12 (33)	2.4	3 (3.66)

ACC =Acute calculous cholecystitis, AAC =Acute acalculous cholecystitis NS =Not stated

gallbladder rupture, peritonitis and haemorrhage. Inadvertent injury of an adjacent organ/hollow viscus may be an immediate complication, but might only be recognised within 24 - 48 hours. Early complications include drain dislodgement and haemobilia. Late complications include drain blockage, dislodgement, secondary sepsis, recurrent cholecystitis, abdominal wall abscess and non-healing of wound/tract.[8, 21]

The reported overall procedure-related complication rate of PC is low, the most common being catheter dislodgement.[8,13,21,22] Pneumothorax is more common when using the transhepatic route, as the puncture site is higher up on the abdominal wall. Haemobilia is rare and bile leakage can range from asymptomatic, to pericholecystic abscess formation, to frank peritonitis requiring surgical intervention. Injury to adjacent organs is extremely rare, owing to imaging guidance.

When compared with LC, patients who normally undergo PC are generally older, with more chronic illnesses. This relation can probably be attributed to the fact that these patients are less likely to tolerate LC, hence PC is used for control of sepsis in both ACC and AAC. PC is associated with less complications than LC, but patients receiving PC are more likely to die, have an increased hospital length of stay and therefore increased cost. This is probably related to the comorbidities and patient clinical condition, rather than the procedure itself. However, as reported by a recent multicentre randomised superiority trial, LC has been shown to reduce the overall rate of major complications, even in high risk patients, when compared to PC drainage.[26]

The overall low, but widely varied procedure-related complication rates, ranging from 2-28% are shown in Table 1. The two largest series however report complication rates under 5%, although none of the studies graded the severity of their complications. Early tube placement has been associated with fewer procedure-related complications and shorter hospital stay as compared to delayed tube placement, especially in cases non-responsive to initial antibiotic therapy.[27]

The overall mortality rates reported in all studies are attributable to either the procedure, subsequent surgery and/or patient co-morbidities and ranged from 2-16%. One study actually reported 100% technical success, 100% subsequent cholecystectomy and no mortalities, but there were only 12 patients in this series. The majority of studies reported subsequent cholecystectomy in 30 - 40% irrespective of the indication for PC. To highlight this point, as described by a systematic review, the overall procedure-related mortality rate of PC itself is reported to be low (0.36%), with the overall 30- day mortality rate going up to 15.4%.[22]

Patient Selection

Some studies conclude that PC can be used as definitive treatment for AC, as in the critically ill, frail or elderly it avoids general anaesthesia in patients who may never be candidates for surgery.[17, 28, 29] However, in one study when compared the gold standard of treatment LC, PC was shown to have little benefit, even in critically ill patients. The authors of this study recommended that PC remain reserved for the specific group of patients who are not surgical candidates.[30] Another comparative study performed, with a matched-pair analysis drew similar results and conclusions, stating that the only advantage of PC over LC was the reduced procedure duration.[31]

A recent multicentre randomised clinical trial (the CHOCOLATE trial) was ended prematurely due to an unacceptably high rate of major complications in the PC arm as opposed to LC.[26] The study methodology used the APACHE II score to define disease severity and included patients with scores over seven, however excluded patients with a score of over 15. It appears that they excluded a subset of patients, with the most severe diseases, who were the very ones most likely to benefit most from PC. Conversely, they included patients who were probably not sick enough to warrant PC over LC based on available evidence.

Alternative methods of gallbladder drainage in such scenarios, as defined by the Tokyo Guidelines, include trans papillary access to the cystic duct via ERCP and EUS-guided transmural access.[2]

Conclusion

We believe that the definition of who is high-risk or unfit for LC lies at the crux as to whether PC is overapplied or used for the appropriate clinical indication as recommended in the Tokyo Guidelines. PC is a valuable alternative to LC in specific clinical settings, to achieve sepsis control in patients presenting with acute cholecystitis. Used in certain scenarios, it may be a life-saving definitive procedure

for patients with high-operative risk. Although the actual inflammation will likely settle with PC, if the cause is gallstones the patient remains at risk of future attacks of cholecystitis and subsequent cholecystectomy should be performed if possible. This risk of future attacks is lower in patients with AAC, with the value of PC being well-appreciated[32] and the need for interval cholecystectomy should be based on their clinical course.

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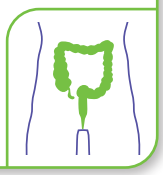

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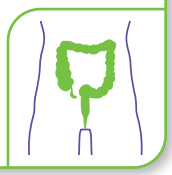

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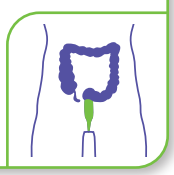

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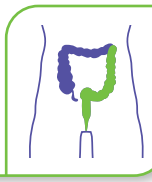

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Rectal Prolapse: The surgical options past and current

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Introduction

A rational approach to the non-operative and operative management of rectal prolapse has developed from advances in the functional and anatomical assessment of these patients, by clinical examination, defecography, endoanal ultrasound and anal manometry. The philosophy of surgical management has changed based on Pescatori's 'iceberg theory'.[1] This theory advocates an approach, based initially on the non-operative management of defecatory dysfunction, that includes addressing associated physiological and psychological variables. The recognition of rectal prolapse as part of a spectrum of posterior organ prolapse in a larger picture of pelvic floor dysfunction has led to a more multidisciplinary approach. The restoration of normal anatomy is no longer regarded as the only goal in rectal prolapse surgery. The restoration of normal bowel function is now considered to be of equal importance. Over 100 surgical techniques have been described during the last century with no accepted standard procedure. As the multidisciplinary management of pelvic floor dysfunction has evolved, however, the list of operations has reduced, leaving just a few routinely advocated procedures, best performed by coloproctologists in specialist units.

At the turn of the twentieth century, the perineal surgical technique dominated the operative management of rectal prolapse, with Thiersch's anal encirclement operation[2] (1891) preceding Mikulicz's perineal sigmoidectomy (1899) and Delorme's mucosal sleeve resection (1900). The first half of this century saw the proliferation of several novel abdominal approaches based on Ripstein's original principle of mobilization and rectopexy[3], then Wells' popular variation, followed by resection rectopexy. The latter, first described by Frykman and Goldberg in 1969, was a post hoc modification to try and solve the persistent problem of constipation that was prevalent in all reported abdominal rectopexy series[5]. The addition of resection to the surgical approach was shown to modify postoperative bowel function and avoid constipation. In more recent years, laparoscopic techniques have shown promise due to improvements in safety and reduction in postoperative morbidity whilst maintaining recurrence rates under 10%.[6]

Surgical procedures have the common aim of correcting the prolapse, restoring normal bowel function, and avoiding recurrence and are categorized according to the whether a perineal or abdominal approach is used. The decision is based on the patient's age and comorbidities, extent of prolapse and the presence of chronic constipation and faecal incontinence. The traditional algorithm has been abdominal rectopexy if young and fit, and perineal surgery if old and infirm.[7]

Perineal surgical approach & techniques

Perineal surgery avoids the morbidity and mortality associated with a laparotomy in the elderly and high-risk patient population. The two most commonly performed perineal procedures are Altemeier's procedure (more popular in North America) and Delorme's procedure (more popular in Europe). Assessment of preoperative continence, other defecatory dysfunction, and the size of the prolapse should be considered with the choice of procedure as the two techniques have different merits in this regard. These 'less-invasive' techniques also merit consideration in young men as they avoid the risk of autonomic pelvic nerve injury with consequent sexual dysfunction associated with abdominal approaches. Recent studies showing reduced recurrence rates to those reported in earlier series have sparked renewed interest in these perineal procedures.

Altemeier's procedure

Perineal rectosigmoidectomy was first described by Mikulicz in 1889.[8] Altemeier popularised this procedure in the United States, where it has remained the preferred perineal technique.[9] The procedure, shown schematically in Figure 1[10], involves a full-thickness resection of the prolapsed rectosigmoid segment with anastomosis at the level of the pectinate line. Perineal rectosigmoidectomy may be more appropriate in the setting of a large prolapse or significant constipation.[11-14] In a retrospective analysis of 45 patients who underwent rectosigmoidectomy a significant decrease in constipation (33.3% preop vs 6.7% postop) and incontinence (77.8% preop vs 35.6% postop) was reported.[11] The latter outcome was greatest in patients with a maximal squeeze pressure > 60mmHg preoperatively. Recurrence rates were as high as 16%[6] although recent series have shown lower rates between 5-10%.[11,15,16] Complications include bleeding from the anastomosis, pelvic abscess, anastomotic stricture and rarely anastomotic leakage.

To assess procedure efficacy several comparative studies have been conducted. In a small study with 10 patients in each arm abdominal resection rectopexy and pelvic floor repair (PFR) was compared to perineal rectosigmoidectomy in elderly females with full-thickness rectal prolapse and faecal incontinence.

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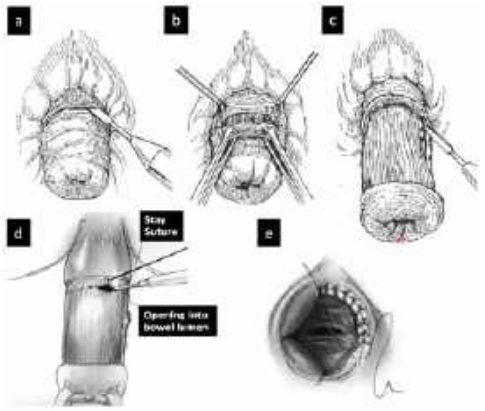

Figure 1.
Schematic diagram showing main steps of Altemeier's procedure: (a) mucosa divided transversally at dentate line, (b) clamped edges of transected mucosa, (c) rectum withdrawn & mesorectum divided, (d) transection of sigmoid colon, (e) coloanal anastomosis (modified from Vernava et al 2007)[10]

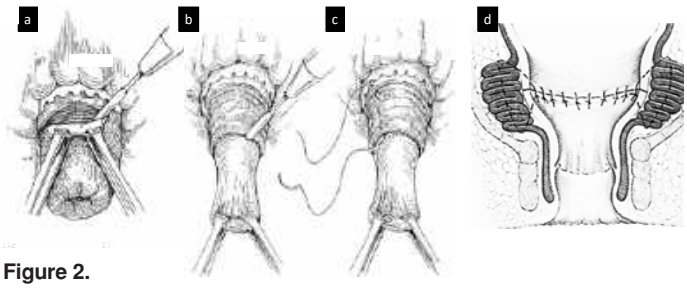

Figure 2.
Schematic diagram showing main steps of Delorme's procedure: (a) circumferential mucosal incision, (b) mucosectomy extended to apex of prolapse, (c) plicating sutures placed at transected mucosal edges, (d) sutures tied circumferentially (modified from Venrnava et al 2007)[10]

They reported no recurrences from resection rectopexy and (PFR) and one recurrence from perineal rectosigmoidectomy. In addition, they showed improved continence after abdominal resection rectopexy and (PFR) when compared to perineal rectosigmoidectomy. Mean resting pressure and compliance were also found to be greater postoperatively in the resection rectopexy and (PFR) group.[17] In another series incontinence worsened in a fifth of the patients and was attributed to resection of the rectal reservoir, and led to additions to the standard procedure of a pouch or levatorplasty to address this shortcoming.[13,18] The Florida Cleveland Clinic group reported that perineal rectosigmoidectomy with levatorplasty resulted in significantly better short-term functional outcomes than either perineal rectosigmoidectomy alone or Delorme's operation. They showed a significant improvement in continence and a lower short-term recurrence rate of 5% 13% and 38% for the three procedures respectively.[16] Kimmins et al followed a series of 68 patients accrued between 1993 and 1999 over a median of 20.8 months. Seventy percent of the surgeries were performed under regional or local anaesthetic and 80% discharged within 24 hours. They reported a complication rate of 10% with no mortality. All patients had complete objective resolution, with a subjective improvement in 80%.[19] In the largest Altemeir series to date, Kim et al reported a recurrence rate of 16% amongst 183 patients.[20] More recently Zbar et al reported on a 15-year experience with the Altemeir procedure plus levatorplasty performed on 80 patients in a single unit with a median follow up of 22 months. They had 3 recurrences in this series, with a perianastomotic abscess.[14] Cirocco et al reported similar good results on 103 patients accrued between 2000 and 2009 with a mean follow up of 43 months, reported no recurrences. Preoperative constipation improved in 94% and incontinence in 85%.[21]

Delorme's procedure

Delorme's procedure was first described by the French military surgeon Edmond Delorme in 1900.[22] Initially regarded as a technically simple and safe operation, the technique fell into disfavour after anecdotal reports of high recurrence rates and high postoperative morbidity and mortality rates. Due to improved techniques, it's popularity has re-emerged as an good option for those not fit enough to withstand an abdominal operation.[23] It can be performed under locoregional anaesthesia, has a short intervention time, carries no risk of intra-abdominal anastomosis or peritoneal adhesions, has reduced postoperative pain and a short hospital stay. Importantly, pelvic and hypogastric nerve injury is avoided so erectile and ejaculatory function are preserved.

The procedure, shown schematically in Figure 2[10], involves a transanal circumferential sleeve resection of redundant anal canal and distal rectal mucosa, with plication of the muscularis layer using circumferential vertical sutures. Delorme's procedure has higher recurrence rates than abdominal procedures, in the range of 10-30%.[6,24] Faecal incontinence is improved after Delorme's procedure[6,24], and constipation and difficulty passing stool are not generally seen. Plusa et al studied the physiological changes after Delorme's procedure, and reported an improvement in rectal sensation but also found lowered compliance in the 19 female septogenarian patients.[25] Two additional studies have reported similar manometric findings.[26,27] Pescatori et al combined the Delorme's procedure with a sphincteroplasty in 33 patients. The recurrence rate was 21%, continence improved in 70% and 44% of patients were cured of their constipation postoperatively.[28] They concluded that the addition of a sphincteroplasty to the Delorme's procedure was most beneficial in those with evidence of concomitant severe pelvic floor dysfunction. Another modification of Delorme's operation was devised by Lechaux et al. They compared Delorme's procedure with Delorme's procedure and an innovative extended transrectal pelvic floor repair in 85 patients, aged from 21 to 97 years They reported the modified technique recurrence rate was 5% compared 21%.[29] Equally significant was the finding that the 44 elderly poor operative risk patients for abdominal surgery had a recurrence rate of 22.5% compared to 5% in the 41 young healthy patients.[29] A more recent study reported a single recurrence in 41 (2.4%) patients undergoing a Delorme procedure with the addition of a post anal repair and levatorplasty, compared to a recurrence rate of 14.28% in the 41 patients undergoing a standard Delorme's procedure.[30] A further comparison to assess the effect of age on outcome was conducted by Fazeli and colleagues. They reported on 52 patients who underwent a Delorme's repair for full-thickness rectal prolapse between 2009 and 2012. Forty-one of the patients were aged less than 50 years. The recurrence rate was 9.75% in the younger group, compared to 18.2% in the older group. Incontinence resolved in 92% of the younger age group patients, and improved in 60% of the older patients.[31] A study by Sielezneff and colleagues looking at selection criteria for Delorme's procedure reported a number of factors associated with potential failure of this technique, including: proximal procidentia with retrosacral separation on defecography, faecal incontinence, chronic diarrhoea, and perineal descent of > 9cm.[32]

Abdominal surgical approach & techniques

The abdominal approach involves some degree of mobilization of the rectum out of the true pelvis and fixation to the sacrum (rectopexy) using sutures or mesh, with or without resection.

Anterior resection alone

Rectosigmoid resection was first described as a strategy to repair rectal prolapse in 1955, based on the observation that after low anterior resection a dense area of fibrosis forms between the anastomotic suture line and the sacrum, securing the rectum to the sacrum.[33] This procedure was particularly well suited to patients with a long redundant sigmoid colon and a history of chronic constipation. Several retrospective reviews have shown higher recurrence rates and a lack of functional improvements.[34] This, coupled with the morbidity associated with a low pelvic anastomosis, has confined this procedure to the history books with no reports on its use after the 1980s.

Abdominal Rectopexy

The rationale for rectopexy is to keep the rectum attached in its desired elevated position until it becomes fixed by scar tissue. After mobilization of the rectum it is fixed to the sacrum by means of sutures or a prosthetic mesh. There are many variations related to the extent of posterior dissection, and the division of the lateral ligaments, which are said to affect the autonomic innervation of the rectum and the anatomical configuration essential for normal defaecation.

Suture or Mesh

Suture rectopexy was first described in 1959.[35] In 10 prospective and retrospective studies published between 1983 and 2001, no mortality was reported with the majority of recurrence rates being under 3% with the exception of one outlier of 27%.[2] Prosthetic or mesh rectopexy, on the other hand, assumes that the insertion of foreign material will evoke a greater fibrous tissue reaction than ordinary suture rectopexy. A Cochrane Collaboration review in 2015 concluded that there is no difference in primary outcomes between different mesh materials used to fix the mobilized rectum.[36] Polypropylene mesh is the most widely used.

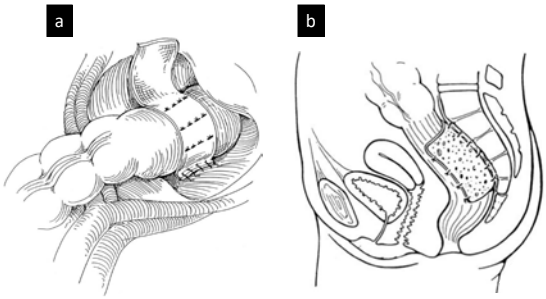

Figure 3.
Schematic diagram showing mesh placement in: (a) anterior (Ripstein), and (b) posterior (Wells) rectopexy (modified from Vernava et al 2007)[10]

Anterior or posterior mesh repairs: early approaches

Historically, the two most widely used mesh rectopexies were the anterior sling rectopexy (Ripstein procedure) and the posterior mesh rectopexy (Wells procedure). The Ripstein procedure, first described in 1952[3], involves placement of mesh around the anterior aspect of the mobilized rectum with attachment of the mesh to the presacral fascia below the sacral promontory, as shown schematically in Figure 3a[10]. Ripstein advocated preservation of the lateral rectal attachments originally describing division of only the upper portion while future iterations have left them wholly intact. In a review article of 8 retrospective and prospective studies (1982 – 2000), mortality rates for the Ripstein procedure ranged between 0% and 2.8%, and recurrence rates between 0% and 13%.[6] The Wells procedure evolved from Ripstein's original repair by affixing the mesh to the posterior aspect of the mesorectum and to the presacral fascia, as depicted in Figure 3b[10], reducing the possibility of rectal obstruction considered one to the drawbacks of Ripstein's anterior mesh placement.[37,5,38] Wells originally described transection of the lateral ligaments, the preservation of which is thought to benefit patients by sparing the autonomic innervation to the rectum and preventing postoperative constipation. Mollen and colleagues confirmed this theory by reporting lower rates of constipation (43% vs 67%), based on colonic transit times, with preservation of the lateral ligaments.[39] Speakman et al showed a 50% greater incidence of postoperative constipation with divided lateral stalks.[40] This may be at the expense of a higher recurrence rate, presumably due to a tendency to incomplete mobilisation of the rectum – rectal prolapse recurred in 19% of patients following preservation of the lateral ligaments[39] and there were 2 cases (17%) of mucosal prolapse following rectopexy with preserved stalks in the Speakman study.[40] Complications of prosthetic mesh repairs include large bowel obstruction, erosion of the mesh through the bowel, ureteric injury or fibrosis, sacral vein haemorrhage, small bowel obstruction, rectovaginal fistula and faecal impaction.

Resection rectopexy

First described by Frykman and Goldberg in 1966[4], this technique involves complete mobilization of the sigmoid colon and rectum to the level of the levator muscles with sigmoid resection and suture fixation to the presacral fascia. Classically described with division of the lateral ligaments, a revised version preserves the lateral attachments with fixation of the rectal mesentery to the sacrum at the level of the sacral promontory. Although originally done to reduce recurrence, sigmoid resection was found to significantly reduce constipation in those patients suffering from this symptom preoperatively.[41,36] Recurrence rates are low, ranging from 0-5%[6] and complication rates range from 0-20% related either to obstruction or anastomotic leakage. Two small prospective randomized controlled trials have compared the outcomes of rectopexy with and without bowel resection. In 1992, Lukkonen et al combined resection with suture rectopexy and compared the outcomes to mesh rectopexy alone. In another study in the same year, McKee et al performed suture rectopexy in both groups of patients, with resection in one group. No recurrent rectal prolapse was reported by either trial. There was a statistically significant difference between groups regarding persistent faecal incontinence, with 33% found to have postoperative incontinence in the resection group versus 21% in the rectopexy group. The biggest advantage of resection was the significant reduction in postoperative constipation (8% vs 50%). In a multicenter review of 643 patients from 15 centres between 1979 and 2001, Raftopoulos et al reported 38 (5.9%) recurrences at a median follow-up of 43 months. The pooled one, five, and 10 year recurrence rates were 1.06, 6.61, and 28.9% respectively. Despite 72% of patients having undergone rectopexy only, they concluded that age, gender, surgical technique, means of access, and rectopexy method had no impact on recurrence rates.

Laparoscopic rectopexy

Similarly to minimally-invasive approaches in other colorectal diseases, laparoscopic rectopexy (using sutures or mesh with or without resection) has been found to have essentially equivalent results to open rectopexy.[42,43,44] Despite being associated with a longer operative time and greater cost, laparoscopic surgery has the advantages of less pain, lower wound infection rates, shorter hospital stay, early recovery and earlier return to work as compared with laparotomy. Boccasanta et al compared functional and clinical results of laparoscopic with open rectopexy in 2 similar groups of patients with complete rectal prolapse and showed that the shorter postoperative hospital stay determined an overall reduction in the total cost of laparoscopic rectopexy,

despite the prolonged operative time and higher cost of surgical materials.[45] Another prospective randomized controlled study by Solomon and colleagues in 2002 concluded that laparoscopic rectopexy had short-term benefits in terms of return to normal diet and mobility, earlier discharge from the hospital, and less morbidity.[46]

Since these publications, laparoscopic skills and equipment have improved considerably in the last 15-20 years and a more recent meta-analysis comparing laparoscopic rectopexy with open repair found laparoscopic rectopexy to be a safe and effective modality comparable to open repairs. Twelve comparative studies on 688 patients showed a statistically significant difference in length of operation and length of postoperative hospital stay. There was no statistically significant difference in morbidity, incontinence, constipation, or mortality between the two groups.[47,36] In more recent years, laparoscopic ventral mesh rectopexy (LVMR), has gained popularity, whereby the anterior wall of rectum is mobilized off the vagina as low as the puborectalis, and mesh is secured anteriorly to the rectum with sutures. The proximal end of the mesh is fixed to the sacrum, as depicted in Figure 4.[48] Although initial descriptions by Loygue and colleagues included both anterior and posterior mobilization, an alternate approach is to perform rectopexy with posterior mobilization along the sacrum only to fix the mesh posteriorly.[12] This avoids complete mobilization and subsequent autonomic denervation of the rectum and is believed to address the common problem of postoperative constipation seen with most mesh suspension techniques. Unfortunately, there are limitations in the published literature regarding LVMR, and to date, there are no prospective randomised studies directly comparing posterior to ventral mesh rectopexy. In a systematic review to assess the effectiveness of LVMR for rectal prolapse (and rectal intussusception) in adults, Samaranayake et al reported on 12 non-randomized case series studies with a total of 728 patients. Seven studies used the Orr-Loygue procedure, with posterior rectal mobilization to the pelvic floor, and five studies used ventral rectopexy without posterior mobilization. They concluded that ventral rectopexy without posterior mobilization had a lower recurrence rate (weighted mean reduction of 3.4%) an improved faecal incontinence (weighted mean reduction of 45%) and a reduction in postoperative constipation (weighted mean decrease of 2.4%).[49] A prospective study by D'Hoore and colleagues looked at the long-term outcome of laparoscopic ventral rectopexy performed at a single center in Belgium on 42 patients after a median follow-up of 61 months. No major postoperative complications were reported, and late recurrence occurred in 2 patients (5%). Once again, symptoms of obstructed defaecation and incontinence resolved in 16 of 19 and 28 of 31 patients respectively. They concluded that the ventral mesh placement and lack of posterior dissection were responsible for these improvements.[48]

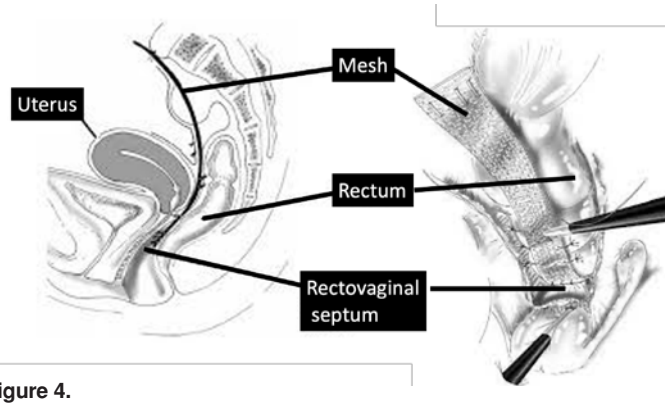

Figure 4.
Schematic diagram showing smesh placement in a laparoscopic ventral mesh rectopexy (modified from D'Hoore et al 2004)[48]

Gouvas et al carried out a systematic review of 1460 patients undergoing LVMR for both rectal prolapse (675 patients) and obstructed defaecation syndrome. They reported recurrence rates ranging from 0-15%, with a mean of 2.4% Conversion rates ranged from 0-14.3%, with a mean 2%, and a mean complication rate of 8.9%. There were no postoperative deaths. The mean intraoperative times ranged from 56 -221 min and was significantly longer with robotic surgery. The intraoperative morbidity was 8.6% (3 cases of intra-abdominal bleeding and 1 perforation of the posterior vaginal wall). Constipation and incontinence frequency improved significantly from 21.4-93.3% to 6.7-22%, and 23.3-92.9% to 0-28.6% respectively. They concluded that LVMR is a safe procedure with a low morbidity and mortality. Complications associated with the prosthesis are rare, despite the theoretical increased risk of synthetic mesh erosion. There is a significant reduction in constipation and incontinence and the recurrence rate is low. However to establish LVMR as the gold standard for rectal prolapse, larger studies with longer follow-up comparing anatomical and functional outcomes to standard rectopexy techniques are required.[50,51]

Conclusion

The need to address symptomatology associated with prolapse as well as the prolapse itself has come from a better appreciation of the pathophysiology of the condition. In carefully selected patients, good results can be obtained with either the perineal or abdominal approach.

The respective roles of abdominal and perineal approaches in the surgical management of full-thickness rectal prolapse, however, remain governed by the patient factors of age, comorbid disease and physiological baseline, and the surgeon's personal bias and experience. Recurrence rates are largely based on retrospective studies with a variety of shortcomings. It is increasingly clear that larger prospective randomized studies are needed to guide the tailoring of the surgical approach to the individual patient with rectal prolapse.

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Immune checkpoint inhibitor induced colitis

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Introduction

Immune checkpoint inhibitors (ICPis) represent an important recent advance in cancer therapeutics.

ICPis target the checkpoint molecules cytotoxic T-lymphocyte antigen-4(CTL4), programmed cell death protein-1 (PD1), and its ligand PD-L1. By preventing inhibitory signals to the immune system, checkpoint inhibitors enhance anti-tumour immunity and perpetuate durable immune activity.[1]

ICPis have become key agents in the management of melanoma and more recently for non-small cell lung cancer (NSCLC) and renal cancer.[2]

In metastatic melanoma they have transformed care, improving the median life-expectancy from months to years and leading to long-term remission in a significant number of cases.[3]

It is anticipated that the indications for ICPi usage will expand, with a wide range of cancers potentially being investigated for single agent as well as combination regimens.[4] Rapid progress in the development of new ICPi agents, frequent use of combination therapies and expansion of indications suggests that the field is rapidly developing.[5]

Currently, there are 7 ICPi's registered with the United States Food and Drug Administration (FDA). Two ICPi's have been approved by the Medical Control Council (MCC) in South Africa and registered with the South African Health Products Regulatory Authority – ipilimumab(anti-CTL4), and pembrolizumb (anti-PD1).[6] Increasingly, other ICPI's (e.g. nivolumab (anti PD-1)) are being requisitioned for local use as unregistered agents through application via Section 21 of the Medicines and Related Substance Act, 1965.

In parallel with their novel mechanism of action, the introduction of ICPi's has led to the recognition of a multitude of immune-related adverse events (irAE's).[7]

Immune – related adverse events have been documented to affect a multitude of organ systems and are most commonly seen in the skin, gastrointestinal tract, liver, and endocrine system.[8] Depending on the immune checkpoint that is targeted, the incidence of toxicity varies. The incidence and severity of irAE's appears to be similar irrespective of the specific tumour-type indicated for treatment.[1]

Current theories suggest that the presence of irAE's predicts improved response to checkpoint inhibitors and subsequently improved overall patient survival.[9] In support of this observation, several studies have found an association between ipilimumab-induced entero-colitis and tumour regression and overall survival (OS).[9-10]

Diarrhoea was an independent risk factor, in one study of 117 patients, who were treated with ICPi's and experienced diarrhoea. The presence of diarrhoea, was an independent predictor of improved survival regardless of the treatment required, and immunosuppressive treatment for this irAE did not significantly affect overall survival.[11]

Diarrhoea and colitis form part of a clinical spectrum. Diarrhoea is defined as increased stool frequency, and colitis involves symptoms of abdominal pain and either clinical or radiologic evidence of colonic inflammation.[12]

The spectrum of severity of irAE's can be mild, requiring only close monitoring and continued therapy, to severe and potentially life threatening.[13] ICPi toxicity requires a high index of suspicion, early detection and appropriate management and as a consequence gastroenterologists are likely to be more regularly involved in the care of these patients.

Background

ICPi induced diarrhoea and colitis is the second commonest irAE, after skin manifestations, and the most common reason for treatment disruption or permanent discontinuation.[14]

Gastrointestinal immune-related adverse events are more frequently associated with anti-CTLA-4 therapy and are more common in anti-CTLA-4 and anti-PD-1 combination therapy than with anti-PD-1 monotherapy.[15]

Of the 2/3rd of patients receiving anti-CTL4 therapy who develop irAE's, 1/3rd involve the gastrointestinal tract and included aphthous ulcers, oesophagitis, gastritis, and entero-colitis typically presenting with diarrhoea.[16]

A recent meta- analysis demonstrated that the spectrum of fatal irAE's differs largely between regimens. In this analysis, colitis was the most frequent cause of irAE death in those receiving anti- CTLA-4 agents (135 (70%) of 193 deaths). Deaths in patients receiving anti- PD-1 or anti- PD-L1 antibodies (n=333) were more widely distributed, with pneumonitis (35%), hepatitis (22%) and colitis (17%) predominating. In patients receiving combination therapies, ICPI- related deaths were mainly attributed to colitis (32 (37%) of 87) or myocarditis (22 (25%) of 87).[17]

Irrespective of the ICPI regimen, irAE with fatal outcomes tend to occur early in the course of treatment and evolve rapidly, especially in patients receiving combinations of agents.[7]

Immune-related diarrhoea and colitis occurs less frequently with PD-1 inhibitors compared with anti-CTLA-4 inhibitors. Severe diarrhoea requiring immunosuppression and cessation of therapy occurs in approximately 1-2 % of patients treated with anti-PD-1/PD-L1 agents compared to 10% of patients receiving CTL-4 therapy.[7]

The time of onset of diarrhoea induced by ICPi is influenced by specific regimens. The anti-CTL-4 median time to onset of diarrhoea is approximately 4–7 weeks after starting treatment (seen

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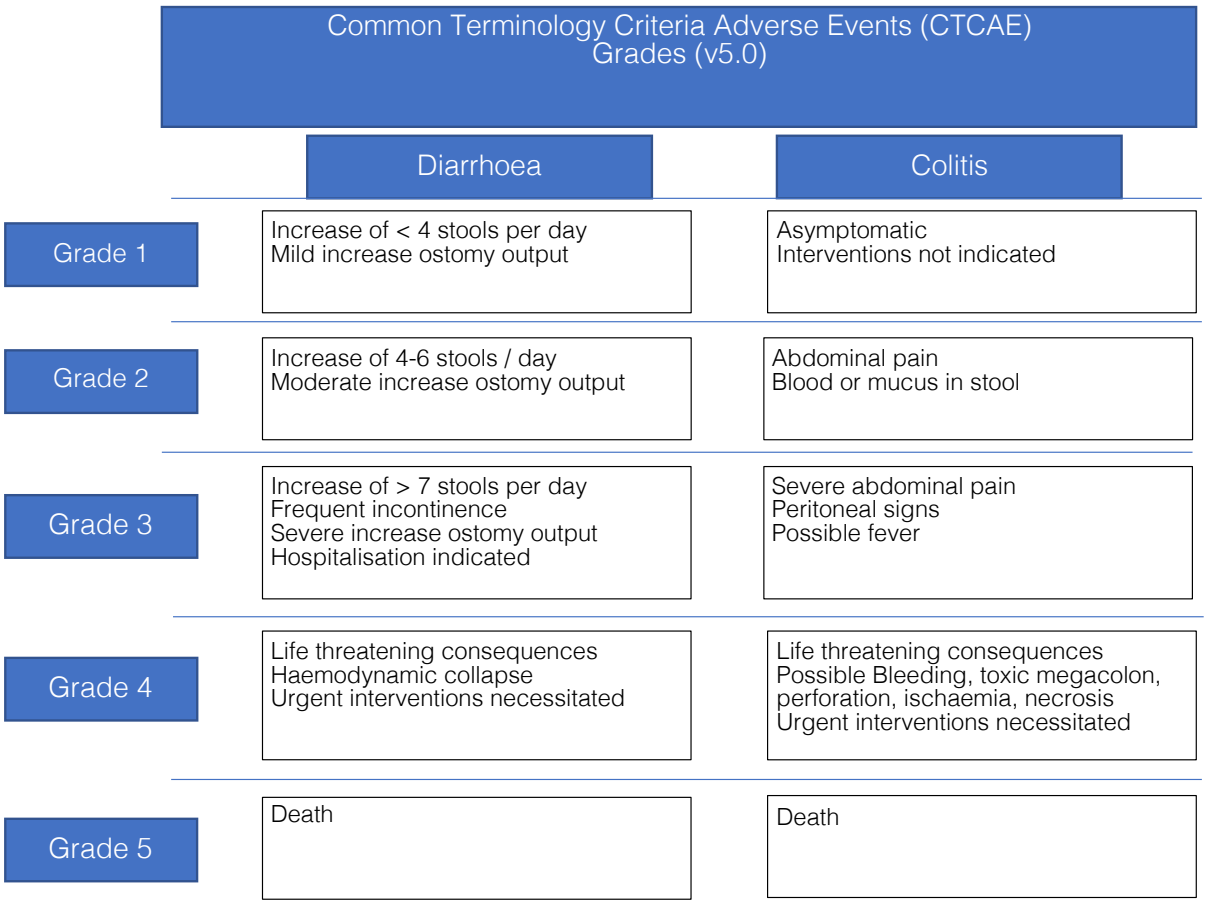


typically between the second and third dose of ipilimumab) though it can occur at any point during treatment.[18] Colitis from PD-1/PD-L1 is less predictable, and whilst early occurrence has been observed, many patients present with colitis months or even years following the commencement of therapy. The range of onset of colitis with all ICPi's varies, with some patients experiencing symptoms as early as 1 week after exposure and others developing symptoms months or even years after the discontinuation of therapy.[2]

Patients with underlying autoimmune disease have largely been excluded from checkpoint inhibitor clinical trials. As a result, data in the inflammatory bowel disease (IBD) population have mostly been acquired from case-reports and retrospective cases series. Pre-existing IBD increases the risk of severe GI adverse events in patients treated with ICPi's. A retrospective analysis of 102 patients with cancer and pre-existing IBD who were subsequently treated with ICPI's showed a 3–4 fold increased risk of gastrointestinal adverse events compared to patients without IBD. Specifically, anti–CTLA-4 therapy and IBD involving the colon before immunotherapy initiation were possible risk factors for GI toxicities.[19]

Nonetheless, response to ICPI therapy in patients with underlying IBD is comparable to what is reported in non-IBD patients.[16] Since patients with IBD are at increased risk of several malignancies that are indications for immunotherapy, further evidence for optimal management will continue to accumulate.

Non-steroidal anti-inflammatory drug (NSAID) use has been associated with an increased risk of anti- CTLA-4 induced enterocolitis.[20]

The microbiome might well be contributing to the risk of immunotherapy induced colitis and therapeutic modulation[21] as well as biomarker identification of the microbiome currently being investigated.[22]

Assessing Severity / Common Terminology Criteria for Adverse Events

The severity of immune-related toxicities is conventionally graded using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), Version 5.0.[23]

The early and correct designation of the grade of toxicity is important as this influences the acute management and guides the timing of the potential re-introduction of ICPi's following discontinuation of this treatment.[18] PD-1 inhibitors are less frequently associated with high-grade toxicities compared to CTLA-4 inhibitors.[1]

Mild diarrhoea (Grade 1) is defined as less than 4 stools per day above baseline. Grade 2 diarrhoea is defined as 4 to 6 stools per day above baseline, while Grade 2 colitis is characterized by abdominal pain or blood or mucus in the stool.[8]

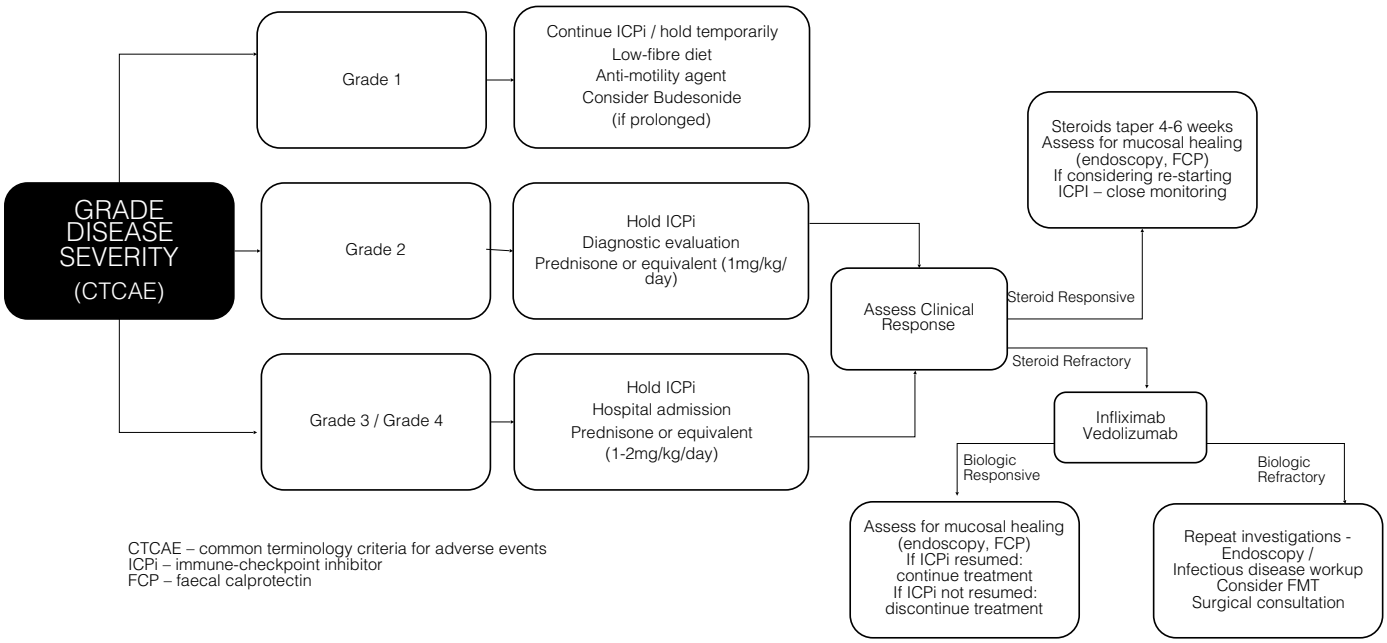
Severe diarrhoea (Grade 3) is defined as ≥ 7 stools per day, above baseline - incontinence is frequently experienced and hospitalisation generally is indicated. Grade 3 colitis is defined by the presence of peritoneal signs, ileus, fever and/or pain.[8, 13-14]

A Grade 4 designation is distinct from Grade 3, reflecting increased severity and the life-threatening nature of symptoms such as haemodynamic collapse, perforation, ischaemia, bleeding, toxic megacolon, ischaemia.[8, 13-14]

In general, the presence of colitis substantially increases the risk of complications including ileus, colonic distension and toxic megacolon, intestinal perforation, or even death.[7] Parallels with acute severe ulcerative colitis (ASUC) in terms of complications and approach to management are pertinent.

Diagnosis and diagnostic considerations

Grade 1 ICPi colitis may be managed symptomatically without extensive workup.[8]



CTCAE – common terminology criteria for adverse events
ICPi – immune-checkpoint inhibitor
FCP – faecal calprotectin

The work up for ICPi-associated diarrhoea/colitis of Grade 2 severity and above generally includes a full blood count (FBC), urine and electrolytes (U+E), thyroid stimulating hormone (TSH), liver function test (LFT) and C-reactive protein (CRP). Immune mediated thyroiditis and immune-mediated hepatitis are associated irAE's which may obscure the clinical presentation.[13]

Screening tests for hepatitis B, HIV serology and tuberculosis should be considered in anticipation of the possible need for infliximab therapy.[13-14]

Stool samples should be sent for Clostridium difficile and assessment for gastrointestinal pathogens. An elevated faecal calprotectin or lactoferrin may indicate an inflammatory cause for the diarrhoea.[8,14]

Abdominal computed tomography (CT) should be considered in patients with Grade 2 or greater toxicities, particularly in patients with fever, bloody stool, or abdominal pain. This aids the assessment of toxic megacolon, exclusion of perforation, and evaluation of other aetiologies to explain the symptomatology.[8]

Endoscopic evaluation is indicated for Grade 2,3 or 4 diarrhoea or evidence of colitis. The frequency of diarrhoea is a poor indicator of the severity of disease on endoscopic evaluation and does not indicate a treatment response in the later stages of the disease.[16,24]

Ileo-colonoscopy with biopsies is the primary investigation, although flexible sigmoidoscopy may initially be preferred for pragmatic reasons, as isolated right-sided disease is uncommon (cost / bowel preparation / time).[25] However, in a recent study, 24% of patients with extensive colitis had more severe signs of inflammation in the right hemi-colon.[16]

A normal mucosal appearance during endoscopic evaluation does not exclude microscopic disease or colitis, and mucosal biopsies must always be obtained(24). Obtaining a biopsy has the advantage of distinguishing ICPi colitis from less common aetiologies such as infectious cause for diarrhoea e.g cytomegalovirus (CMV).[9]

Patients with upper gastrointestinal symptoms such as nausea or vomiting should also undergo oesophago-gastro-duodenoscopy with biopsies.[20]

Endoscopic features are similar between those receiving anti-CTLA-4 and anti-PD-1/PD-L1 regimens.[10]

Characteristic endoscopic findings of ICPi-associated colitis range from a normal mucosal appearance to mucosal abnormalities typically seen in inflammatory bowel disease, including loss of vascular pattern, exudates, granularity, friability, and ulcerations.[26]

Mucosal inflammation is typically but not always continuous. Endoscopic ulceration or a higher endoscopic Mayo score has been associated with a higher probability of steroid-refractory colitis necessitating infliximab therapy.[9,10]

Despite endoscopic parallels between IBD and ICPi colitis, the histopathologic findings are characteristically different.[20]

The most frequently reported microscopic features in ICPi related colitis include predominant acute inflammatory changes (cryptitis and crypt micro-abscesses), increased crypt epithelial cell apoptosis with crypt atrophy and dropout, and a predominantly lymphocytic inflammatory infiltrate in the lamina propria.[9,20]

Another pattern of inflammation observed in approximately 10% of patients resembles lymphocytic colitis with increased intraepithelial lymphocytes and a mononuclear infiltrate in the lamina propria. Notably, chronic inflammatory changes such as crypt distortion and branching, basal lympho-plasmacytosis, and Paneth cell metaplasia are typically absent.[9,16]

It is recommended that endoscopy should be repeated in patients who do not respond to immunosuppression therapy or to confirm that the colitis has remitted in support of the resumption of ICPi therapy.

Faecal calprotectin may be a useful alternative to repeating the endoscopic evaluation and can be used to monitor disease activity.[18]

Management

Optimal management requires early identification of the disease, accurate staging and intervention. Once the diagnosis is confirmed, therapy is dependent on the grading of the disease.[13]

Grade 1 ICPi colitis may be managed by the treating doctor without the need for extensive evaluation or consultation with a gastroenterologist. Anti-diarrhoeal agents such as loperamide may be used for symptomatic relief, and most patients can safely continue ICPi therapy. These patients should be closely monitored for dehydration and a worsening colitis.[8,14]

For Grade 2,3 or 4 severity, further investigations are needed to rule out alternative causes, and for the consideration of immunosuppressive treatments. ICPi treatment should be withheld and oral or intravenous corticosteroids administered, with a starting dose equivalent to 1 mg/kg/day of prednisone.[13,14]

After symptoms are adequately controlled, corticosteroid should be slowly tapered over a 4–6 week period, given the high risk of relapse.[14]

If clear symptomatic improvement is not observed after 2–3 days of corticosteroid therapy, the dose may be increased to a dose of 2 mg/kg/day of prednisone (or methyl-prednisone equivalent).

US FDA approved Immune checkpoint inhibitors

Drug	Trade Name	Target	Target
Pembrolizumab	Keytruda	PD-1	Melanoma
			Non-small cell lung carcinoma
			Classic Hodgkins lymphoma
			Squamous cell carcinoma head and neck
			Urothelial cancer
			Gastric cancer
			Solid tumors with microsatellite instability
Ipilimumab	Yervoy	CTL-4	Melanoma
Nivolumab	Opdivo	PD-1	Melanoma
			Non-small cell lung carcinoma
			Renal cell carcinoma
			Hepatocellular carcinoma
			Squamous cell carcinoma head and neck
			Urothelial cancer
			Colorectal cancer with microsatellite instability
Durvalumab	Imfinzi	PD-L1	Urothelial cancer
Atezolizumab	Tecentriq	PD-L1 Non-small cell lung cancer	
			Urothelial cancer
Avelumab	Bavencio	PD-L1	Marked cell carcinoma
			Urothelial cancer

Adapted from:
Reddy et al, Clinical and Translational Gastroenterology (2018) 9: 180

Alternatively, a single dose of infliximab 5 mg/kg may be considered with a second dose 2 weeks later, if there is evidence of an ongoing colitis.[8,14]

CTLA-4 inhibitors should be permanently stopped for Grade 2,3 or 4 colitis, while PD-1/PD-L1 inhibitors may be restarted in Grade 2 and 3 colitis once symptoms have resolved or improvement to a Grade 1 severity has been achieved.[2]

Patients with Grade 3 and 4 toxicities typically require hospitalisation, and treatment with 2 mg/kg/day of IV methylprednisolone should be commenced and continued until a considerable improvement in symptoms has been achieved. Intravenous corticosteroid therapy can be converted to an oral corticosteroid with slow tapering over at least 4 weeks.[7,8]

Infliximab should be strongly considered if symptoms are not controlled after 2 days of high-dose IV corticosteroids. If patients are refractory to infliximab (inadequate response after two doses have been administered 2 weeks apart) or if treatment with infliximab is contraindicated, then vedolizumab is a consideration.[27]

Infliximab is highly efficacious with a clinical response rate in excess of 80%. A proportion of patients may only need a single dose (5 mg/kg) for full symptomatic resolution. Around 1/3rd of patients may relapse or have an incomplete response and may require a second dose, which should be administered within 2 weeks. Additional doses may further be required ongoing symptoms persist.[16,28]

Alternatively, other anti-TNF agents, such as adalimumab and golimumab, might also be a consideration in the management of ICPi colitis especially in patients who demonstrate infusion reactions to infliximab.[29]

Screening for tuberculosis and varicella zoster virus status, as well as serology for HIV, hepatitis B and C viruses, should be considered in all patients requiring intravenous corticosteroids and may even be justified in all patients starting combination therapy with anti-CTLA-4 and anti-PD-1, given the high risk of entero-colitis.[14]

Alternative strategies for treatment refractory ICPi-induced colitis include calcineurin inhibitors (usually tacrolimus) and mycophenolate mofetil. Faecal microbiota transplant is an investigational approach that may have promise, although little is known about the microbial characteristics of ICPi – induced colitis.[2,29]

Patients with normal endoscopic examinations and evidence of ICPi induced microscopic colitis confirmed on biopsies of the colon are treated similarly, with some evidence to suggest a more aggressive course in these patients.[26] Alternatively, topical corticosteroids, such as budesonide or beclomethasone dipropionate are options for consideration.[30]

Overall, one-third to two thirds of patients with ICPi -induced colitis either do not respond to high-dose intravenous corticosteroid therapy, or have a relapse requiring an increase in the corticosteroid dosage during the time of steroid tapering[16] and typically require treatment to be escalated. Following relapse after corticosteroid withdrawal, other options include reintroduction at the last effective dose of corticosteroid therapy, a slower tapering regimen, a repeat of the intravenous corticosteroids or the introduction of infliximab therapy.[14]

Relapses in patients with protracted exposure to corticosteroids, or other immune - suppressants, necessitates a re-evaluation which includes repeat endoscopic evaluation with biopsies to exclude other diseases such as superimposed infections.[15]

Strategies to prevent recurrence of colitis after rechallenging ICPI's are the target of ongoing investigation. The use of prophylactic budesonide has not shown clinical benefit and is not recommended. Traditional luminal IBD therapies such as the aminosalicylates have not been investigated. The use of vedolizumab prior to reintroduction has shown some promise in a

small case series.[31]

Conclusion

ICPi - colitis is an entity which is likely to be more frequently encountered by gastroenterologists as the immune-oncology sphere expands and the long-term survival of patients is prolonged. Rapid identification, assessment and intervention in ICPi -colitis is important to prevent therapy-related morbidity and complications.

The appropriate management of immune-related toxicities and rational co-decision making with regard to the continuation of important therapies is vital.

Close collaboration between medical and oncology colleagues is important in order to increase awareness of new therapies and fine tune the management and complications of ICPi – colitis.

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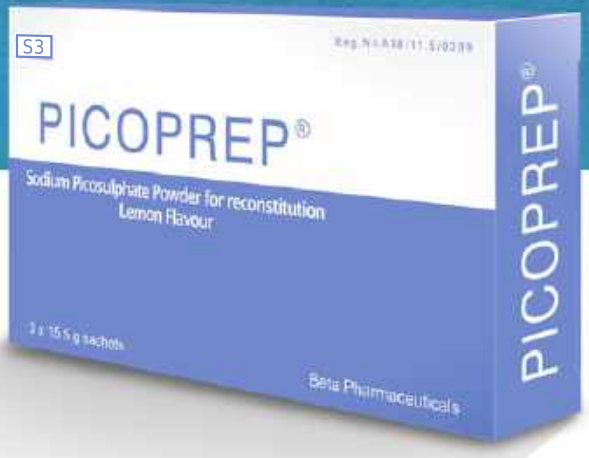

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Colonoscopy access and the adenoma frequency in Africa: the need for data and time for action

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Introduction

The first complete fibre-optic colonoscopy was reported in 1966, and the instrument has since undergone remarkable evolution.[1] The modern version is now a video-endoscope, with a wide range of tip movement, high definition images and advanced image enhancement in contradiction to the rudimentary eyepiece instrument of old. These improvements make accurate identification and characterisation of pathology in the colon and terminal ileum a reality, while parallel advances in accessories have increased the therapeutic possibilities. Therapeutic interventions delivered at colonoscopy include polypectomy, endoscopic mucosal resection, endoscopic submucosal dissection, dilatation of strictures and stent insertion for malignant obstruction. Thus, patients can potentially have premalignant lesions treated curatively by polypectomy reducing the risk of them ever developing colorectal cancer (CRC).[2,3] Furthermore, the widespread use of both screening and diagnostic colonoscopy has resulted in CRC being detected at an earlier stage when surgery is still curative. This has contributed to the falling incidence and mortality rates of CRC in some high-income, high-incidence countries such as Australia, New Zealand, Iceland and Japan.[4]

Colorectal cancer in subSaharan Africa

However, these benefits of colonoscopy have yet to reach sub-Saharan Africa on a large scale. In fact, there is increasing evidence that colorectal cancer is steadily rising in sub-Saharan Africa, belying conventional wisdom that it is a rare disease in this population.[5] Although changes in diet and lifestyle undoubtedly play a role in this rise, improvements in diagnosis, and increasing access to healthcare across the sub-region almost certainly contributes. Colonoscopy is increasingly available, in major urban centres across Africa, as is access to cross-sectional imaging particular CT scaning for accurate cancer staging.[6] Despite these changes, the data on the true incidence of colorectal cancer in most African countries remain unreliable, as quality population-based cancer registries are uncommon, and many cases remain undiagnosed.[7] Colonoscopy coverage is inadequate, and the number of doctors, let alone specialists such as gastroenterologists, general surgeons, colorectal surgeons and histopathologists is woefully inadequate.[8]

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Colonoscopy volume in South Africa

These deficiencies are best illustrated by the situation in South Africa, which, despite having one of the most advanced health care systems in Africa, still has huge unmet needs in the provision of colonoscopy. The volume of colonoscopy in the academic centres in South Africa was last reported in 2008, with the seven GI training units performing 6100 procedures annually then.[9] Currently, the University of Cape Town unit now performs 2000 colonoscopies annually, a 37% increase from 2008, while associated regional hospitals and some district hospitals perform approximately 600 annually. Thus approximately 2600 colonoscopies are performed within the UCT catchment area annually, and assuming that this is mirrored by the University of Stellenbosch, then approximately 5,200 colonoscopies are performed within the state sector in the Cape Metropole (population 3.4 million). If this is extrapolated to the South African population covered by public hospitals of 51 million the annual number of colonoscopies would be ≈ 71,600. In contrast, in the UK, approximately 650,000 colonoscopies are performed annually for a population of 60 million, by a vastly greater number of gastroenterologists and endoscopy units.

In South Africa, there are 0.06 gastroenterologists per 100 000 population, which is well below the recommended minimum of 0.22/100 000, and compares poorly with the 1.4 3/100 000 in high income countries like the UK.[10] The lack of physical resources for all endoscopy procedures in the state sector in South Africa has been well documented in KZN, with 12 endoscopy units (2 in tertiary level hospitals and 10 in regional hospitals) for 8 million people.[11] In 2016, 22,353 endoscopy procedures of all types were performed in KZN, which is approximately 10% of the number (260,000) performed annually in the UK for a similar population. Although this study did not state the number of colonoscopies, they probably account for 20 – 30% of all procedures, then approximately 4,470 to 6,705 were performed. If this is extrapolated to a population of 51 million this would yield a

Table 1. Comparison of annual colonoscopy volume in Private and State sectors in South Africa.				
Insurer's SA population (39% of total)	**No = 3,480683**			
Endoscopists Category	Annual Volume			
	Year			
	2015		2019	
	No	%	No	%
Surgeon	29,561	64%	38,588	66%
Physician	7,510	16%	11,815	20%
Gastroenterologist	9,216	20%	8,133	14%
Total	46,287		58,536	
Annual Average	52,412			
Insured SA Population	**No = 8,924829**			
Extrapolated	118,685		150,092	
Annual Average	134,388			
SA Uninsured population	**No = 51,075171**			
Estimated annual average *	42,750 - 71,600			
SA Population				
Extrapolated average if all SA insured	791231		1000615	
	895,923			
SA Uninsured population	**No = 60,000000**			
Extrapolated average if all SA uninsured	50,300 - 84,235			
United Kingdom	**No = 60,000000**			
Current annual number	650,000			
Derived from assumptions stated in the text				

range of 28,500 to 42,750 colonoscopies annually. These KZN and Cape Metropole volume extrapolations are compared with that from one of the major Health Insurers (Discovery) in Table 1.

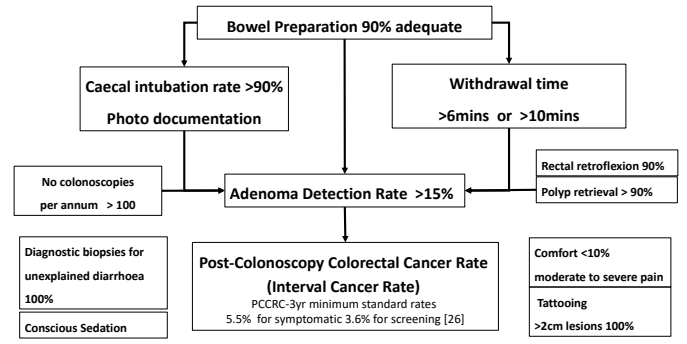
This shows that the private sector annual colonoscopy volume per capita is 37% higher than the UK, and has increased by 26% over 4 years. The comparison between the private and the state sector illustrates the dichotomous nature of the health system in South Africa, with a 10-fold volume gap between the state and private sectors.

Quality of Colonoscopy

The quality of these colonoscopies is unknown and likely varied. A great number of colonoscopies in South Africa are performed by general surgeons, with a smaller number by physicians, who have not had focussed colonoscopy training as registrars (Table 1).

Even for the gastroenterologists who perfrom just under 20% of the colonoscopies in the country (circa100), there is little data on the quality of their colonoscopy practice. Colonoscopy training during gastroenterology fellowships in South Africa has focussed on threshold numbers with as yet no trainee-centred competency-based assessment universally implemented by the training units or required for registration. Competency assessment requires the routine documentation of key performance indicators (KPI), which are used internationally to monitor colonoscopy quality. These KPI's include caecal intubation rate (CIR >90%), withdrawal time (>6minutes), quality of bowel preparation (>90% adequate) and adenoma detection rate (ADR > 15%).[12-14, 14-16] The UK guidelines, are summarised in Figure 1.[6]

Figure 1. UK guideline definitions for KPI's in colonoscopy



This figure details those already mentioned and other KPI's standards used for quality improvement purposes and highlights their interdependance particulalry in relation to the quality of bowel preparation.

Data on ADR in sub Saharan Africa

Whereas the CIR and several other KPIs measure the performance of the individual practitioner, and can be reliably used across populations the ADR is dependent on the prevalence of colonic adenomas (colorectal cancer precursor lesions) in a population. Of these performance indicators, the ADR is arguably the most crucial in South Africa and the rest

of the continent.[15] The frequency of adenomas at colonoscopy offers alternative way of augmenting the limited data on the burden of colorectal cancer. Furthermore, the frequency of adenomas can act as a potential early warning system of the likely trajectory of colorectal cancer incidence given the evolving epidemic in Africa. The paucity of information of these KPI's in South Africa has been addressed in recent reports on the performance of endoscopy units in the public sector in Cape Town, and at a large private academic hospital in Johannesburg.[16,17] These studies provide reasonable datasets to assess the quality of colonoscopy. The ADR's in South Africa and other SubSaharan countries are shown in Table 2.

The overall ADR's range from 12 % in a public sector hospital in Cape Town, to 15.6% in a private academic hospital in Johannesburg. These figures compare well with the threshold of 15% set by most international gastroenterology societies. However, there is great variability in the ADR in the black population in these studies. In Johannesburg, the ADR in the black population was much higher than in Cape Town, whose figures are closer to those reported for Zambia, Zimbabwe and Nigeria. The high ADR in the study in Johannesburg could represent a high colorectal cancer risk in the black population served by this private facility, who are affluent and more likely to be exposed to the environmental risk factors of colorectal cancer (diet, sedentary lifestyle, obesity, diabetes mellitus).[18] However, it is also possible that this was due to selection bias, with individuals at higher risk of colorectal cancer (family history, and familial colorectal cancer syndromes in particular),being offered colonoscopy. Thus, the findings may not apply to the general population, but they would

Table 2. Colonoscopy based studies with adenoma detection rates in different SubSaharan countries

Place	Period	No	Population	PDR	ADR
South Africa					
Johannesburg	2018-19		Screening		
Overall		686	&		15.6%
White		543	Symptomatic		15.3%
Black		54			18.5%
Asian		74			17.6%
Cape Town	2014 -17		Average risk		
Overall		992	Symptomatic		12%
White		103			15.5%
Black		119			5%
Asian		13			15.4%
Coloured		757			13%
Zimbabwe					
Harare	2014-17		Symptomatic		
Overall		1805		7.3%	
White		1236		8%	
Black		460		5%	
Asian		109		9%	
Zambia					
Lusaka	2008-15		Symptomatic		
Black		570		7.2%	
Nigeria			Symptomatic		
Black	2007-13	415		16.1%	6.8%

PDR Polyp Detection Rate
ADR Adenoma Detection Rate

still support targeted screening colonoscopy in selected individuals in the black population.

One major limitation of the two studies in South Africa is the small sample size amongst the black population, which is likely reflective of the catchment population of the two hospitals. This should be addressed by similar studies in other provinces in South Africa, possibly through a national colonoscopy database. Elsewhere in Africa, there have been very few studies which estimated ADRs. In Nigeria, the ADR was estimated to be 6.8% whilst the polyp detection rate among the black population was 5% in Zimbabwe and 7.2% in Zambia.[19-21] These studies also have a low sample size, and in some cases this was accrued over many years, suggesting the existence of significant bottlenecks in access to colonoscopy services. There is also inadequate histology data, which explains why in some cases, only polyp detection rates were available. Finally, the study population exhibit great heterogeneity, particularly with regards to age and indications for colonoscopy, that renders comparisons with international benchmarks, derived mainly in the screening population older than 50 years, less than ideal. However, the availability of these studies suggests the existence of focal points that can be leveraged on to slowly build capacity in quality colonoscopy, and to generate data that can guide practice. A number of studies on colorectal cancer are also on-going, and the results may provide further clarity on the pattern of disease in our populations.[22]

There is a need to collect more data and SAGES and the Colorectal Society should drive this process. A national electronic record system of endoscopic procedures, can help facilitate such data collection, and standardise practice. This should include a registry for familial colorectal cancers, as systematic screening provides undoubted mortality benefits for these individuals.[23] Expanding colonoscopy registries should be a priority that will provide information to inform health policy and advocate for the provision the physical and human resources required to drive equitable access to colonoscopy and more effectively manage colorectal cancer.

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AMGEN 40 YEARS

Inflammatory bowel disease and Tuberculosis: epidemiology and dilemmas

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Introduction

Inflammatory bowel disease (IBD) has become a global disease.[1] In the past it was a disorder mostly prevalent in North American and European populations, but according to recent epidemiological studies, IBD is diagnosed more frequently in traditionally low-incident regions such as Asia, the Middle East, Eastern Europe and Africa.[2-6.] Aside from the epidemiological shift, changes in therapeutic strategies have resulted in immunosuppressive therapy (IST) being used earlier and more often as first-line medical treatment compared to past practices. Included in this armamentarium are tumour necrosis factor-alpha (TNF-α) antagonists which have enhanced management further, especially in cases previously refractory to conventional immunomodulators (IMMs). However, the risk of developing tuberculosis (TB) is significantly higher in patients using IST, and in particular TNF-α antagonists[7]. This is a concern in the South African and Western Cape population where active and latent TB (LTB) infection rates are amongst the highest in the world.[8] The increasing burden of IBD in this environment therefore makes the use of IST extremely challenging and warrants investigation with a view to developing local treatment guidelines.

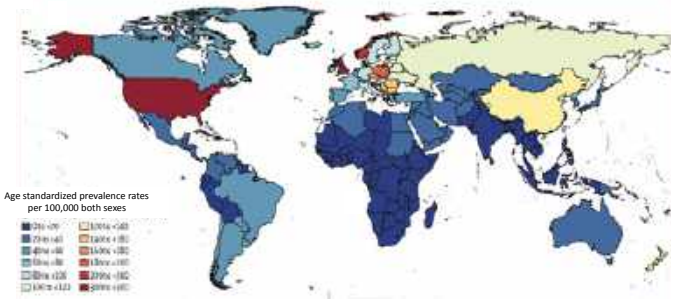
Epidemiology of IBD

Ulcerative colitis (UC) and Crohn's disease (CD) are the most common types of IBD. IBD unclassified (IBDU) is assigned to the remaining 10-15% of cases where there is initially difficulty in establishing a definitive diagnosis of UC or CD. The diagnosis is made based on a combination of clinical, radiological and endoscopic findings together with supporting histological features on biopsy specimens.

The pathogenesis is still not completely understood despite extensive research in this area. Our current understanding suggests that proposed mechanisms involve a complex interplay between a subject's dysregulated immune system and their altered gut microbiome, which are activated by various environmental triggers in individuals with a genetic susceptibility for the disease.[9]

Traditionally the burden of disease was predominantly in HIC where IBD today still affects 1.4 million North Americans and more than 2.5 million people in Europe. This corresponds with incidence rates of 24.0 and 11.5 per 100,000 person years (PY) and a prevalence of 294 and 213 cases per 100,000 persons for UC & CD respectively in these regions.[10] The burden of IBD in 2017 was just under 7 million and the global prevalences are shown in Figure 1. They show marked variation and highlight continental and national geographic differences in IBD. There is an observable though not entirely consistent north-south gradient relative to latitude from the equator. In USA there were more hospitalisations for IBD in the northern than the southern states and lower rates of disease in southern European countries than northern [11,12] An inverted relationship is noted in the southern hemisphere as high rates of IBD in Australia and New Zealand are more comparable to those in North America and Europe.[13,14] than many Asian Countries. It is argued that geographic variations in IBD are mediated mainly by environmental risk factors[15]. Decreased UV sunlight exposure in regions furthest from the equator are associated with vitamin D deficiency, possibly contributing to earlier IBD onset and progression.[14]

Figure 1.



In 2017, there were 6·8 million cases of IBD globally.
The age-standardised prevalence rate increased
79·5 (75·9–83·5) per 100,000 1990
84·3 (79·2–89·9) per 100,000 2017.
The age-standardised death rate decreased
0·61 (0·55–0·69) per 100,000 in 1990
0·51 (0·42–0·54) per 100,000 in 2017

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Figure 1 also compares the 1990 to 2017 prevalences and shows there is an overall increase in the age-standardized prevalence rate of 5 and a reduction in the age-standardized death rate of 0.1 per 100,000. The graphic also shows that African Nations prevalences are a sixth of that seen in UK and the United States and are more comparable to data from South America and the Indian subcontinent.

The 21st century has seen a distinct change in disease patterns as IBD has emerged in non-western countries where previously its occurrence was considered to be rare. In Japan, the prevalence of CD has increased from 2.9 in 1986 to 13.5 per 100 000 persons in 1998, whilst in Hong Kong the prevalence of UC has increased from 2.3 to 6.3 per 100 000 persons over a 9-year period[16]. Countries in the Middle East are also experiencing a similar trend and in Iran the incidence of IBD increased from 0.62 to 3.11 and the prevalence from 4.69 to 40.67 per 100,000 from 1990 to 2012.[17]

In contrast, the high incidence witnessed during the latter part of the 20th century in Western countries has gradually stabilised and rates in previously high-burden areas have started to plateau.[18] Elsewhere the prevalence continues to escalate and with its current trajectory, the projected burden of disease is likely to be substantially higher in the future.

The reasons for this epidemiological transition are likely multifactorial and include aspects such as vigilance by health staff, easier access to hospitals and clinics and improvement in diagnostic equipment and technology in the Low and Middle Income Countries (L&MIC.) The contribution of progressive healthcare to this transformation is probably small and it is more likely that changes are linked to social and economic progress and the adoption of a modern and 'westernised lifestyle' by the population in developing countries.[19] IBD epidemiological patterns from the past have often demonstrated a parallel relationship between disease emergence and urbanisation and industrialisation of society.[20]

Migration studies support this theory, as subjects that immigrate from L&MIC to western countries are also at increased risk of developing IBD[21,22] In the United Kingdom (UK), the incidence of UC in South Asians that have settled in Leicester has increased from 14.3/105 to 17.2/105 population/year over a period of two decades. In addition to quantity, disease behaviour has also progressively worsened as the extent of disease in the second-generation migrants appears to be comparable to the native population and is more severe than in first-generation and new migrants.[23]

IBD in Africa is still considered to be rare. There are no population-based epidemiological studies to accurately assess and quantify the burden of disease. In South Africa (SA), IBD data is limited to hospital-based cohort studies from the 1970s and '80s.[24-26] From 1970 -1984, there was a clear increase in the incidence of UC from 4.0 to 7.5, and CD from 1.5 to 4.7/100 000/year in the greater Cape Town area.[27] Many other African countries have also experienced socioeconomic improvement over recent decades and case series published during this same period indicate an increasing burden of disease.[28,29]

Tuberculosis

TB is also a global problem and one of the leading infectious causes of mortality worldwide. In 2016 there were an estimated 10.4 million incident cases and more than 1.6 million deaths related to TB. South-East Asia, Africa and the Western Pacific regions are responsible for over 75% of all cases whilst Europe and the Americas together account for only 6% of the total, clearly highlighting the huge disparity in disease distribution between HIC and L&MIC. African countries contribute significantly to this burden (25%) with Nigeria and South Africa together accounting for 4% of the global total. An additional complicating factor in Africa is the high proportion of TB cases that are co-infected with HIV, with rates in some areas in southern Africa exceeding 50%[30] South Africa currently has one of the highest TB rates in the world.[31] In 2009 the City of Cape Town (CCT), which is a metropolitan district of the Western Cape, TB incidence rate is 877/100,000.[32]

Pulmonary TB (PTB) is the main form of the disease, but extrapulmonary TB (EPTB), which affects all other organs, makes up about 15-20% of all diagnosed cases. Disseminated TB is another form of the disease used to describe spread of the primary lung infection to other parts of the body via the blood or lymph stream and occurs in 1-2% of immune competent individuals. The abdomen is the sixth most common site affected outside the lungs and contributes to 5-17% of extrapulmonary[33] and 2% of global TB cases. Estimating the burden of intestinal TB though is not straightforward as many publications use the terms of abdominal & gastrointestinal TB interchangeably. In 2015, gastrointestinal involvement was diagnosed in 5.9% of all TB cases in England and accounted for 10% of the EPTB total.[34] Higher rates were found in a South African tertiary hospital, where 42.6% and 27.5% of TB cases were extrapulmonary and abdominal respectively.[35]

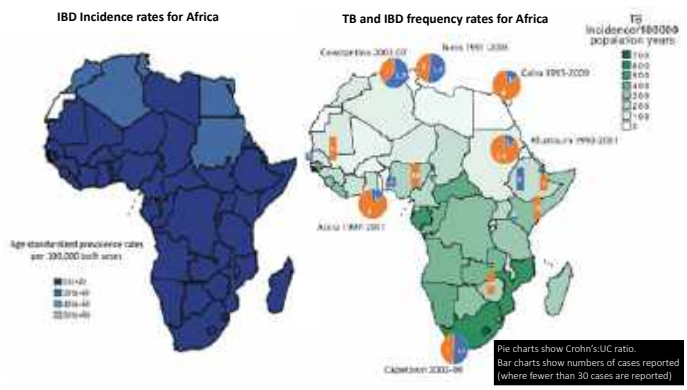
Diagnosing intestinal and EPTB has many challenges. Clinical presentations are non-specific and there are many difficulties in establishing a definitive diagnosis from the affected organ. An immunocompromised state is one of the main risk factors for these forms of TB and a high index of suspicion is warranted in this group. Studies investigating the clinical profile of abdominal TB subjects confirm that rates of co-infection with HIV are higher, particularly in endemic countries as well as in migrant populations currently living in low-burden settings.[35] Gastrointestinal TB is also sometimes indistinguishable from CD based on its predominant ileo-caecal location, endoscopic and radiological findings, with some instances requiring empiric treatment of one condition to exclude the other.[36]

The mainstay of managing PTB is Rifampacin Based Therapy and treatment is highly successful in immunocompetent individuals at curing the infection provided they are compliant with six months of treatment. Those who are immunocompromised by HIV or IST have a higher mortality. Despite many strategies to simplfy treatment regimens to improve compliance this remains a problem particualry in adolescents and young adults and vulnerable groups such a prison immates. As a result there has been a marked increase in TB resistance to Rifampacin (RR) Multiple Drugs (MDR) and worse of all almost all the drugs Extremely Drug Resistant XDR with the latter for many being incurable. Thus becoming infected with incurable TB adds layer of risk to individuals who are receiving IST for IBD.[37]

The influence of latent TB infection (LTBI) is also a significant factor due to the potential of such cases to later progress to active TB. LTBI refers to people infected with Mycobacterium TB (MTB) without clinical, radiologic or microbiologic evidence of active disease. It is believed to affect about a third of the world's population and contributes to the large reservoir of TB cases in high TB burden countries like South Africa.[38] There is as yet no gold standard for LTB diagnosis worldwide but two screening tests are currently available to assist in establishing a diagnosis: the older tuberculin skin tests (TSTs) using the Mantoux technique and the modern interferon-gamma releasing assay (IGRA) blood tests the QuantiFERON-TB® Gold In-Tube (QFT-GIT) and the T-SPOT.TB® tests[39].

TSTs use purified protein derivative (PPD) is the tuberculin material that is a mixture of antigens from Mycobacterium (M.) TB and *M. bovis* - Bacille Calmette-Guérin (BCG) the antigen used for vaccination and several other nontuberculous mycobacteria (NTM). Once injected under the skin, it causes a

Figure 2.



T-lymphocyte mediated delayed-type hypersensitivity response in infected individuals, that manifests 48-72 hours later as an area of induration around the injection site.

TSTs are influenced by multiple factors that can lead to false-negative and false-positive reactions, thereby also affecting the sensitivity and specificity of these Tests.[40] False positives are caused by non tuberculosis mycobacteria, BCG Vaccination, administration of the wrong antigen, or incorrect interpretation of the TFT as the the size of the induration that constitutes a positive result varies from 5-15mm. The latter can result in a False negative test which can be also be caused by anergy, recent TB infection, concominat viral, bacterial or fungal infection, immunosuppressive drugs, low protein states, any cause of lymphopenia or incorrect storage of the antigen.

These limitations led to the development interferon-gamma releasing assay (IGRA) blood tests. The QFT-GIT test uses an enzyme-linked immunosorbent assay (ELISA) technique to measure the concentration of interferon gamma (IFN-γ) produced within a whole blood sample in response to a single mixture containing of MTB-specific antigens (culture filtrate protein 10 (CFP-10) and early secretory antigenic target protein 6 (ESAT-6), TB7.7). The T-SPOT.TB test is similar, but uses an enzyme-linked immunospot (ELISPOT) assay to measure the number of IFN-γ producing mononuclear cells (spots) isolated from whole blood in response to CFP-10 and ESAT-6 contained in separate mixtures.

In 2005, the Food and Drug Administration (FDA) approved the use of the newer IGRAs to improve the sensitivity and specificity. Although influenced less by the factors affecting TST results, IGRAs have higher rates of indeterminate results in patients taking IST.[41] In addition, IGRAs are costly to perform and require appropriately resourced and well trained laboratory technicians making their routine use in resource constrained countries difficult to implement.[42]

When comparing test sensitivities between IGRAs, there is good evidence to indicate that T-SPOT.TB is superior and can be explained by differences in technical methodology.[43] The QFT-GIT assay is tested on a whole blood sample which may contain insufficient circulating mononuclear cells whereas the T-SPOT. TB assay requires isolation of a standard number of peripheral mononuclear cells first before exposure to TB antigens. Lymphopenia in particular is therefore likely to have a greater negative impact in QFT-GIT than T-SPOT.TB performance.

Medical therapy in IBD

IBD is an incurable disease. Therefore, the aims of management are to induce remission during acute attacks and to prevent further relapses of disease. This can be achieved either through medical or surgical interventions or a combination of both.

Therapeutic options largely depend on the location, severity and pattern of disease present. The Montreal classification is used to classify disease location in IBD patients.[44] Disease activity and severity is determined using the Crohn's Disease Activity Index (CDAI) and Truelove & Witt's criteria for CD and UC respectively.[45,46]

The reliance on medical treatment in particular has expanded over the past few decades and plays an influential role in altering the natural course of IBD. A review article by Annese et al, to evaluate the impact that IST has had on IBD outcomes, concluded that surgery and colectomy rates have declined since their addition to the therapeutic armamentarium, irrespective of factors such as initial disease severity or time of diagnosis.[47]. In addition, a shift in treatment strategy from the traditional ''step-up'' to an aggressive ''top-down'' approach has contributed significantly to the earlier introduction and widespread use of IST.[48]

The launch especially of biologics towards the latter half of the 1990's has greatly improved IBD outcomes and represented a significant breakthrough in management. Severe cases, especially those resistant to conventional agents such as steroids, Methotrexate (MTX) and the thiopurines 6-Mercaptopurine (6MP), and its prodrug Azathioprine (AZA) and are now being introduced early in the management in those with moderately severe disease TNF-α antagonists are now been increasingly used for therapy and many international guidelines, including South Africa, recommend their use in IBD patients with moderate to severe luminal disease when conventional drugs fail to achieve remission. This is estimated to represent 10-15% and 5-10% of refractory CD and UC cases respectively.[49]

IBD medical therapy and the risk of TB

However, there is a strong correlation between IST use and the risk of developing opportunistic infections and tuberculosis .[50]

In a United States (US) study, the incidence of TB was higher in patients with moderate-to-severe CD compared to the general population (rate ratio, 2.79; 95% CI, 2.14-3.63). In the same study they also evaluated the the effect of various treatment regimens on the risk of developing TB. They found the risk was higher in patients using any combination therapy of steroids, conventional immunosuppressive (IS) drugs or TNF-α antagonists compared to monotherapy (hazard ratio (HR), 7.4; 95% CI, 2.1-26.3 vs HR, 2.7; 95% CI, 1.0-7.3). In IS drug use alone, the study found that TB risk was greater in this group than the general population (rate ratio, 2.5; 95% CI, 1.0-6.2) and escalates as additional therapeutic agents are added (rate ratio, 9.1; 95% CI, 2.5-33.2 & 18.5; 95% CI, 4.1-82.6 for steroids and anti-TNF-a agents respectively).[51]

In another study UC patients receiving IMMs were compared to a treatment-naïve group, There was a higher incidence of infections in those in the treatment arm but this was not statistically significant nor specific to TB.[52]

With regard to specific medications, IBD patients using corticosteroids, AZA/6MP or Infliximab had a higher risk of developing opportunistic infections (OIs) (Odds ratio (OR) 3.3, 95% CI: 1.8-6.1; OR 3.8, 95% CI: 2.0-7.0; OR 4.4, 95% CI: 1.1-17 respectively). The risk increased synergistically when combinations of these medications were used. TB was not listed in the spectrum of OIs that patients contracted in this study and AZA/6MP use was most commonly associated with viral infections.[53]

In the era before biologicals were introduced, the risk for TB in IBD patients was greater than the general population, especially in those subjects using corticosteroids (OR 1.88, 95% CI: 0.68-5.2 and OR 4.19, 95% CI: 1.38-12.72 respectively). No subjects using AZA/6MP or MTX, within a 12 month exposure window before the end of follow up, developed TB.[54] The relative

risk for developing TB compared to the general population is much higher in patients taking adalimumab and infliximab in relation to other TNF-α antagonists monoclonal antibody agents (e.g. golimumab and certolizumab pegol) or biopharmaceuticals that target integrins (e.g. vedolizumab) and interleukins (e.g. ustekinumab) in the inflammatory pathway.[55]

TNF is an important cytokine in an individual's immune response to combat infections like TB, where it is responsible for granuloma initiation and maintenance.[56,57] Therefore TNF-α antagonists in particular, as well as systemic steroids in the pre-biologics era, have also been linked to reactivation of LTB and de novo TB infections in the IBD population.[58] Using data from the FDA's Adverse Event Reporting System, Keane et al reported an association between TB and the use of infliximab (a chimeric monoclonal antibody TNF-α-antagonist. Aside from the higher risk of TB, subjects in this study developed mainly EPTB and disseminated disease, both forms synonymous with diagnostic difficulties and higher rates of mortality than PTB.[59]

TB incidence in IBD

The challenge of TB in the IBD population has therefore become a growing topic of discussion worldwide following its link with the use of TNF-α antagonists. Due to the high cost of this therapy though, there are very few studies in the literature that address this specific problem, particularly in L&MIC countries in Africa where TB is endemic. Alternatively, attempting to estimate TB risk accurately from randomised controlled trials (RCTs), where LTBI screening protocols are very strict, has many limitations on account of the small number of diagnosed incident TB cases as well as the absence of control groups for comparison.[60]

Available studies have mainly been conducted in IBD cohorts exposed to TNF-α antagonists, where much higher TB rates are reported compared to the general IBD population. In a single-centre retrospective IBD study that assessed the risk of TB in TNF-α antagonists exposed versus naïve patients, the risk is significantly higher in the former group [adjusted OR (aOR), 11.7; 95% CI, 1.4-101.1; P=0.011].[61] In Korea, an intermediate TB-burden nation and one of the primary contributors globally to this research topic, TB affects up to 4.2% of their IBD cohort that use biological therapy and has a peak IR of 3710 per 100,000 PY of follow up [62,63] By comparison an American study, using data from their national cohort of military veterans with IBD, had a substantially lower TB incidence of 0.06% and an IR of 28 per 100,000 PY. [64]

Therefore, the risk of TB in IBD patients using TNF-α antagonists is considerably lower in HIC than in MIC and LIC but altogether still much higher than the general IBD population not exposed to this therapy. Further analyses reported from these studies reveal that differences exist in TB clinical characteristics between study cohorts, which subsequently influences on management. In a multicentre study from Spain there were higher rates of extrapulmonary and disseminated TB compared to PTB, and a third of all cases were diagnosed within 3 months of TNF-α antagonist initiation.[65] Similar findings were noted in a Korean study where the median time to TB was also 3 months, but PTB was the dominant location.[66] In Hong Kong where the risk of TB was evaluated in patients with immune-mediated diseases using TNF- α antagonists, the median time to TB was 14 months.[67] A shorter interval to TB suggests that diagnosed cases are likely as a result of reactivation of latent infection whereas longer intervals raise the concern of newly-acquired disease. This has important implications for pre-biological LTB screening as well as the need for continued TB surveillance in patients already on therapy.

The incidence of IBD and TB in Africa is shown in Figure 2. There is currently only a single publication in Africa that addresses this growing problem. Deetlefs et al recorded the highest TB incidence of 12% in a general IBD cohort, although the bulk of cases (>55%) preceded the diagnosis of IBD. Using multivariate logistic regression models, extensive CD and ethnicity were the variables identified in this study as statistically significant risk factors for TB development. However, the author noted that the role of ethnicity in this instance was likely influenced by differences in socio-economic status and proposed that other causes for this finding required investigation.[68] There are currently very few studies in TB endemic countries that quantify the burden of disease in IBD patients exposed to TNF-α antagonists, highlighting the expensive nature and scarcity of this treatment in resource-poor countries.

Guidelines have subsequently been introduced and are now available in many countries outside of Africa to assist with risk stratification and management of latent and active TB in IBD patients using IST. A central component in all recommendations is to adequately test for latent and active TB prior to commencing therapy. Screening though has often been neglected or inadequately performed in this high-risk group. Vaughn et al determined that the level of adherence by gastroenterologists to follow screening guidelines for TB prior to starting TNF- α-antagonists only approached two-thirds of their cohort and less than one-fifth had adequate documentation of TB risk factors.[69] In addition, there are many inconsistencies and conflicting recommendations between guidelines from different countries, mainly related to the choice of screening tests, interpretation of results and therapeutic options for preventative chemotherapy. Guidelines are also based predominantly on research from countries with a low TB prevalence which may not be applicable to MIC and LIC countries due to the diverse characteristics of TB infection in different regions of the world.[70-72]

Conclusion

IBD rates are increasing in TB endemic countries. The established benefits of IST are being counteracted by the high risk of infection associated with their use. But there is limited evidence of this risk in IBD patients living in this environment and what strategies should be employed to protect them. The study of TB in IBD patients in South Africa is important and may later assist in formulating local guidelines, which can be used as a template for other TB endemic countries whose incidence of IBD in the future is likely to increase.

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Small bowel obstruction in pregnancy secondary to midgut malrotation: the value of MRI

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Introduction

We present the case of a young 21-year primigravida at 24 weeks of gestation, who presented with an acute on chronic history of small bowel obstruction. This case highlights how the difficulties in diagnosis were resolved with MRI and how the diagnosis of malrotation influenced our decision for a surgical approach. A paucity of literature with only a few case reports internationally lead us to believe that documentation would be of value and interest to acute care surgeons and gastroenterologists.

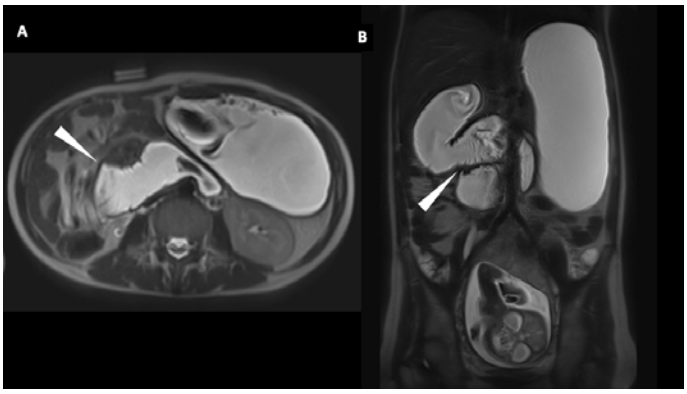
Case report

A 21-year primigravida with no past medical or surgical history presented to our Obstetric department at 23 weeks of gestation, with a 4 months history of vomiting post prandially that had worsened over the last week. She had loss of weight and appetite. She had, no night sweats or chills, prior TB or TB contacts and was COVID symptom screened negative.

She was dehydrated and hypotensive, with a hyponatremic, hypochloremic metabolic alkalosis and acute kidney injury present on arterial blood gas with raised inflammatory markers. Her abdomen was soft, non peritonitic, with a palpable uterus below the level of the umbilicus. No sucussion splash was elicited. Her fluids and electrolyte abnormalities were slowly corrected by appropriate intravenous fluid therapy.

Hyperemesis gravidarum or septic ileus from Gram negative sepsis were considered the most likely diagnoses. Plain radiographs of the abdomen was not requested as we felt it was contra-indicated. Despite appropriate supportive management including intravenous nutritional support no clinical improvement was noted over the following days. A nasogastric tube was placed for the patient and vomiting subsided but did not cease completely. Upper endoscopy was normal. Due to ongoing symptoms despite conservative treatment a decision was made to perform a MRI, as to not cause any harm to the developing foetus. Plain radiographs were not requested due to the risk associated to the foetus and the likely poor diagnostic yield. The MRI showed a midgut malrotation and possible volvulus. (See Figure 1A and B)

Figure 1. MRI T2 weighted images A. Axial view and rotation and B Coronal view with arrow showing showing the point of obstruction and and small bowel in the right lower quadrant



She was counselled regarding the relative risks of possible adverse effects to both her and her unborn child from a volvulus against those from surgery and anaesthesia. She agreed with our recommendation to undergo a laparotomy. At surgery she was found to have a midgut malrotation with congenital Ladd's bands causing a simple obstruction with no volvulus or bowel ischaemia. (See Figure 2A and B) The bands were released with peristalsis noted distally. The post-operative course of the patient and foetus was uneventful She had resolution of her symptoms prior to discharge with a viable foetus. Joint surgical and ante-natal follow is planned.

Discussion

Midgut malrotation is an embryological anomaly, occurring as a result of failure of anti-clockwise rotation of the primitive gut around the superior mesenteric artery during early

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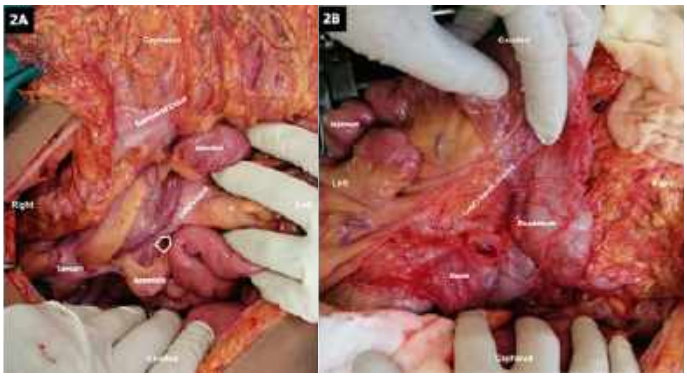
Figure 2. A. Intestinal malrotation evident intra-operatively without enteric ischaemia with arrow showing a Ladd's Band and the point of rotation. B Shows the Ladds band partially divided



foetal growth and development.[1,2] It may be complete or incomplete, and may be associated with the presence of Ladd's bands, which are benign peritoneal attachments; the surgical procedure for the release of these bands is appropriately referred to as Ladd's Procedure in which the bands are incised sharply to release the previously obstructed bowel.[1,3,4]

Midgut malrotation most commonly presents in early childhood. It's documentation in adulthood is rare with published series showing an approximate incidence of 0.2-0.5% with no data on the frequency of its presentation in pregnancy.[2-4]

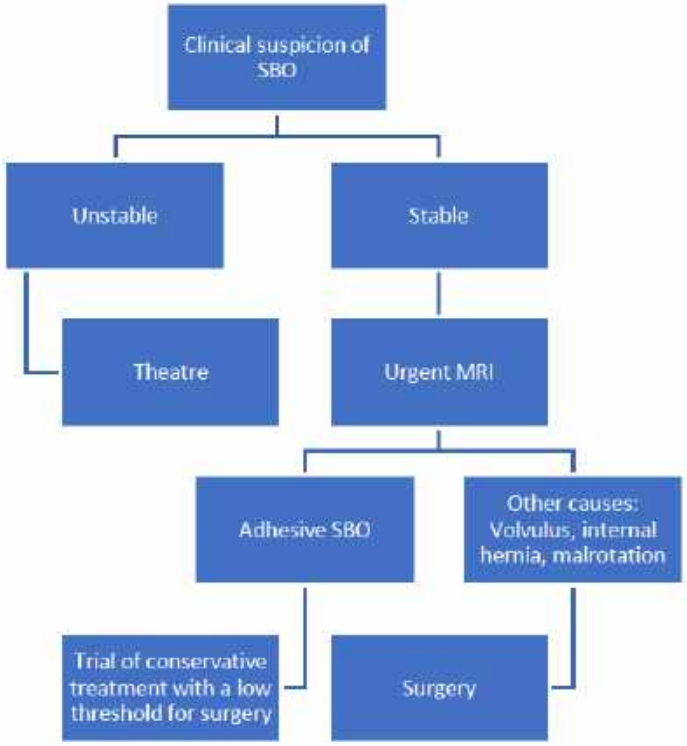
The diagnosis of SBO in pregnancy can be problematic as the symptoms of nausea and vomiting are often blamed on the pregnancy as they were in this case so that in the absence of peritonism a conservative management approach is adopted. Adhesions from prior surgery, appendicitis, Meckels diverticulae, internal hernias, intussusception, or possibly the presence of non-benign intra-abdominal lesions are all potential causes of ileus or SBO.[5] Congenital malrotation with volvulus, is an entity described in few international case reports, and is noted to carry a high morbidity and mortality for the mother and her unborn child if undetected.

Plain radiographs especially in early pregnancy are avoided due to the potential harm ionising radiation to the developing foetus a factor cause delay in the diagnosis and hence the appropriate treatment of SBO.[6] In 2013 the American College of Radiology came to a conclusion that MRI provides good anatomical assesment of the small bowel obstruction including the level of obstruction and does not pose any documented adverse effects on the developing foetus.[7] As a results a proposed treatment algorithm for the management of SBO in pregnancy has been set put forward by Webster PJ et al. (See Figure 3)[8]

This means that the previously advised prompt surgery for all suspected SBO in pregnancy can be changed to a more conservative approach in those with simple adhesive obstruction when other more sinister causes such as volvulus have been excluded by MRI.[9]

In terms of managing mid gut malrotation without features to suggest volvulus or ischaemia there are only case reports to guide the clinician to adopt a longterm conservative approach or to pursue a more aggressive, early surgical approach. We chose the latter as we felt that surgery would take away the risk of a catastrophic midgut volvulus with ischemia with mimimal risk to the mother and the feotus.

Figure 3. Proposed treatment algorithm of SBO in pregnancy[9]



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References: 1. IQVIA, MIDAS Database, MAT September 2019 [IQVIA Copyright 2019. All rights reserved]. **2.** MIMS Volume 59 Number 10, November 2019. **3.** Thomson ABR. Are the Orally Administered Proton Pump Inhibitors Equivalent? A Comparison of Lanosprazole, Omeprazole, Pantoprazole, and Rabeprazole. *Curr Gastroenterol Reports* 2000;**2**:482-493. **4.** OMEZ Package Insert; Dr Reddy's Laboratories (Pty) Ltd. 2007. S4 Omez 40. Each capsule contains omeprazole 40 mg. Reg. No. 34/11.4.3/0301. Dr. Reddy's Laboratories (Pty) Ltd. Reg. No. 2002/014163/07. Block B, 204 Rivonia Road, Morningside, Sandton 2057. Tel: +27 11 324 2100, www.drreddys.co.za. For full prescribing information refer to package insert approved by the medicines regulatory authority. ZA/02/2020-2022/OMEZ/005. 38086 03/20

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SAGES VIRTUAL CONFERENCE 2020

6 – 13 August 2020

SAGES Virtual 2020 in Numbers

Number of registrations: 542
Number of sessions / hours: 15 sessions over nearly 20 hours
Number of international speakers giving live presentations: 10
Number of international speakers giving recorded presentations: 10
Number of countries online: 33

Argentina • Australia • Bangladesh • Belgium • Botswana • Brazil • Cameroon • Colombia • England • Ethiopia • Germany • Ghana
Greece • India • Israel • Italy • Kenya • Mozambique • Namibia • Nigeria • Norway • Pakistan • Peru • Russia • Somalia • South Africa
South-Korea • Sudan • Switzerland • Tanzania • USA • Zambia • Zimbabwe

Thoughts from the organisers

Who would have thought that the 2020 SAGES Conference would have ended up being a virtual one? In all honesty, who would have guessed that 2020 would be the year we would put the internet to the ultimate test.
As with any other conference, virtual offered its own challenges, learning that you are completely at the mercy of the internet and technology. It's up, you're on, it's down, and you're off.
When the conference started on 6 August, the organisers and the technical team were set up and ready. Individual and remote command centres to run the conference, tackling things as they arose. The focus: To deliver a wonderful first virtual conference experience
As with anything, communication was at the centre of running the conference. The organisers kept in touch with the technical team, delegates, speakers and chairs through various communication tools, making use of WhatsApp groups, Zoom, and the live support feature on the conference platform. Keeping everyone informed and updated at all times. The virtual platform allowed for immediate and constant communications with all conference parties.
Yes, the virtual conference had a few challenges, but I am sure that you will agree that having the option to attend the conference in your pajamas was something one could get used to. Also the only travelling required was to get up from your seat to make coffee and go to the bathroom. All of these things contributed to a very successful virtual SAGES Conference.
But, just as important as the organisers, technicians and the system were the delegates, speakers and chairs. Without them it would not have been a conference.
Also, the support received from the trade was overwhelming and absolutely invaluable.
Cheers to everyone involved in the success of the first SAGES virtual conference and the hope that the next time we meet will be in person.

Eastern Sun Events Team


Denise


Cindi


Lizl


Margaret


Sam


Wanda

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The support received from the trade was overwhelming and absolutely invaluable. It enabled SAGES to broadcast the conference at no cost to the delegates.

Thursday 6 August 2020
Upper GI Session
The upper GI session at this year's virtual conference sought to cover aspects of gastroenterology we often come across but are not certain how to manage, those we see often and need to revisit and update our knowledge on, and rare conditions that we need to consider especially when things do not make sense. The oesophagus took centre stage.

The session started with a talk by Dr Didintle Mokgoko, who covered sub-epithelial lesions of the oesophagus. Most endoscopists would have come across these at some point in their careers, but would not be certain how to approach them. The endoscopic appearance and management of those lesions where nicely compacted into a 15 minute talk, with great take home points for the delegates. The role of endoscopic ultrasound in investigating these lesions was also highlighted.

Dr Vikash Lala then talked about the effect of opioids on the oesophagus. This is one of the causes of oesophageal dysmotility that we need to be aware of in the investigation of patients with dysphagia, in the absence of a mechanical cause for those symptoms. The use of opioid analgesia is not only increasing in patients with malignancies, but also those with chronic pain syndromes. A thorough history will help point clinicians towards the right investigations to make a diagnosis, and to manage this complicated group of patients appropriately.

The last talk of the session by Prof. Remi Sweis on reflux disease management, gave the delegates an update on the current management of reflux disease. The definition of reflux, endoscopic appearance and investigations were covered. The important role of performing high resolution manometry, ambulatory pH and impedance studies, and the bravo capsule in those unable to tolerate the catheter were nicely demonstrated. We were truly honoured to have Prof Sweis as one of the speakers in our session.

We hope the session gave the delegates a useful approach to patients presenting with these oesophageal conditions, and will guide them in their daily practice.

Dr Manoko Neo Seabi

Dr Christina Karapanou

Friday 7 August 2020
Put on your Oxygen Marks before helping others : Abbvie Symposium
Dr Christina Karapanou
Cognitive Behavioural Psychotherapist

COPING STRATEGIES
When your brain detects danger in your environment, behavioural changes are activated. These are called 'COPING STRATEGIES'. Coping strategies are natural defence mechanisms, but we need to control them. The psychological process of activating coping strategies is called ADAPTATION and NORMALIZATION. We adapt and normalize using critical thinking strategies. The 4 coping strategies are:

- **Fight**: I am stronger than the threat. I will stage a war against it –you need to examine whether this is making you functional or toxic
- **Flight**: I will avoid the threat and all information about it
- **Freeze**: I will hide away from the threat – almost obsessive compulsive
- **Fawn**: I will deal with the threat and continue to live my life (functional coping strategy)

We need to understand what our coping strategies are. We can have a combination of two coping strategies at a time. A strong fight response could be dangerous as it could cause mental exhaustion and burnout.

SEPARATING EMOTIONS FROM BEHAVIOUR
When consulting patients with chronic diseases, always separate emotions from behaviour. If you separate emotions from behaviours/facts, you will be able to have a conversation of reason with patients, to better understand their level of functionality. Emotions cloud their judgement. Talk about how they feel later.

NOOTROPICS IS EVERYTHING
Nootropics is the way we think (Mental Models). When you speak to a patient, what you tell them is a STIMULUS, which sets off a COGNITIVE PROCESS followed by a RESPONSE. You cannot control the COGNITIVE PROCESS (what they think). Patients will always analyse what they are told. You can control the STIMULUS (what you tell them). To change behaviour, work on the STIMULUS (how you communicate with them).

HEALTH ANXIETY VS HEALTH FEAR

You need to profile your patients and separate health fear vs health anxiety. Health anxiety is an obsessive and irrational worry about having a serious medical condition (formerly known as hypochondria). Patients with heath anxiety should be referred to a mental health professional or they should be managed in collaboration with a mental health professional.

COGNITIVE PERCEPTION OF ILLNESS

Doctors need to understand the mental path of the patient – how patients understand their illness. The cognitive perception of illness is measured by functionality and survival instinct trigger. This is measured during the day. How many times per day is a patient thinking about his/her survival? There are three profiles of patients:

- **HEALTHY SELF:** This patient has negative thoughts and thinks about his/her illness 30% of the day. This patient is considered to be a functioning patient.
- **ILL SELF:** This patient has negative thoughts and thinks about his/her illness 50% of the day. This patient needs to make an effort to function and sustain a good quality of life. Explaining therapeutic plans to this patient will be difficult. Start with how the patient is feeling. Understand the mental profile.
- **SICK SELF:** 80% of thoughts are around illness. Patients surrenders and seeks attention. Patient and family are desperate. If you as the treating physician are tired, the equation is disastrous.

DIFFERENCE BETWEEN STRESS AND BURNOUT

Stress is not bad. It raises your productivity. It creates some physical and mental symptoms such as tiredness and forgetfulness. Burnout is a continuous process of mental, psychological, emotional and physical exhaustion. Some of the manifestations are: inability to rest or sleep well, active brain and emotional exhaustion.

According to WHO, there are certain dimensions of your life that you should pay special attention to. Research shows that medical professionals only pay attention to:

- Partner/Love relationships
- Fun &Travel
- Money/Finance

You are a priority. If you don't take care of yourself, you will not be able to care for your patient. After the COVID-19 pandemic, we will redefine norms and create something new.

Dr Cathryn Edwards – former Visiting Lecturer at GSH and immediate past President of the British Society of Gastroenterology

Sages Virtual: A New Frontier for the Annual Conference

In March 2020, South Africa entered a nationwide lockdown to reduce the spread of SARS-CoV2. SAGES took the unprecedented step to move to a virtual congress for its annual gathering. This meant a new digital approach to the meeting and allowed international speakers to participate with ease.

Endoscopy Session – Chaired by Shiraz Gabriel
On the 8th of August, SAGES held a virtual session on the effect COVID-19 has had on endoscopy services.

Dr Dirkie Clasen GI Fellow at Tygerberg, opened the session with a description of the measures taken at Tygerberg in response to the pandemic. Endoscopy for upper and lower gastro-intestinal diseases, is deemed to be an aerosol generating procedure, which poses a risk of transmission of infection to staff and patients alike.
Dr Classen illustrated the need for appropriate planning, education of staff, theatre allocation, planning of endoscopy lists, correct personal protective equipment(PPE) usage and efficient infection and prevention control guidelines, all in line with international guidance on endoscopy practice.
Early preparation led to optimal use of theatre lists, PPE and staff and patient protection. Only emergency cases were done and every referral was assessed on an individual basis with consultant input. To date, with appropriate screening, PPE and triaging – no one in the department has contracted the virus.

Dr Cathryn Edwards – former Visiting Lecturer at GSH and immediate past President of the British Society of Gastroenterology – gave an overview of the recovery of endoscopy services in the deacceleration phase of the pandemic. Using an international evidence base, referencing the AGA, Asia Pacific Guidance and BSG Endoscopy Guidance, she discussed the principles of restarting endoscopy focusing on a 'screening and testing strategy' (Hayee et al Gut 2020) which would permit a safe service restart with lower levels of PPE usage. The increase in capacity this generates would restart service activity up to 75% of the normal, depending on case mix and this recovery alongside senior clinical triage of referrals and biomarker stratification of case priority were highlighted as key strategic objectives.
Dr Edwards went on to discuss, specific biomarkers: qFit, faecal calproctectin and serological markers in conjunction with a non -biopsy protocol for adult coeliac disease. The lecture then focused on innovations which might change approaches to cancer screening, along with novel diagnostics and innovations to improve safety in the endoscopy environment. The environmental consequences of endoscopy were also briefly discussed. The presentation concluded with a summary of opportunity for change, specifically the importance of data collection, service evaluation trials in the South African context

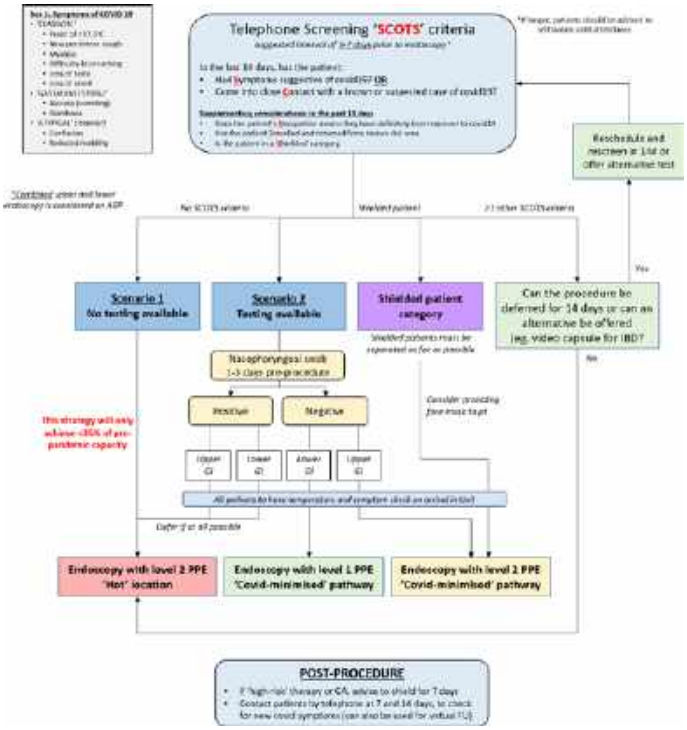
and the importance of supporting/mentoring the workforce.
A panel discussion followed. Dr Gabriel from Tygerberg Hospital, Prof Setshedi, from Groote Schuur Hospital, Dr Coovadia from Panorama Hospital and Dr Forgan from the Surgery Department at Tygerberg Hospital, shared their experiences with endoscopy in the COVID-19 era and highlighted the unique challenges this virus has posed to endoscopy practice.

Polypectomy – Chaired by Tim Forgan
Dr Forgan then introduced a state of the art lecture given by Dr John Anderson, an UK expert on colorectal polyp management who outlined a best practice approach to polypectomy.
Key messages were the use of saline or polypectomy mix to lift even small polyps prior to removal to ensure complete clearance of all polypoid material. Cold and hot snare techniques were discussed, and the importance of careful visualization of the colonic mucosa alongside good bowel preparation.
Discussions were interactive and lively and illustrated the resilience and enthusiasm of the South African Endoscopy community when facing the challenge of COVID-19.
Immediately post event, FAQs were produced from the session on Restarting Endoscopy for the SAGES website and they are reproduced here in full (below).

FAQs and Responses from @Cathryn Edwards

Q1 We have been randomly screening asymptomatic staff, very interesting that your staff infection rate was 14.7 % which reflects the same infection rate that we picked up when our testing started. This included staff across the board including kitchen, laundry, security, admin, nurses and doctors and was hence assumed to be community acquired. This has progressively come down - with last week no staff testing positive. Please comment on staff infection.

@CathrynEdwards responding
In the published literature, overall 3.8% of Health Care Professionals (HCP) in China were infected compared with 8.3% of HCP in Italy.
I noted with interest Wayne Simmonds report of 14.7% in his hospital. This raises several questions and means that unless comprehensive testing of staff and contact tracing is undertaken, we will not understand whether infection is community or hospital acquired (and therefore what the real risk of acquiring COVID-19 in the workplace is).
What we do know is that front line health care professionals in the UK and USA (data published online in the Lancet Public Health July 31st) reported an increased risk of a COVID positive test for front line Health Care Professionals (adjusted HR 3·40, 95% CI 3·37–3·43) Secondary and post hoc analysis suggested that adequacy of PPE, clinical setting and ethnic background of staff also influenced this risk. The adequacy of PPE did not completely reduce the risk of infection in this very large cohort of workers (www.thelancet.com/public-health https://doi.org/10.1016/ S2468-2667(20)30164-X)
Of great interest also would be the true asymptomatic carriage rate of HCPs working in endoscopy. I have seen unpublished data from Cambridge estimating this to be around 3%
If the aim is to create COVID-minimized environments for 'safer' endoscopy, then at very least staff should not be moved between COVID ward service to COVID minimized areas of the hospital, without first screening and testing of that staff cohort. It would then seem sensible to have a test and trace policy for all staff working in the COVID minimized area. Hayee et al (Hayee B, Thoufeeq M, Rees CJ, et al. Gut Epub ahead of print: doi:10.1136/gutjnl-2020-321688) stress the need for follow up surveillance of all patients treated in the Unit by phone screening for symptoms – this can be part of virtual follow up of patients, so that the effectiveness of patient testing and separation can be estimated.
In my view similar information needs to documented for staff working in front line areas such as endoscopy. This will be valuable not just now but in terms of planning for subsequent waves of the pandemic.



From Hayee et al Gut 2020 Hayee B, Thoufeeq M, Rees CJ, et al. Gut Epub ahead of print: . doi:10.1136/ gutjnl-2020-321688

Q2 In IBD patients who have had COVID-19, how long after recovery would you recommence faecal calprotectin monitoring in view of the fact that COVID can persist in stool for prolonged periods of time?

@CathrynEdwards responding
Faecal Calprotectin has been shown to be raised in patients with COVID-19 related diarrhoea. There is a short 'post script' in GUT published by Hubert Tilg's group in Austria (Gut August 2020 Vol 69 No 8).
The question above can be interpreted in several ways:-

In a patient without known IBD and symptoms of diarrhoea do you get a rise in faecal calprotectin as a result of COVID-19?

Answer: Yes and this rise seems to be correlated with serum IL-6 levels but not CRP

How much of the 'FC rise' in a patient with IBD (who is also COVID positive and who has diarrhoea), is a result of COVID induced disease flare -

Answer: This is unknown but COVID is likely to trigger disease relapse. It is possible that SARS-CoV2 which is known to infect epithelial cells causing cytokine and chemokine release, may

trigger acute intestinal inflammation characterised by the infiltration of neutrophils, macrophages and T cells.
No evidence exists as to whether co-infection with SARS COV -2 increases your chance of IBD relapse but the direct invasion of gut epithelial cells triggering an inflammatory response, might suggest that this is likely.

If the question is about the safety of labs performing FC in patients with or without IBD when COVID status is either positive or unknown then the following are relevant considerations

There should be no additional risk to the processing of samples if infection control standard practices are applied. The issue for labs will be one of capacity.
We should continue to rely on FC's in our population of IBD patients for monitoring,, as this is less invasive than a colonoscopy for mucosal assessment. At a time when endoscopy is a 'scare resource' then (limited) colonoscopy should be reserved for new diagnoses i.e. acute disease and to exclude concomitant pathology which would alter treatment options.
In the report from the Austrian group quoted above the presence of SARS COV-2 viral RNA in stool was found in 30% of patients (12/40 patients). This occurred only in patients who had no diarrhoea or who had ceased to have diarrhoea (all patients had COVID 19 but 22 had no GI symptoms). No viral RNA was detected in patients with active diarrhoea.

Q3 **Lower GI equally results in aerosols, especially if air insufflation being used. I think there is a case for advanced PPE for lower GI as well as we know virus is shed in stools.**

@CathrynEdwards responding
Agree that the air- suction function on a colonoscope has the capacity to create aerosols but the question here is around 'infectivity' of the faecal aerosol generated. The BSG has acknowledged this in, Rees et al Restarting gastrointestinal endoscopy in the deceleration and early recovery phases of COVID-19 pandemic: Guidance from the British Society of Gastroenterology. Clinical Medicine 2020 Vol 20.No4: 352-8
''The overall risk to staff and patients is likely to depend on the stage of the COVID-19 infection, the viral load and the infectivity of the secretions involved. As a consequence, not all endoscopic procedures may carry the same risk to staff. The infectivity of upper airways and nasopharyngeal secretions are well established. For this reason, the requirement for enhanced (level 2) PPE for upper GI endoscopic procedures is unlikely to change in the foreseeable future. If it becomes possible to demonstrate that antibodies are protective, and this, when combined with negative viral swabs, can show that the transmission of infection is unlikely, then this might change.
*The situation regarding lower GI procedures is less clear. Viral RNA can be detected in stool for several weeks, but viable virus is not present.**
*This is consistent with viral dynamics from sputum and lung where multiple studies have shown presence of non- viable virus for prolonged periods. It is reasonable, therefore, to categorise lower GI procedures as having lower transmissibility risk than upper GI procedures. Thus, if patients have been screened and are asymptomatic for 14 days prior to endoscopy and have a negative nasopharyngeal swab, this should allow the use of less stringent infection control policies for lower GI procedures. This could facilitate higher throughput and aid service recovery and would also allow use of lower levels of PPE for lower GI procedures.'' *there has been one study by Wang of demonstrating viable virus culture from stool. Wang W, Xu Y, Gao R, Lu R, Han K, Wu G, et al. Detection of SARS-CoV-2 in Different Types of Clinical Specimens. JAMA. Published online March 11, 2020. doi:10.1001/jama.2020.3786*
The accepted wisdom is that the colonic luminal environment is hostile to the survival of viable virus although viral RNA particles are detectable even when nasopharyngeal swabs have become negative. This means that PPE whilst necessary can be reduced to level 1 (surgical mask plus visor but not mandated FF3 mask or American N99 equivalent for enhanced or level 2 PPE) on the understanding that you have the ability to screen and test your patients. If the patient is SARS COV -2 positive (or unknown status) the full PPE (enhanced or level 2 PPE) is indicated until knowledge is updated. Since this debate BSG has issue updated guidance https://www.bsg.org.uk/covid-19- advice/bsg-multi-society-guidance-on-further-recovery-of-endoscopy-services-during-the-post-pandemic-phase-of-covid-19/

Q4 Who should lead a national endeavour to improve data collection for endoscopy and GI cancers

@Cathryn Edwards responding
At its most basic level, this is a question about the good governance of record keeping. All units should be responsible for logging all endoscopic activity and endoscopic patient related outcome measures. I understand that not all units will have electronic endoscopy records, but patients notes could be 'coded' for the presence of absence of lower and upper GI cancers as part of prospective audit. This will give an estimation of cancer rates per endoscopies performed. Ideally the endoscopic diagnosis of cancer should feed directly into the South African National Cancer Registry (NCR) and this then might attract some central funding from government.
It would be fantastic to think that the COVID -19 pandemic will lead to new opportunities to create regional and national programmes of data collection as part of a wider strategy for endoscopy training and KPIs for GI disease diagnosis. It is absolutely necessary to standardise this reporting. I would suggest initially, that the creation of the data sets should be led by academic institutions with a high level of clinical input. A multi-stakeholder approach to funding would be necessary

Q5 Quantitative FIT. Can someone from private say if this Is available and what it costs.

Answer from SAGES SA
A South African website indicates that it can be purchased for around R200.

@Cathryn Edwards responding
The funding for new biomarkers to aid clinical practice is always a struggle, but if the outcome is a more focused approach to colonoscopy within nationally recognised guidelines then this will create the opportunity to leverage a better market price for such tests. Meantime, the use of a validated quantitative test in the context of the South African population should be part of a rapid access clinical trial/ service evaluation to demonstrate validity and cost effectiveness. Universities should take the lead in setting up such programmes working with SA College of Physicians and Specialist societies such as SAGES to then set guidelines for best practice.

Q6 What about COVID Free COVID light Hospitals to improve access for endoscopy. Reality or dream?

@Cathryn Edwards responding.
My personal view is that this model would work in SA if agreement could be secured about testing and screening. There are various models which might apply: the same unit could be used for both

'hot' emergency and COVID- minimised work providing that these services were separated out, working at different times using strict infection control protocols. There would need to be regular screening and testing of staff and ideally 'hot' and 'cold' teams of staff would cover each service arm.
Another solution is that 'hot' cases are only performed in designated areas such as emergency theatre, with the Endoscopy Unit maintained exclusively as a COVID -minimized. environment. See Hayee et al for a fuller description of how this might work including the principle of linear patient flows. A separate site for networked elective services is a further alternative.

Q7 Are there any statistics worldwide on the incidence of patients developing COVID post endoscopy

@Cathryn Edwards responding
There is no evidence for the transmission of COVID because of an endoscopy procedure per se: remembering that at the peak of the pandemic it is likely that attendance at hospital in high risk areas might carry an increased risk of transmission to patients. A hint at real world experience is given in Repici's paper in Gut Repici A, et al. Gut 2020;0:1–3. doi:10.1136/ gutjnl-2020-321341 . One patient tested COVID positive and 7 others developed symptoms, out of 851, during follow up after endoscopy in the Netherlands (period Jan – March 2020). There was no suggestion that the transmission was due to the endoscopy itself but the paper recognised that this is not a well evidenced area.
Logically however, we believe our decontamination procedures for scopes and cleaning protocols for the endoscopy environment (including the need to let a room 'settle' before cleaning to ensure that any possible fomites can be dealt with in the cleaning process) to be appropriate for the SARs Cov-2 virus. The risk appears to be the other way around in that Health Care Personnel without the appropriate protective equipment are at risk of becoming infected.
''Of 968 HCWs in these centres, 42 (4.3%) were tested positive for covid-19, and 6 (0.6%) had to be temporarily hospitalised (for a mean of 8 days, none on intensive care unit (ICU)). Of these 42 cases, 85.7% occurred before the introduction of safety measures, including personal protective equipment (PPE) and case selection/reduction in GI endoscopy''.

Q8 The governmental advisory group has only Public Health and Infectious diseases experts. How can we get a gastroenterologist or other sub specialists on that committee

Answer from SAGES
MAC in South Africa has sub committee

- Pathologists and Laboratory
- Clinicians
- Public Health
- Research

In Clinicians group there are ID, physicians and critical care specialist
There should be a more diverse group sub specialist in clinicians sub-committee, but how we do that am not sure.(SG)

Rupert Leong

Sunday 9 August 2020
IBD Session

The Sunday morning IBD session started at 09:00 with a symposium, hosted by Janssen, on 20 20 Vision in IBD. The speaker, Alessandro Armuzzi from Italy, spoke on the use of Ustekinumab (STELARA®) in Crohn's and Ulcerative colitis both as a first line drug and in those patients that have failed anti TNF's.

The SAGES IBD session commenced with a 'pot pouri' by Gerhard Rogler presenting highlights from DDW 2020 on varying subjects such as the effect of a gluten -free diet on the microbiome, the use of probiotics to prevent C difficile infection in patients on antibiotics, early laparoscopic ileal resection in patients with Crohn's Disease and a number of aspects regarding the use of Biologic therapy in IBD. He highlighted that with newer Biologics such as Ustekinumab and Vedolizumab combination therapy with immune -suppressive drugs may not be essential.

Rupert Leong from Australia gave an excellent overview of IBD surveillance colonoscopy. The aspects covered included the differences between sporadic vs IBD related colorectal cancers, surveillance of IBD patients using dye spray chromoendoscopy and comparisons with NBI, and the use of targeted resection, endoscopic resection and colectomy in patients with neoplastic lesions. Prior to his presentation I spent a few minutes sharing with Rupert the problems facing speakers presenting from home during which he reminded himself that it was time to put on his jacket and take care of his dog! Towards the end of the presentation Rupert's dog could be heard barking in the background. The dog, wearing a little jacket for warmth, got stuck in the dog-flap of the kitchen door, and only escaped by wriggling out of the jacket! Rupert found the jacket on one side of the door and the dog on the other!

Next up was Alesandro Armuzzi who presented ''Treatment objects in IBD' and highlighted that Biologics have presented a re-definition of treatment goals in IBD with clearly defined end points that are clinical relevant and easy to define. In Crohn's Disease a target of deep remission and in Ulcerative colitis complete remission using treat to target regimens is now feasible.

The final talk of the IBD session was by Gill Watermeyer who focussed on the common mistakes made in managing acute severe ulcerative colitis highlighting the need to introduce a surgeon early on in the flare and not prolong steroid therapy indefinitely. She also emphasised that better outcomes could be achieved by introducing a Biologic therapy earlier.

The IBD morning closed with an Adcock Ingram symposium with Geert D'Haens presenting on the use of Remsima® SC the world's first infliximab biosimilar in IBD, which has been shown in a number of trials world-wide to be an effective substitute for the parent drug Revellex® with the advantage of considerable cost savings.

The online stats showed the IBD session to be extremely popular with many people participating.

Chris Kassianides

Radu Tutuian

Tuesday 11 August 2020
General Gastroenterology

Many of us who encounter patients with gastro-oesophageal reflux disease on a regular basis know that diagnosis and treatment of this condition can be challenging at times.
On the first day of the virtual conference, we were given a very interesting up-to-date overview of the investigation of reflux disease by Dr Rami Sweis (Consultant Gastroenterologist
University College London Hospitals with a special interest in foregut pathophysiology).

Following the enthusiastic response to last year's Takeda Twilight Symposium 'Shades of Grey in Diagnosing GORD', Prof Radu Tutuian, Head Physician of Gastroenterology/Hepatology at Burgerspital Solothurn in Switzerland, member of the European Society for Neurogastroenterology and Motility and acting president of the Swiss Neurogastroenterology and Motility Group joined us again this year on 11 August 2020 for our virtual conference. His talk was entitled 'The Spectrum of NERD', and highlighted the numerous symptoms related to oesophageal disorders and the fact that most patients with these symptoms have normal upper endoscopy, necessitating further testing using pH/impedance studies to distinguish normal from abnormal gastro-oesophageal reflux using the Lyon Consensus guidelines for reflux testing.

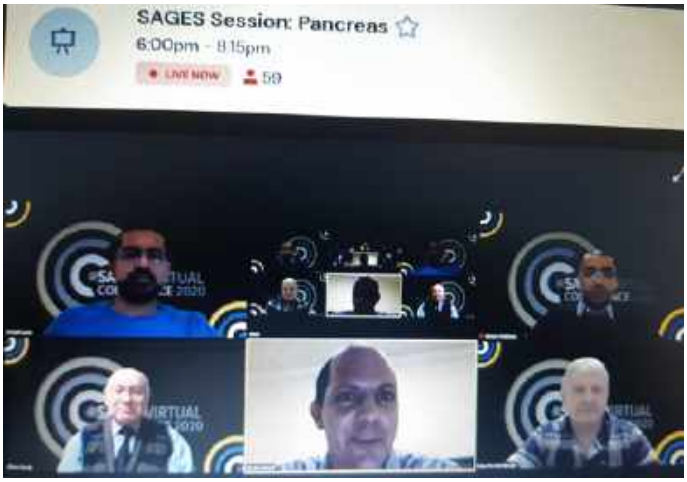
Following Prof. Tutuian's introductory presentation, Dr Sassa Botha presented a case of a patient with extra-oesophageal symptoms (cough and dysphonia) and normal upper endoscopy. Despite an acid exposure time of 5.7%, the patient had a normal number of reflux episodes and a negative symptom association. In addition he was noted to have absent contractility on high resolution manometry testing.

Prof. Tutuian took us through both the high resolution manometry and the pH impedance studies. He explained his clinical decision-making process including analysis of the evidence for GORD on testing, treatment options and possible side-effects of treatment.

The process was repeated after Dr Debbie Nel presented a case of reflux hypersensitivity, where the patient had normal acid exposure time and number of reflux episodes but positive symptom association. This patient had experienced negative side effects on neuromodulator therapy (amitryptiline) and the case sparked some suggestions from the audience as to possible alternative treatment strategies.

Despite the virtual nature of the talk and the case presentations, audience participation was encouraged and the session did end up being rather interactive, with both questions and treatment suggestions being offered.

The various forms of reflux disease can be tricky to diagnose and even more challenging to treat. More sessions like this, virtual or otherwise, will hopefully improve our use and interpretation of these special investigations and ultimately improve therapeutic outcomes for our patients.



Top Vikash Lala, all, Dinen Parbhoo, Bottom Chris Ziady, Martin Brand, Jorg Reichenberger

Wednesday 12 August 2020
Pancreas Session

During the recent virtual SAGES congress a panel discussion between Dr Chris Ziady, Dr Jorg Reichenberger, Dr Vikash Lala, Dr Dinen Parbhoo guided by Prof Martin Brand discussed pancreas-based case studies. Here follows a point summary of each of these cases.

Case 1: Severe acute pancreatitis secondary to hypertriglyceridemia

- Hypertrigylceridemia interferes with common biochemical tests, resulting in false low serum amylase levels, false low sodium and false high anion gaps.
- Plasmapheresis decreases circulating triglycerides, but does not conclusively affect acute pancreatitis mortality
- Patients with worrisome features including persistent hypocalcaemia, worsening lactic acidosis and worsening organ dysfunction should be considered for therapeutic plasma exchange
- Multimodal lipid modifying therapy should be instituted as soon as the patient is able to tolerate oral intake, and continued long term with a target triglyceride level of less than 10mg/l to prevent recurrent attacks of acute pancreatitis

Recommended read: *Severe Hypertriglyceridemia-Related Acute Pancreatitis*. Stefanutti C et al.. Therapeutic Apheresis and Dialysis 2013.

Case 2: Auto-immune pancreatitis (AIP) in black South African male

- IgG4 seropositivity and the presence of jaundice are significant independent factors predictive of relapse in AIP patients
- A magnetic resonance cholangiogram is useful to rule out concomittant cholangiopathy

- Biliary drainage is useful to prevent biliary infection and use of brushing and cytology can differentiate IgG4-SC from biliary malignancy, however in mild uncomplicated cases steroid treatment may be commenced without draining the biliary tree.
- Retuximab is reserved for disease relapse

Recommended read: *International consensus for the treatment of autoimmune pancreatitis.* Okazaki K et al.. Pancreatology 2017.

Case 3: Neo-adjuvant chemotherapy in resectable head of pancreas ductal adenocarcinoma (PDAC)

- Neoadjuvant chemotherapy or neoadjuvant chemoradiotherapy significantly improve overall survival of borderline resectable as well as resectable PDAC
- Neoadjuvant therapy results in similar rates of resection compared to upfront surgery
- Neoadjuvant therapy results in a significantly increased R0 margin rate as well as more negative lymph nodes
- A selective approach to staging laparoscopy should be used. Tumor diameter greater than 3cm, the anatomical site of the tumor site (body and tail) and CA 19-9 levels greater than 200ng/dL may warrant laparoscopy.

Recommended read: *Neoadjuvant Therapy for Resectable and Borderline Resectable Pancreatic Cancer: A Meta-Analysis of Randomized Controlled Trials.* Cloyd JM et al. J. of Clin. Med. 2020

Case 4: Side branch IPMN (SB-IPMN) in uncinate process

- Acute pancreatitis is not an uncommon presentation of SB-IPMN
- There appears to be an approximate 10% incidence of occult malignancy in SB-IPMN presenting with acute pancreatitis
- ERCP sphincterotomy may prevent recurrent acute pancreatitis
- There is an increased incidence of high grade dysplasia and carcinoma in-situ in cysts 2-3cm diameter

Recommended read: *Revisions of international consensus Fukuoka guidelines for the management of IPMN of the pancreas.* Tanaka M et al.. Pancreatology 2017.

Case 5: Incidental (non-functional) pancreatic neuro-endocrine tumors (pNET's)

- Watchful waiting is justified in the management of small (≤1.5cm diameter), asymptomatic non-functional pNETs.
- Small NF-pNET's may be followed up with 6 monthly imaging studies
- But, small pNET's may metastasize, tumors >1.5cm should be considered for surgical excision
- Serum chromogranin has several false positives, amongst others including the use of proton pump inhibitors, renal dysfunction and atrophic gastritis

Recommended read: *Consensus guidelines update for the management of functional p-NETs (F-p-NETs) and non-functional p-NETs (NF-p-NETs).* Falconi M et al.. Neuroendocrinology 2016.

Thursday 13 August 2020
Liver Session

New therapeutic targets for hepatitis B were discussed by Geoff Dusheiko. Current HBV therapies suppress viral replication but do not generally cure the disease, as they do not eliminate cccDNA, or integrated viral genomes. The aim of new therapies is to achieve a functional cure, which has been defined as sustained loss of HBsAg, with or without acquisition of anti-HBs and undetectable HBV DNA six months after completing treatment. This definition recognises that HBV genomes are not cleared from the liver. The life cycle of HBV involves several steps: viral entry, uncoating, nuclear import, transcription, nucleocapsid assembly reverse transcription and viral secretion from host hepatocytes. Currently numerous investigational agents are being developed to either interfere with specific steps in HBV replication or as host cellular targeting agents, that inhibit viral replication, and deplete or inactivate cccDNA, or as immune modulators.
Two types of virions are secreted from the hepatocyte: a population of complete DNA containing virions containing mature nucleocapsids with the partially double-stranded, rcDNA genome and a larger population containing an empty capsid with no DNA or containing RNA. Measurement of HBV RNA in serum is proving a useful biomarker of cccDNA transcription. A reduction in the HBsAg antigen load could improve immunomodulatory strategies, but HBsAg is derived from both cccDNA and integrated viral genomes. Several steps in the replication of HBV are potential drug targets. Numerous agents are under development. The most advanced treatments were discussed. Combination strategies will likely invoke deepening the inhibition of HBV replication, lowering viral antigen concentrations (particularly HBsAg) and enhancing the immune response. Potential new treatments include targeted HBV entry inhibitors, core (capsid) inhibitors, or perturbations of capsid morphogenesis, RNA interference therapies, HBsAg interaction and assembly or release inhibitors, and multiple immunomodulatory agents including toll like receptors agonists, immune checkpoint inhibitors, and therapeutic vaccines. Experimental treatments include inhibitors of cccDNA formation, inducers of cccDNA cleavage or transcription inhibition and epigenetic modifiers or immunological engineering of T cells. HBX protein, a regulatory protein, enhances cccDNA transcription and is an attractive viral target to silence cccDNA transcription.
Trials are progressing to combination therapy as additive or synergistic effects are sought. These trials will provide important insights into the biology of HBV and perturbations of the immune response, required to effect HBsAg loss at different stages of the disease. Synergistic mechanisms will likely be needed to incorporate a decrease in HBV transcription, impairment of transcription from HBV genomes, loss of cccDNA or altered epigenetic regulation of cccDNA transcription, and immune modulation or immunologically stimulated hepatocyte cell turnover.
Geoff Dusheiko

COVID-19 and the liver
SARS-CoV-2 is a single, positive-stranded RNA virus that replicates using a virally-encoded RNA-dependent RNA polymerase. SARS-CoV-2 binds via hidden receptor-binding domain on the spike protein and is internalized into target cells through angiotensin-converting enzyme 2 (ACE2), acting as a functional receptor. Cell entry requires priming of the spike protein by cellular serine protease TMPRSS2

and other proteases and co-expression with ACE2 is required.
The liver is a potential target for infection and the cholangiocytes express ACE2 receptor at a 20x higher concentration than in hepatocytes: 59.6% vs 2.6%. This ACE2 expression is similar to that on Type 2 alveolar cells. ACE2 expressed on small vessel endothelium but not on sinusoids and is not expressed in Kupffer cells, T and B cells.
The pathophysiology of COVID-19 involves multiple pathways including direct virus-mediated cell damage; dysregulation of RAAS as a consequence of downregulation of ACE2 related to viral entry leading to decreased cleavage of angiotensin I and II; endothelial cell damage and thrombo-inflammation and ultimately dysregulation of the immune response and hyperinflammation caused by inhibition of Type-1 IFN signaling by the virus, T cell lympho-depletion, production of proinflammatory cytokines, especially IL-6 and TNF . *(Gupta; Nature Medicine 2020)*

Although liver injury in COVID-19 is usually mild and transient, the frequency of elevated serum liver biochemistries in hospitalized patients with COVID-19 ranges between 10% to 58%. The transaminases are primarily elevated at 1-2x upper limit of normal and seldom greater than 5x upper limit of normal. The AST is usually higher than the ALT. Normal to modestly elevated Total Bilirubin levels occur early in disease process but significant increases in serum ALP and GGT are rarely reported. Liver injury is more common in severe COVID-19 with elevated AST and ALT levels and low albumin levels being associated with mortality risk. Rare cases of severe acute hepatitis are described in patients with COVID-19. *(Liver International. 2020;40: 998; Clin Liver Disease 2020;15(5):175)*

The underlying aetiology of deranged liver enzymes is often multifactorial. It may be due to the SARS-CoV-2 infection itself, immune-mediated damage, provoked inflammatory cytokine storm, COVID-19 complications (myositis, cardiac complications, hypoxia/ischaemia), drug-induced liver injury and unrecognised underlying liver disease. Liver histopathology findings range from moderate micro-vesicular steatosis with mild, mixed lobular and portal inflammation to focal necrosis; sinusoidal dilatation and diffuse intra-hepatic vascular thromboses. (*Lancet Respir Med 2020;8:420; Mod Pathol 2020; 33:1007; Zhonghua Bing Li Xue Za Zhi 2020;49:411)*

Chronic liver disease (CLD) especially cirrhosis is a mortality risk factor for COVID-19. The SECURE-Cirrhosis and COVID-Hep registries have reported COVID-19 mortality of 7% for non-cirrhotic CLD, 32% for cirrhotics and 17% for liver transplant recipients. Mortality correlates with baseline Child-Pugh class and MELD score: 63.0% mortality in Child-Pugh class C cirrhosis: OR 28.07 (4.42–178.46), p<0.001 vs 12.2% in CLD without cirrhosis. Decompensation can occur in the absence of COVID-19 respiratory symptoms. *(Moon et al; J Hepatol May 2020)*

There is no evidence that patients with stable CLD without advanced fibrosis/cirrhosis due to Hepatitis BV and C have increased susceptibility to or worse outcomes with COVID-19. There is a risk of HBV reactivation related to COVID-19 therapies such as Tocilizumab and corticosteroids and one may need to treat HBV to prevent flares. There are no contraindications to initiating HBV or HCV in patients with or without COVID-19, but need to consider drug-drug interactions.
A recent meta-analysis from 3 Iranian studies of Sofosbuvir/Daclatasvir showed that time to clinical recovery (<14 days) favoured Sofosbuvir/Daclatasvir as well as conferring a survival benefit of 5.4 % (5/92) vs 20% (17/84), p=0.013 *(https://cattendee.abstractsonline.com/meeting/9307/presentation/3933)*

NAFLD is associated with COVID-19 progression; OR of 6.4 (95% CI: 1.5-31.2) and obesity in NAFLD is associated with a 6-fold increased risk for severe COVID-19. NAFLD, particularly those with higher non-invasive fibrosis scores; diabetes and obesity; should be considered high risk for COVID-19.*(Clin Liver Dis 2020;15(5):195)*

Immunosuppressed patients have higher SAR-CoV-2 viral titres and prolonged viral shedding.
There is a dichotomous relationship between corticosteroids and COVID-19, whilst individuals already taking corticosteroids may be at an increased risk of adverse outcomes from COVID-19, those with established severe COVID-19 disease seem to paradoxically benefit from corticosteroid introduction. Immunosuppression including in liver transplant recipients, should not be reduced in an attempt to reduce the risk of COVID-19. The usual indications to reduce immunosuppression apply: increasing lymphopenia, or bacterial/fungal superinfection in cases of severe COVID-19.
There is no contraindication to the use of low molecular heparin (LMWH) in hospitalised cirrhotics with COVID-19, but it is unclear whether cirrhotics should receive early treatment with enhanced or therapeutic anticoagulation. In terms of more detailed guidance regarding management of individuals with CLD and liver transplants, both EASL and AASLD have excellent guidance documents *(AASLD COVID-19 Guidance 25 June 2020; EASL JHEP Reports 26 July 2020)* and the SECURE-Cirrhosis and COVID-Hep registries provide up-to-date outcomes for CLD and liver transplantation.
Wendy Spearman

Alcohol Associated Liver Disease (AALD)
Mark Sonderup

AALD is a clinico-pathological spectrum of disease, all associated with significant consumption of alcohol and potentially modified by co-factors such as concomitant iron overload or chronic viral hepatitis.[1] The basic liver injury of chronic alcohol use is steatosis. With continued use, some develop alcoholic steatohepatitis or alcohol associated hepatitis with progressive fibrosis and ultimately cirrhosis and its incumbent complications. Pathologically the process from steatosis to steatohepatitis to fibrosis is not linear and all pathologies can co-exist (see figure 1). The drivers of who develops progressive disease and who does not is complex, but the gut and its interplay with the liver is central to the pathological processes.[2] Increased gut permeability secondary to alcohol and other factors, drives enhanced translocation of bacterial products and other pro-inflammatory factors into the portal system.[3] Upstream this activates cytokine driven Kupffer cell activation and inflammation both within the liver and systemically. Progressive liver fibrosis through stellate cell activation drives fibrosis progression to cirrhosis.

A simple but important clinical aspect when assessing a patient with AALD is liver size. Hepatomegaly in the setting of AALD implies the presence of steatosis (±hepatitis). Irrespective of the degree of fibrosis, the presence of steatosis, to an extent represents a degree of ''reversibility'' provided sustained abstinence is achieved. However in those who present with alcohol associated hepatitis, the prognosis becomes more problematic independent of liver size. In this scenario, consideration must be given to additional therapeutic interventions that can offset the excess mortality associated with alcohol associated hepatitis. These patients invariably present with a ''systemic inflammatory response'' type syndrome with fever, neutrophilia, jaundice, coagulopathy and possible encephalopathy.[4] Differentiating this from sepsis is difficult and appropriate cultures and sepsis markers need to be sent to the laboratory. This syndrome and its ensuring mortality was first described in 1966 with a 1 month mortality of 33%.[5] Given the exuberant inflammatory nature of alcohol associated hepatitis, Maddrey published his ''Discriminant Function'' in 1978.[6] A score above 32 and the 1 month use of prednisone at 40mg daily was associated with an improved short term outcome. Steroid use was contraindicated in untreated sepsis and in those with GI bleeding.

The use of steroids has been controversial given the excess

risk of sepsis consequent to its use. Equally, pentoxifylline as an alternative, despite its theoretically potential benefits, given its mechanism of action (anti-TNF), has demonstrated conflicting results in non-randomized trials. Almost 50 years after the first publication of alcoholic hepatitis, the STOPAH (Steroids Or Pentoxifylline in Alcoholic Hepatitis) study was published.[7] It was the first randomized control trial 4 arm study with placebo, prednisone only, pentoxifylline only and prednisone and pentoxifylline arms. Outcome supported the use of prednisone with no benefit over combination therapy. However the mortality benefit was short term viz. 28 days with no difference in benefit beyond that. Overall mortality at 3 months was 29%. This short term mortality benefit was at the expense of excess infection risk and per protocol those with GI bleeding, infection or renal insufficiency were excluded. A more recent meta-analysis suggested a role for steroids but emphasized that the mortality benefits are limited to the short term and is lost beyond 6 months.[8]

A more concerning aspect of STOPAH is the quantum of patients who continued to drink with only 37% abstinent at 1 year. It is evident that despite the need for better therapies, the issue of alcohol excess is more transversal and patients require intensive intervention and support to maintain abstinence. Newer therapies for alcohol associated hepatitis are needed. Data on the use of GM-CSF has been incongruent and newer data from randomized control trials of the use of IL-1 receptor antagonist, anakinra together with GM-CSF or zinc supplementation versus prednisone is awaited. Targeting of other inflammatory mediators such as IL-22 and ASK-1 is also underway.

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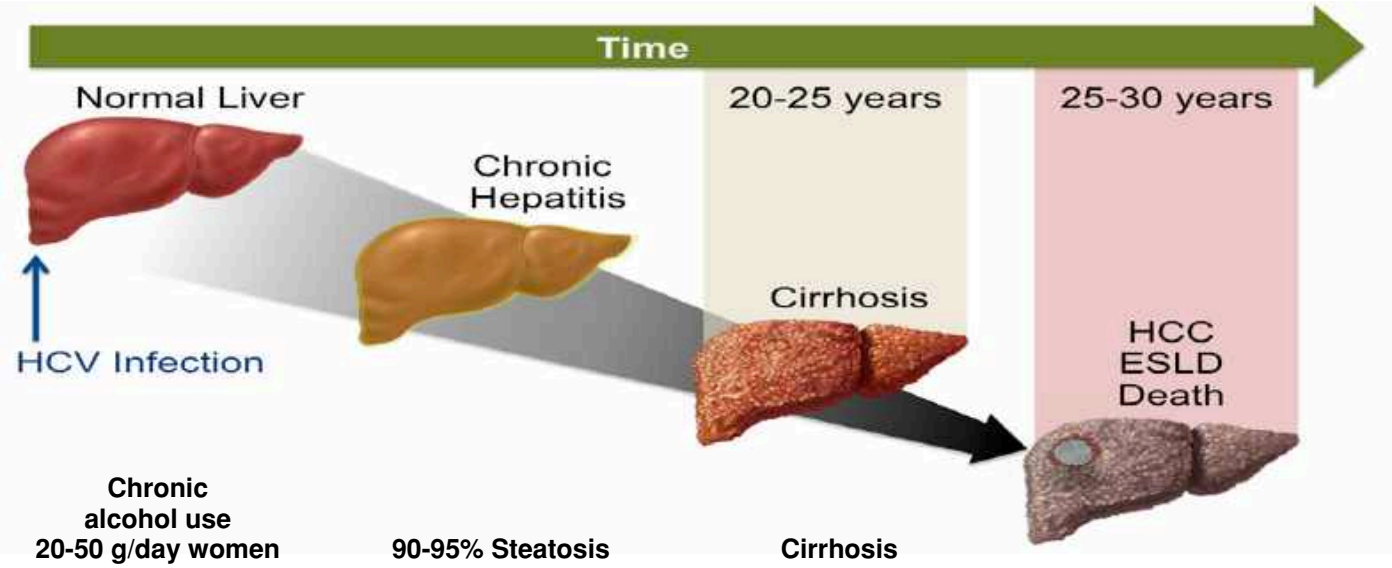
Figure 1. The clinico-pathological spectrum of alcohol associated liver disease



The Solly Marks Scholarship

PURPOSE

The purpose of the award is to honour the memory of Professor Solly Marks by recognizing clinicians or researchers of distinction in the field of gastroenterology/hepatology on an annual basis. This is an educational grant that is to be used for the upskilling of an individual and that will benefit the general good of gastroenterology in South Africa, as Prof Marks would have wanted. It is not to be used as a top up fund, but rather for a specific endeavour.

IF AWARDED, GRANT FUNDING MAY BE USED FOR:

1. A finite research project.
2. Buying out of time from teaching or clinical responsibilities to enable the nominee to make substantial headway in a large research project or to complete a Masters or PhD.
3. Paying for research assistance.
4. Supporting a period of travel for research purposes (in or outside South Africa).
5. Conference attendance.
6. Attending a gastroenterology/hepatology course, which will advance the nominee's skills.

BUDGET

The funding level is up to a maximum of R 100 000 per award, which must be fully accounted for by the end of the grant period.

ELIGIBILITY

1. Nominations will only be accepted from members of SAGES in good standing for at least a year.
2. Nominations from trainees/ fellows in formal GIT fellowship posts will be considered. However, the project should be completed before the end of the gastroenterology/hepatology fellowship.
3. Researchers/ basic scientists in the field of gastroenterology or hepatology will be eligible.

SUBMISSION PROCESS

There is no application template for this funding opportunity. All applications must be typed. Applicants' written motivation should include:

1. A CV.
2. A letter of motivation indicating the applicant's specific intended use of the award.
3. If applying for an educational activity, proof of that activity must be submitted (e.g. letters of invitation, advertising brochures etc). If the educational activity is attendance of a conference, this will only be funded if the individual is presenting an abstract and *will not be funded retrospectively*.
4. If applying for a research project, a proposal must accompany the application, including a budget.
5. Applications for research projects that have ethics approval will have an advantage.

DEADLINES AND MEETING DATES

Applications will be considered once a year.
Deadlines for submission of applications must be sent to Karin Fenton at karin.fenton@uct.ac.za no later than January 15th 2021.
The academic sub-committee which meets before the SAGES meeting will decide on the recipient based on the merits of the proposal. Outcome dates: Scholarships to be announced in February 2021

CONDITIONS

1. The grant will only be paid once proof of ethics approval has been received. Should the study not be commenced within one year of the grant being awarded, the grant is to be returned.
2. The successful applicant will be required to submit a report to the committee before the SAGES meeting in the following year after the award.
3. Any publications emanating from such funding must acknowledge the Solly Marks Scholarship.

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SAGES Virtual Conference 2020 Abstracts - 6th August

Review: Ebstein-Barr Virus (EBV) status in Inflammatory Bowel Disease patients attending Out Patients at Tygerberg Hospital

DJJ Claassen, MS Gabriel, KM Coovadia, A Abdesalam, R El Fleet, O Etwati

Introduction: Ebstein-Barr Virus(EBV) infection has a wide variety of potentially life-threatening clinical manifestations in Inflammatory Bowel Disease(IBD) patients, such as lymphoproliferative disorders, gastric and esophageal cancers. Regular testing and screening for EBV in IBD patients are not routinely done even though it is described as a proposed trigger in the ethiopathogenesis of IBD. An increased risk for EBV related complications exist in patients on immunomodulators such as the Thiopurines. Routine screening for EBV remains very low and we tried to determine the prevalence of EBV infection in our IBD cohort.

Method: A retrospective folder review of IBD patients attending Tygerberg Hospitals IBD clinic between April – June 2020 was done. EBV status, treatment regimen, colonoscopy reports and routine blood results done, were recorded.

Results: 120 patient folders were reviewed. Crohn's Disease was the most common disease(63%) amongst our patients and EBV screening was done on 40 patients. All tested patients were on Azathioprine. Patients on biologic therapy showed no positive EBV serology. 25% of tested patients had active EBV status, but very few had evidence of active colitis on endoscopy(1/10). There was no correlation between C-reactive Protein and EBV status.

Conclusion: IBD patients who previously tested positive for EBV have an increased risk for developing treatment related complications like lymphoma when commenced on immunosuppressive therapies like thiopurines. In keeping with International guidelines, EBV screening should be done on all IBD patients being commenced on immunosuppressive therapy.

Syphilitic Hepatitis

M Ben Hkouma[1], Yusuf Moolla[1], VG Naidoo[1], KA Newton[1]

[1] Department of Gastroenterology, Nelson R Mandela School of Medicine, University of KwaZulu-Natal, Inkosi Albert Luthuli Central Hospital, Durban

Introduction: Syphilis is well known to have protean manifestations. Herein we describe a patient who presented with jaundice secondary to syphilitic hepatitis.

Case Report: A 25-year-old HIV positive woman on anti-retroviral treatment since 2017 (CD4 = 700 cells/mm^3) presented with a one-month history of jaundice and was referred for an ERCP. A maculopapular rash on the palms and soles and focal alopecia was noted by the endoscopist. Due to the absence of biliary dilatation on liver ultrasound and clinical findings, the ERCP was not undertaken. There was no history of alcohol or use of any medication except anti-retroviral treatment. There was no hepatosplenomegaly or ascites. Liver function tests showed a mixed picture (ALT 120U/L, AST 109U/L, ALP 459U/L, GGT 102U/L) with a total bilirubin of 135umol/L. Tests for viral hepatitis and autoimmune hepatitis were negative. The Rapid Plasma Reagent (RPR) was positive (titre 1:32) and TPHA was also positive. Liver histology showed periportal and centrilobular focal necrosis and bile duct inflammatory infiltrates. These features were in keeping with syphilitic hepatitis despite absence of spirochaetes. Following three doses of benzathine penicillin, there was a significant improvement in the liver function test.

Conclusion: The clinical presentation of syphilis in patients coinfected with HIV is not well defined. Syphilitic hepatitis occurs in the secondary phase but is a rare clinical manifestation. Awareness of the cutaneous manifestations alerted the endoscopist to this unusual diagnosis and avoided unnecessary ERCP. This case highlights an unusual cause of jaundice and emphasizes the importance of the clinical assessment before undertaking endoscopic procedures.

Demographic, Endoscopic and Histological Profile of Esophageal Cancer in the Gastroenterology Service of the Central Hospital of Maputo from January 2016 to December 2018

Muhammad Ismail*[1] ; Liana Mondlane[1] ; Michella Loforte[1]; Luzmira Dimande[1] ; Sheila Machatine[1] ; Roqueia Cumbane[1] ; Ema Nassone[1]; Regina Jorge[1] ; Gany Mussagi[1] ; Óscar Pérez[1]; Carla Carrilho[2], Jahit Sacrlal[3] & Prassad Modcoicar[1]

[1] Gastroenetrology Unit (Maputo Central Hospital)
[2] Pathologic anatomy unit (Maputo Central Hospital)
[3] Faculty of medicine (Eduardo Mondlane University)

Background: Esophageal cancer (EC) is a major public health problem in Mozambique and is on the list of major causes of morbidity and mortality. It is the seventh most common cancer worldwide in terms of incidence (572.000 new cases / year), and sixth in overall mortality (509.000 deaths/year), with over 80% of all cases and deaths occurring in developing countries. In Mozambique esophageal cancer was the seventh most common cancer in males and the fifth in females between 1991 and 2008.

Objective: To analyze the demographic, endoscopic and histological profile of esophageal cancer patients observed at the Gastroenterology Service of Maputo Central Hospital in the last 3 years (2016-2018).

Methodology: It was done a cross-sectional hospital-based epidemiological study using retrospective primary data focusing on demographic aspects and endocopic and histological findings. A retrospective analysis of the existing information of patients classified as esophageal cancer diagnosed with upper gastrointestinal endoscopy (UGE) observed from January 1, 2016 to December 31, 2018 at the Maputo Central Hospital Gastroenterology Service.

Results: Of the 205 cases included in the study, there was a higher frequency of females with 56.6% (116/205). The average age was 59.5 years with standard deviation of ± 12.9 years. Most of the patients in this study were native to southern Mozambique, with 92.7% (190/205), of which Maputo made up 53.2% (109/205). Regarding race, 99.5% (204/205) were black. The most affected endoscopic location was the middle third with 48.8% (100/205), followed by the lower third with 29.8% (61/205) and the upper third with 21.5% (44/205). Squamous cell carcinoma was the most frequent, with 92.7% (190/205), followed by adenocarcinoma with 4.9% (10/205).

Conclusion and recommendation: Due to the high number of observed cases of esophageal cancer, a high degree of clinical suspicion is needed for timely diagnosis and more effective treatment. Updated incidence studies are needed throughout the country to understand the true impact of esophageal tumors on the Mozambican population.

Key words: Esophageal cancer, Scamous cell carcinoma, Adenocarcinoma, Upper digestive endoscopy, epidemiology.

Paediatric Acute Liver Failure; A retrospective review from a South African Tertiary Centre

R Mlotha Mitole, E Goddard, R De Lacy

Background: Acute liver failure describes a fatal clinical syndrome resulting from extensive loss of functional parenchymal liver mass due to severe liver damage, triggered by various factors. Early recognition and initiation of specific therapy may improve outcomes and reduce the need for liver transplantation, a treatment modality not universally available in resource constraint areas. There is paucity of data describing this syndrome in Sub-Saharan Africa in children.

Objectives: This study aims to retrospectively review and determine the clinical presentation, aetiology, complications & outcome of acute liver failure in children admitted at the Red Cross Children's Hospital (RCWMCH).

Methods: Retrospective review of all records of children under 13 years admitted at the RCWMCH from January 2005 to December 2016 with acute liver failure, meeting inclusion criteria, after obtaining ethical approval. Demographic variables, clinical presentation and investigations were captured, with determination of outcomes at 6 weeks of diagnosis.

Results: Study included 24 children, age range varied from 0.2 months to 135 months (Average 25.6 months) Diarrhoea, jaundice, respiratory distress, hepatomegaly and encephalopathy were common clinical features. Aetiology was infection in 33.3 % of cases (n=8, 2 of whom had autoimmune hepatitis comorbidity) and hepatitis A was most common infectious cause (n=4, 50%). Causes were indeterminate in 29.2%. Two patients had autoimmune hepatitis without co-morbidity; Reye syndrome 12.5% and 17% had miscellaneous causes.

Conclusion: Viral hepatitis A is the leading infective cause of acute liver failure in this study cohort and 29.2% of cases were indeterminable. INR >4 and Bilirubin > 210umol/l were predictors of poor outcome. Follow up study is recommended to better understand clinical spectrum and outcomes of children with acute liver failure in this setting.

Gaucher Disease in Adolescent in Maputo Central Hospital – Case Report

E Nassone[1], M Ismail[1], I Jone[2], F Fernandes[2], F Pinto[3], L Madeira[3], R Giugliani[4], M Loforte[1], R Victor[1], A Gany[1], R Cumbana[1], L Mondlane[1], O Perez[1], P Modcoicar[1]

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[2] Pathological Anatomy Service – Hospital Central de Maputo, Mozambique
[3] Medical Genetic Service – Hospital Central de Maputo, Mozambique
[4] Medical Genetic Service – Hospital das Clinicas de Porto Alegre, Brazil

Introduction: Gaucher disease is a rare autosomal recessive disease that affects up to 1 in 40,000 live births in the general population. It is caused by low levels of glucocerebrosidase (GCase), an enzyme that breaks down a fatty chemical in the body called glucocerebroside resulting in fat-laden Gaucher cells build up in areas like the spleen, liver and bone marrow. A standard blood test for diagnose is a beta-glucosidase leukocyte (BGL) test to evaluate the enzyme activity, however most physicians are unfamiliar with Gaucher disease with makes early diagnosis difficult. The basis of treatment is enzyme replacement therapy (ERT) and substrate reduction therapy (SRT). Gaucher disease is divided in 3 distinct types based on the neurological features. Neurological involvement plays a key part in the prognosis and life expectancy of these patients.

Methods: 15-year-old female, black, with a history painless abdominal distension, insidious onset. At examination abdomen were distended with grade 4 splenomegaly. Analytically she had anaemia (9.1g/dL) and low platelet count (127). Negative for HIV, syphilis and hepatitis B and C. Abdominal ultrasonography and CT scan revealed homogeneous hepatosplenomegaly. She underwent total splenectomy due to hypersplenism which spleen cytology revealed probable Gaucher cells and immunohistochemistry was positive for CD68. Hepatic biopsy was performed due to abdominal asymmetrical onset growth on the right hypochondria with cytology revealed probable lysosomal storage disorder compatible with Gaucher disease. Biochemical investigation for Gaucher disease confirmed an enzyme deficiency coupled with the accumulation of lyso-Gb1 compatible with Gaucher disease.

Results: The patient was classified as Gaucher disease Type 1 and is currently in an evaluation process to undergo for treatment.

Discussion: Gaucher disease is a rare disease and it is difficult to diagnose in low in-coming countries as Mozambique. The Type 1 Gaucher disease is treatable but the drugs are not available in the National Health System. It is essential manage this cases in a multidisciplinary team with one geneticist or Gaucher specialist who can monitor and make adjustments to the treatments as necessary. This is the second case diagnosed in Mozambique, which is the reason was decided to share this case in order to have subsidies on the management protocols.

Hepatitis A virus infection in a patient with Crohn's disease

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Introduction: There is a paucity of literature with regard to Hepatitis A virus (HAV) infection in patients with inflammatory bowel disease (IBD). Herein we describe a case of severe HAV infection in a patient receiving azathioprine and infliximab for Crohn's disease.
Case presentation: A 46yr old man with ileo-colonic Crohn's disease since 1997 had a right hemi-colectomy for a contained perforation in 2003. He was subsequently managed with azathioprine and infliximab. He presented with jaundice in November 2019, as a result of acute HAV infection. Initial liver function tests were as follows: Total bilirubin: 142umol/L, ALP: 204U/L, GGT 731U/L, ALT: 1913U/L, AST: 2154U/L. There was no history of HAV vaccination. Despite cessation of medication, there was a prolonged cholestatic phase following a gradual decline in transaminases over the next six months. A moderate increase in stool frequency was reported. This was conservatively managed and re-initiation of IBD treatment was deferred while awaiting improvement in liver tests.

Conclusion: This case describes HAV infection in an IBD patient on medications that have potent effects on the immune system. HAV screening and vaccination of IBD patients should be considered at the time of diagnosis in endemic regions. For IBD patients that develop acute HAV while on treatment, the appropriate management strategy will most likely need to be individualised.

Poorly Differentiated Squamous Cell Carcinoma of the Stomach - A Rare Case

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Introduction: Gastric carcinoma is one of the most frequent causes of death worldwide, with adenocarcinoma being the most prevalent type with more than 90%. The epidermoid variant is very aggressive, extremely rare and has an incidence between 0.04 to 0.7% worldwide. It is more frequent in

men over 60 years old, with a 3:1 ratio. The pathogenesis is uncertain, several theories relate to chronic damage to the gastric mucosa by corrosive acids, congenital syphilis or prolonged ingestion of cyclophosphamide, predisposing to epidermoid metaplasia. The short-term prognosis is poor compared to gastric adenocarcinoma, with an overall 5-year survival of less than 10%.

Aim: Present a clinical case of atypical localization of gastric squamous cell carcinoma.

Methods: 69-year-old patient, male, with 2 month history of progressive epigastric pain, associated with postprandial vomiting, weight loss and asthenia. At examination, he was cachectic, jaundiced and pale. Abdomen was distended, with ascites, painful at epigastric palpation.

Analytically CA19.9: 24.12, HBSAg and HCVAc negative. Upper endoscopy showed near the esophagogastric junction, an ulcerated nipple-like lesion, extending to the small curvature of the stomach. Biopsy was taken. Histology was compatible with poorly differentiated squamous cell carcinoma.

Results: He evolved with clinical worsening and died on the 6th day after histological confirmation.

Conclusion: Gastric squamous cell carcinoma, is a rare pathology, and it is imperative to have a high degree of clinical suspicion in elderly patients with alarm signs.

Social and demographic profile of inflammatory bowel disease at Maputo Central Hospital between 2016 – 2018

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Introduction: Inflammatory bowel disease is a heterogeneous group of pathologies that include: Ulcerative colitis, nonspecific colitis and Crohn´s disease. It has an idiopathic etiology. Genetic susceptibility, immune response and environmental factors play an important role in the pathogenesis, affecting approximately 1.4 million people in the United States and 2.2 million in Europe. South Africa and Australia have an intermediate impact. It is important to know its prevalence, to raise a diagnostic suspicion and thus have a timely therapeutic approach to prevent serious complications.

Aim: Describe the demographic profile of inflammatory bowel disease at the Maputo Central Hospital, from 2016 to 2018. Raise awareness about the early diagnosis of this entity, which is an important risk factor for the development of colorectal cancer.

Methods: This is a retrospective, descriptive, quantitative, hospital-based study at the Maputo Central Hospital over a period of 3 years (2016 to 2018). A database of histological results from endoscopic biopsies performed on patients with suspected inflammatory bowel disease was evaluated on an Excel spreadsheet, and the frequency of variables such as age, sex and type of inflammatory disease was checked. In the age group from 16 to 75 years old, 22 cases of inflammatory bowel disease were diagnosed. Of the diagnosed cases, 21 were of ulcerative colitis, 1 of Crohn´s disease. There was a significant difference in terms of gender, with males being the most prevalent in the 3 years (15/7). The average age was 49.9 years old, with standard deviation +- 18.4 years.

Conclusion: This is the first study on inflammatory bowel disease in Mozambique. In some regions of the world where inflammatory bowel disease was rare, although still low compared with western countries, incidence is rising dramatically. The early diagnosis of inflammatory bowel disease is important due to the high malignant potential of this entity. In this study, we found a low frequency of inflammatory bowel disease, which is in line with epidemiology in Africa. Larger epidemiological studies and establishment of local and regional registries are needed, and all of this will require greatly increased access to endoscopy and histology services.