1

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Recommended by guidelines for the prevention of HE recurrence[4,5]

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Abridged Prescribing Information. Dirifa Rifaximin Tablets 200 / 400 / 550mg. Each film Coated Tablet Contains: Rifaximin Ph. Eur. 200/ 400 / 550mg. Indications: Travelers/Infectious Diarrhea: Rifaximin 200 mg is indicated for the treatment of infections diarrhea in adults. Limitation of use: Rifaximin should not be used in patients with diarrhea complicated by fever or blood in the stool or diarrhea due to pathogens other than Escherichia coli. Hepatic Encephalopathy: Rifaximin 400 mg for the treatment of Hepatic encephalopathy. Rifaximin 550mg for reduction in risk of overt hepatic encephalopathy (HE) recurrence in patients ≥18 years of age. Dosage and Administration: Dosage for Travelers/Infectious Diarrhea: Recommended dose of rifaximin is one 200 mg tablet taken orally three times a day for 3 days. Rifaximin can be administered orally with or without food. Dosage for Hepatic Encephalopathy: The recommended dose of Rifaximin is 400mg tablet taken orally three times a day with or without food. One 550 mg tablet two times a day, with or without food. Contraindications: It is contraindicated in patients with hypersensitivity to Rifaximin, any of the Rifamycin antimicrobial agents, or any of the excipients. Hypersensitivity reactions include exfoliative dermatitis, angioneurotic edema and anaphylaxis. Warning: Rifaximin was not found to be effective in patients with diarrhea complicated by fever and/or blood in the stool or diarrhea due to pathogens other than Escherichia coli. Discontinue Rifaximin if diarrhea get worse or persist more than 24-48 hours and alternative antibiotic therapy should be considered. Clostridium difficile associated diarrhoea has been reported with nearly all antibacterial agents including Rifaximin. Development of drug-resistant bacteria. Severe (Child-Pugh C) Hepatic impairment: Caution should be exercised when administering Rifaximin to patients with Severe Hepatic impairment (Child-Pugh C). Precautions: Safety and efficacy has not been established in patients aged < 12 years with 200 mg. Pregnancy and lactation: Pregnancy category C. It is not known whether rifaximin is excreted in human milk, a decision should be made to discontinue nursing or to discontinue drug, taking into account the importance of the drug to the mother. Geriatric use: No overall differences in safety or effectiveness were observed between responses between the elderly (patients aged 65 years or above) and younger patients, but greater sensitivity of some older individuals cannot be ruled out. Renal impairment: The pharmacokinetics of Rifaximin in patients with impaired renal function has not been studied. Hepatic impairment: No dosage adjustment is recommended because rifaximin is presumably acting locally. Nonetheless, caution should be exercised when rifaximin is administered to patients with severe hepatic impairment. Overdosage: No specific information available on the treatment of overdosage with Rifaximin. In the case of overdosage, discontinue Rifaximin Tablets, treat symptomatically, and institute supportive measures as required. Storage: store in a cool and dry place. Keep out of reach of children. Manufactured in India by: Lupin Limited, 4th Mile, Bhasmey, Karmarey- Bhasmey Block, Duga Ilaka, East Sikkim, Sikkim- 737132, India Marketed by: Abbott India Limited, Angel Space, Lifestyle Bldg. No D4, Gala No 7 to 10 & 17 to 20 Gr. Floor, 107 to 110 & 117 to 120, First Floor, Pimplas Village, Bhiwandi, District Thane, Tal: Bhiwandi – 16 (Thane Z5) 421302 Maharashtra, India

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Latest concepts in inpatient hepatic encephalopathy management

Thoetchai (Bee) Peeraphatdit, Patrick S. Kamath, Michael D. Leise

Abbreviations

ACLF	Acute-on-chronic liver failure
BCAA	Branched-chain amino acids
CLIF-C ACLF	Chronic Liver Failure Consortium ACLF Score
DAMPs	Damage-associated molecular patterns
ESPEN	European Society for Parenteral and Enteral Nutrition
FDA	Food and Drug Administration
HE	Hepatic encephalopathy
IL	Interleukin
LOLA	L-ornithine L-aspartate
LT	Liver transplant
MARS	Molecular adsorbent recirculating system
MELD	Model for end-stage liver disease
PAMPs	Pathogen-associated molecular patterns
RCT	Randomized controlled trial
TIPS	Transjugular intrahepatic portosystemic shunt

Patient Scenario 1

A 35-year-old female with past medical history of compensated alcoholic cirrhosis presented with altered mental status after alcohol binge drinking. On physical exam, her vital signs were stable. She was only oriented to self and had marked jaundice and asterixis. Her laboratory result showed leukocyte count of 15×10^9/L, creatinine of 5.7 mg/dL (with baseline of 1.0 mg/dL), aspartate aminotransferase of 288 U/L, alanine aminotransferase of 119 U/L, alkaline phosphatase of 383 U/L,

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total bilirubin of 28.6 mg/dL, direct bilirubin of 23.8 mg/dL, and International normalized ratio of 3.1. Urinalysis showed pyuria and urine culture showed *Escherichia coli* >100,000 cfu/mL. She was diagnosed with hepatic encephalopathy (HE), urinary tract infection, severe alcoholic hepatitis, and acute-on-chronic liver failure.

Discussion

This patient had hepatic encephalopathy in a setting of acute-on-chronic liver failure (ACLF) given that she had acute renal injury as an extrahepatic organ failure. Patients with HE in the context of ACLF had a heightened risk of mortality compared to isolated HE. Thus, early detection of extrahepatic organ failure was vital for risk stratification purposes and to determine the need for organ support. Intensive care unit admission should be considered as she was likely to require renal replacement therapy. In addition, she would require treatment for severe alcoholic hepatitis and urinary tract infection, the precipitating factors for hepatic encephalopathy.

Patient Scenario 2

A 66-year-old female with decompensated nonalcoholic steatohepatitis cirrhosis and chronic kidney disease presented with worsening altered mental status for 2 days. She had compliant with the maintenance lactulose regimen that had been started after one prior episode of precipitated HE. Her vital sign demonstrated slight tachycardia with heart are of 114/min with normal blood pressure of 145/77 mmHg. Her oxygen saturation is 95% on room air. She was awake but confused and not able to answer any questions. Asterixis was noted. The white blood cell count was 8.5×10^9/L and the creatinine was at her baseline of 1.7 mg/dL. The microscopic urinalysis showed >50 white blood cells/high power field and the urine culture was positive for *Escherichia coli*.

Discussion

Because the patient did not have any other evidence of extrahepatic organ failure other than hepatic encephalopathy, she was diagnosed with isolated hepatic encephalopathy. Because she had recurrent episode of hepatic encephalopathy while on lactulose, rifaximin was added. In addition, the urinary tract infection which was the precipitating factor was treated.

Patient Scenario 3

A 65-year-old male with decompensated nonalcoholic steatohepatitis cirrhosis, model for end-stage liver disease (MELD) score of 13, was admitted with persistent hepatic encephalopathy. He had multiple previous admissions for episodic overt hepatic encephalopathy and no precipitating factors were identified. His examination was consistent with the West Haven Criteria (WHC) Grade 3 HE. He did not respond to lactulose, rifaximin, and zinc therapy. Computed tomography of the abdomen with intravenous contrast demonstrated a large splenorenal shunt.

Discussion

The patient should be considered for splenorenal shunt embolization for persistent HE not responding to medical treatment and relatively low MELD score (MELD <15). Previous studies showed that approximately 45–70% of patients with refractory HE had large portosystemic shunts discovered on evaluation and that the embolization of the portosystemic shunt was a safe and effective treatment. The patient received the embolization of the splenorenal shunt and his hepatic encephalopathy significantly improved.

Introduction

Hepatic encephalopathy (HE) is a major neuropsychiatric abnormality seen in patients with decompensated cirrhosis or portosystemic shunting. The clinical presentation ranges from subtle brain function changes that require neuropsychometric testing for diagnosis to a hepatic coma state. The severity of HE can be graded into covert HE (West Haven Criteria Grade 0–1) and overt HE (West Haven Criteria Grade 2–4). Most patients with overt HE will require inpatient management and this will be the focus for this chapter.

Overt HE occurs in approximately 30–45% of patients with cirrhosis and 10–60% of patients with transjugular portosystemic shunt (TIPS) [1–3]. In the U.S. Nationwide Inpatient Sample, the National estimate of annual incidence of overt HE admission is 110,000–115,000. The average length of inpatient stay was 8.5 days and the average total inpatient charges were $63,108 per case [4]. Moreover, overt HE is associated with increased risk of mortality in hospitalized patients with cirrhosis independently of the severity of cirrhosis (adjusting for the MELD score) [5] or extrahepatic organ failures [6].

Management of the hospitalized patient with overt HE focuses on correcting the underlying precipitating factors and providing pharmacologic treatment that reduces ammoniagenesis. Most patients will require maintenance medication to prevent recurrence of HE and to prevent hospital readmission.

Hepatic Encephalopathy in Acute-on-Chronic Liver Failure

For the past two decades, the concept of acute-on-chronic liver failure (ACLF) has been proposed on the basis that patients with chronic liver disease or cirrhosis who developed acute unexpected hepatic decompensation and extrahepatic organ failure have significant increased risk of short-term mortality [7]. Three different definitions have been proposed from three different regions of the world [8–10]. The most current definition by a working group on behalf of the Working Party of the World Gastroenterology Organization is as follows: "ACLF is a syndrome in patients with chronic liver disease with or without previously diagnosed cirrhosis which is characterized by acute hepatic decompensation resulting in liver failure (jaundice and prolongation of the international normalized ratio) and one or more extrahepatic organ failures that is associated with increased mortality within a period of 28 days and up to 3 months from onset" [11].

The prevalence of ACLF is difficult to assess given the difference in the ACLF definition. In the European multicenter study, the prevalence among hospitalized cirrhotic patients with acute decompensation was 31% [8]. A study from the U.S. Nationwide Inpatient Sample reported ACLF prevalence of 5% among hospitalizations for cirrhosis in 2011 [12]. With the increase in ACLF recognition, there is an emerging concept that differentiates hepatic encephalopathy that occurs in the setting of decompensated cirrhosis from that arising in the context of ACLF.

Isolated Hepatic Encephalopathy

Isolated hepatic encephalopathy occurs in a setting of decompensated cirrhosis without evidence of extrahepatic organ dysfunction. Isolated hepatic encephalopathy seems to occur in older cirrhotic patients who are inactive drinkers. It is not clearly associated with hepatic dysfunction but rather develops in the setting of chronic diuretic use. There is no significant inflammatory reaction. The prognosis is good even in those requiring intensive care unit admission and mechanical ventilation for airway protection [13, 14].

Hepatic Encephalopathy Associated with Acute-on-Chronic Liver Failure

Hepatic encephalopathy associated with ACLF occurs in the setting of extrahepatic organ failures. It seems to occur in young cirrhotic patients who are active drinkers [14]. This type of HE is associated with hepatic dysfunction and bacterial infections. In contrast with isolated hepatic encephalopathy, HE associated with ACLF has a grave prognosis. In addition to hyperammonemia that is observed in both types of HE, the significant inflammatory reaction found in ACLF may explain this prognostic gap [15].

Pathophysiology of Hepatic Encephalopathy in Acute-on-Chronic Liver Failure

In this chapter, we focus on the pathophysiology of HE in the setting of ACLF. Jalan et al. proposed the pathophysiology of ACLF using a four-part model of predisposing event, injury resulting from precipitating event, response to injury, and organ failure (Fig. 1) [7, 16]. Predisposition is the underlying chronic liver disease. Injury can be from multiple etiologies, e.g., bacterial infection, alcohol intake, viral hepatitis, reactivation of hepatitis B, gastrointestinal bleeding, drug-induced liver injury, ischemia, infection, or surgery. The inflammatory response is important as suggested by the presence of increased C-reactive protein and an increase in leukocyte count. In the setting of bacterial translocation, lipopolysaccharide and other pathogen-associated molecular patterns (PAMPs) trigger Kupffer cells to release proinflammatory cytokines, namely IL-1, IL-6, and tumor necrosis factor alpha, which induce inflammatory reaction by leukocyte recruitment and oxidative stress. In addition to bacterial translocation, sterile processes such as alcohol, ischemia, or surgery can elicit an inflammatory response by damaging hepatocytes and with subsequent release of damage-associated molecular patterns (DAMPs) (Fig. 1). Organ failure is the final step

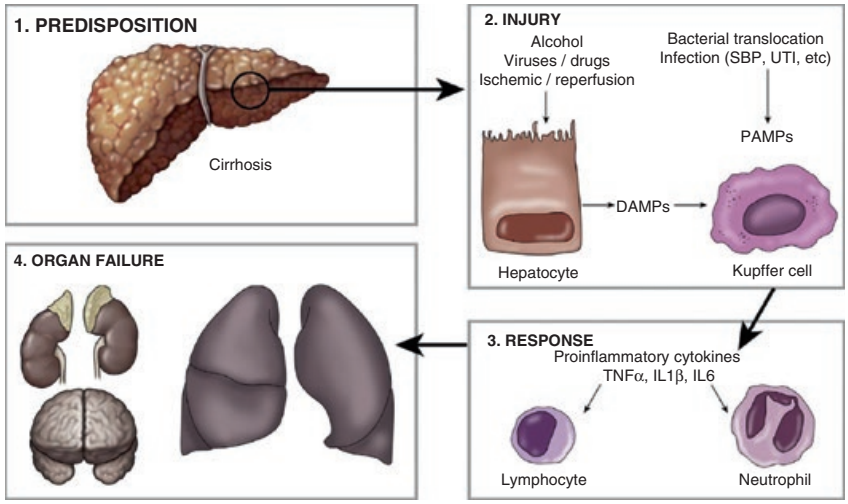

Fig. 1: Pathophysiology of ACLF. Asrani et al. [7]. *PAMP* pathogen-associated molecular pattern, *SBP* spontaneous bacterial peritonitis, *TNF* tumor necrosis factor, *UTI* urinary tract infection

of the pathway. An increase in the number of organ failure is associated with increase in the mortality rate [8].

The pathophysiology of HE in ACLF is multifactorial and hyperammonemia and systemic inflammation are important factors [2]. Studies in animal models have shown that induction of hyperammonemia leads to brain edema and the reduction of ammonia level could reduce brain swelling [19]. In addition, reduction in ammonia level prevented brain edema and delayed the development of coma in response to LPS challenge in an animal model [20]. Clinically, HE associated with ACLF may lead to cerebral edema and increased intracranial pressure whereas isolated hepatic encephalopathy typically will not [21]. Cerebral edema has been observed in imaging studies [22] and confirmed by electron microscopic studies in animal models showing astrocyte swelling and collapsed microvessels [23].

Management of Hepatic Encephalopathy in the Hospitalized Patient

General Approach

Early risk stratification to differentiate isolated HE from HE associated with ACLF is necessary (Fig. 2). This is due to the significant difference in short-term mortality between these two groups [14]. Prognostic scores including the chronic liver failure-sequential organ failure assessment (CLIF-SOFA) score may be utilized to determine the severity of ACLF [8]. If HE associated with ACLF is detected, intensive care unit admission should be considered. Airway protection should be considered in all patients with grades 3–4 HE, particularly those with ACLF, or if there is evolving respiratory failure. Inotropes or vasopressors should be considered to maintain adequate cerebral perfusion.

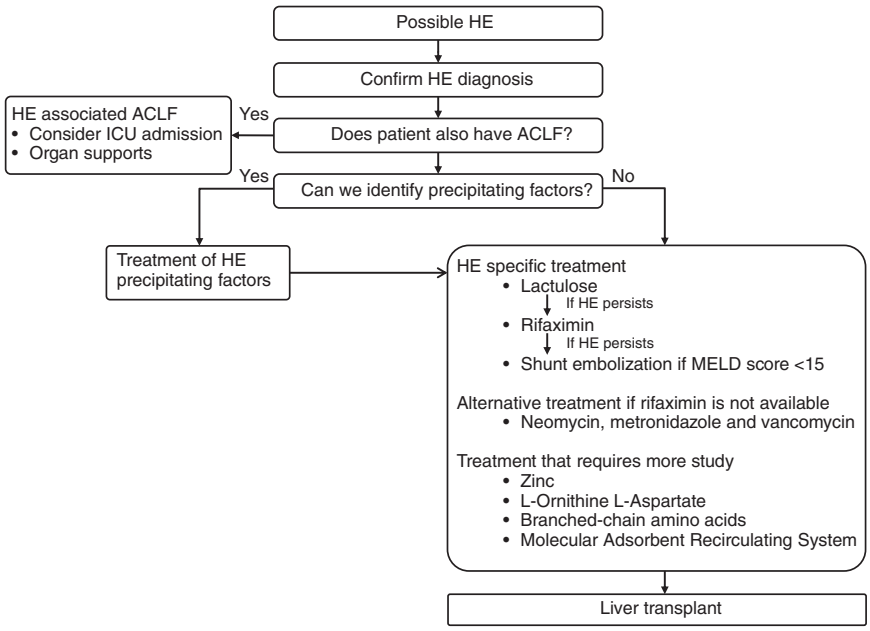

Fig. 2: Management of hospitalized patients with hepatic encephalopathy.

In addition to the treatment of HE that is present at hospital admission, there is also a potential benefit from preventing the progression of HE. In a study from 1,560 patients from the North American Consortium for Study of End-stage Liver Disease evaluating hospitalized patients with cirrhosis, the maximum HE grade and not the admission HE grade was found to be prognostic for mortality independently of the extrahepatic organ failures [6].

Direct Treatment at Precipitating Factors

The most common precipitating factors of HE are diuretic use, bacterial infection, and alcohol use [14]. Any identifiable precipitating event should be promptly treated and early antibiotics administration should be considered when infection is suspected.

Specific Treatment

Nonabsorbable Disaccharides

Nonabsorbed disaccharides (e.g., lactulose and lactitol) and nonabsorbable antibiotics (e.g., neomycin and rifaximin) represent the mainstay of specific treatment for HE. Lactulose (b-galactosidofructose) and lactitol (b-galactosidosorbitol) reduce ammonia absorption in the colon by acidification of the colon resulting in the conversion of ammonia to ammonium, shifting the colonic flora from urease- to nonurease-producing bacterial species, and by their cathartic effect.

A large meta-analysis in 2004 showed that nonabsorbable disaccharides were superior to placebo. However, when only high-quality trials were included, nonabsorbable disaccharides were found to have no effect on HE [24]. The inconsistent finding in this study is most likely explained by the heterogeneity of HE in previous nonabsorbable disaccharide clinical trials. For example, an overt HE episode may occur in the setting of acute liver failure, acute-on-chronic liver failure, or may be precipitated by a reversible precipitating factor [25]. Although a pivotal trial to prove its effectiveness is lacking, nonabsorbable disaccharides continue to be recommended as the first-line therapy because of decades of clinical experience supporting its effectiveness [26].

Rifaximin

Rifaximin is a rifampicin derivative and is mostly unabsorbed by the intestine. Rifaximin is Food and Drug Administration (FDA) approved only for prevention of recurrent HE based on a large multicenter randomized trial [27]. Interestingly, it was not effective in preventing HE in a setting of a transjugular intrahepatic portosystemic shunt (TIPS) [28]. For treating episodic overt HE, the data suggests that rifaximin has equivalent efficacy compared to nonabsorbable disaccharides [29–31]. Although rifaximin is better tolerated in most studies compared to lactulose, the question of using rifaximin as monotherapy for overt HE remains unanswered given the small number of trials. The use of rifaximin in addition to lactulose for overt HE is supported by a randomized controlled trial (RCT) that found a higher proportion of HE reversal in rifaximin and lactulose group compared to lactulose and placebo group (76% vs. 50.8%, $P < 0.004$) in patients with overt HE [32]. This study also reported a significant decrease in mortality in the rifaximin and lactulose group compared to lactulose and placebo group (23.8% vs. 49.1%, $P < 0.05$). However, the generalizability of this finding is limited because of the higher-than-expected mortality rate observed in the control arm (49.1%) when compared to the reported inpatient mortality due to HE in the United States (15%) [4, 33].

Neomycin, Metronidazole, and Vancomycin

Neomycin is a poorly absorbed aminoglycoside. It is used to decrease gut bacteria-derived ammonia and it is approved by FDA for use in episodic overt HE but not chronic HE. Earlier RCTs did not find difference in its efficacy when compared to lactulose [34] or placebo [35]. Neomycin was widely used in the past. However, the evidence for neomycin in episodic overt HE is weak, and its use is complicated by the risk of ototoxicity and nephrotoxicity. There are small trials supporting the short-term use of metronidazole and vancomycin [36, 37]. However, the risk of neurotoxicity and vancomycin-resistant enterococci colonization limit its long-term use.

Zinc

Zinc is important in ammonia reduction pathways both for ammonia conversion to urea in liver and for ammonia conversion to glutamine in skeletal muscle. Zinc deficiency is very common

in cirrhosis. Zinc supplement has been shown to increase the speed of urea formation from ammonia and amino acid [38]. Data to support zinc use are very limited and the results are mixed. Furthermore, previous RCTs (n = 15–90) included chronic HE in the study, thus limiting the generalizability in episodic HE setting [39–41]. The most recent RCT of 79 patients with overt HE showed that zinc supplement was effective in deceasing HE grade and blood ammonia levels [42]. This is the only recent study with evidence to support the use of zinc in HE. The optimal dose of zinc supplement remains unknown.

L-Ornithine L-Aspartate

L-Ornithine L-aspartate (LOLA) is not available in the United States, but it is frequently used for HE treatment outside the United States. The mechanism of LOLA is to increase ammonia reduction in both liver and skeletal muscle. In the liver, LOLA can increase urea formation by stimulating ornithine transcarbamylase and carbamoyl phosphate synthetase. In skeletal muscle, LOLA can stimulate glutamine synthesis. Data to support the use of LOLA are mainly in the setting of chronic HE and the efficacy of LOLA in episodic overt HE is not validated [43, 44]. One study from Pakistan evaluated LOLA as adjunctive treatment versus placebo in patients with episodic overt HE and found higher improvement rate of HE grade 2 in LOLA compared to placebo group [45].

Branched-Chain Amino Acids

Branched-chain amino acids (BCAAs) consist of valine, leucine, and isoleucine. In skeletal muscle, BCAAs are the substrate for glutamate which is used to synthesize glutamine in ammonia detoxification. The decrease in BCAA level and the increase in aromatic acids have been observed in cirrhosis and hepatic encephalopathy [46]. Studies have evaluated the effects of BCAAs, either intravenously or orally. For cirrhotic patients, two RCTs found that BCAAs improved important composite end points of death/hospitalization metrics in one study [47] and hepatic failure, variceal bleeding, hepatocellular carcinoma, and mortality in a second study [48]. In the recent meta-analysis of 16 RCTs with 827 patients with hepatic encephalopathy [49], BCAAs had a beneficial effect on hepatic encephalopathy (RR 0.76, 95% CI 0.63–0.92) but there was no difference in mortality (RR 0.88, 95% CI 0.69–1.11). Currently, the European Society for Parenteral and Enteral Nutrition (ESPEN) guideline provides a grade A recommendation for the use of BCAA-enriched enteral formula in patients with hepatic encephalopathy who require enteral nutrition [50]. For parenteral nutrition, ESPEN guideline provides a grade A recommendation for the use of BCAAs in hepatic encephalopathy grades 3 and 4 [51].

Percutaneous Embolization of Large Portosystemic Shunts

Patients with large portosystemic shunts usually present with persistent HE resulting in episodic hospital admission and coma. In some patients with HE, large portosystemic shunts are accessible

to embolization. Multiple retrospective studies have reported the efficacy and safety of the embolization of large portosystemic shunts in refractory HE [52–55]. In a European multicenter study (n = 37), 59% and 49% were free of HE at 100 days and 2 years, respectively. The HE recurrence was less in those with MELD score of 11 or less [52]. In a US series (n = 20), 100% (20/20) achieved immediate improvement and durable benefit was achieved in 92% (11/12) at 6–12 months after the procedure [55]. The overall procedural complication rate was 10%. One patient had bacterial cholangitis and another patient required readmission from pain at the puncture site. Importantly, 35% (7/20) developed evidence of worsening portal hypertension at some point within 12-month follow-up time [55]. In a Korean case-control series (n = 17), the 2-year HE recurrence rate was lower in the embolization group (40% vs. 80%, P = 0.02) but there was no difference in the 2-year overall survival rates (65% vs. 53%, P = 0.98). In addition, they observed an improvement in overall survival in the embolization group (100% vs. 60%, P = 0.03) in the subgroup analysis of only patients without hepatocellular carcinoma and with MELD score < 15 [54].

Molecular Adsorbent Recirculating System

Albumin has been shown to be a multifunctional protein with antioxidant, immunomodulatory, and detoxification functions [56]. Molecular adsorbent recirculating system (MARS) was introduced in 1999 and is based on the concept of albumin dialysis. MARS was designed to remove protein- and albumin-bound toxins, such as bilirubin, bile acids, nitrous oxide, and endogenous benzodiazepines. In addition, MARS also removes non-protein-bound ammonia that accumulates in liver failure [57]. Although there was no survival benefit observed in previous trials, MARS did show a beneficial effect on HE treatment. In a study designed specifically to evaluate the effect of MARS on HE, 70 patients with grades 3–4 HE were enrolled. The MARS-treated patients were found to have a higher proportion of patients with a 2-grade improvement in HE when compared to standard treatment alone. The MARS-treated patients were also found to have more rapid improvement [58]. The RELIEF trial enrolled 189 patients with ACLF and showed higher proportion of patients with HE grade 3 or 4 improvement to HE grade 0 or 1 in MARS-treated patients (15 of 24; 62.5%) compared with standard therapy (13 of 34; 38.2%), which trended toward significance (P = 0.07) [59]. In a small study, MARS had a statistically significant effect on improvement of HE in nine patients with alcoholic hepatitis and HE [60]. The FDA initially approved the use of MARS for grade 3–4 HE related to decompensation of chronic liver disease but has since retracted its approval. In summary, MARS is a reasonable option for patients with severe HE refractory to standard medical therapy.

Liver Transplantation

Liver transplantation (LT) is the most definitive treatment option for HE. Therefore, cirrhotic patients with HE and MELD ≥15 should be evaluated for liver transplantation. It is important to distinguish other conditions such as neurodegenerative diseases like Alzheimer's, and Wernicke's encephalopathy, which would not improve after liver transplant. Although HE should improve

after LT, pretransplant episodes of HE are associated with impair of posttransplant neurological outcome [61]. Data are limited for liver transplant outcomes in patients with HE in the setting of ACLF. Although posttransplant survival rates for ACLF have been reported to be 80–90%, long-term outcome is scarce [10]. Patients with ACLF usually have high MELD scores but they may have LT contraindication such as active infection, and hemodynamic instability with the need for inotropes.

With the current organ allocation system using the MELDNa score, HE does not result in a higher prioritization for LT. However, there are cases with severe HE who would benefit from LT, particularly in the context of ACLF. A new scoring system, chronic liver failure consortium ACLF score (CLIF-C ACLFs), has been developed and validated in cirrhotic patients with ACLF. This score will need further evaluation to determine whether it can accurately discriminate or rank individuals according to their mortality risk, before it could be utilized for organ allocation in ACLF setting [62].

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Pharmacological and clinical treatment of irritable bowel syndrome

Maciej Sałaga, Paula Mosińska

Abstract

Irritable bowel syndrome (IBS) is a functional gastrointestinal (GI) disorder with an unknown etiology, which is a growing major concern worldwide. Since the pathophysiology of IBS is barely understood there is no specific treatment for this disorder and numerous treatment options aiming at various pharmacological targets located not only in the GI tract, but also in the central nervous system (CNS) are available. In this chapter we provide an overview on drugs that are currently available for IBS therapy with regard to the type of the disease. We discuss their mechanisms of action, evidences for their effectiveness emerging from clinical trials as well as virtues and drawbacks of the most commonly prescribed medications. Furthermore we highlight the practical aspects of the use of certain drugs, such as possible adverse events and contraindications. Moreover we introduce selected complementary and alternative medicine (CAM) methods that have been proven effective in clinical tests.

Keywords: Irritable bowel syndrome, Intestinal transit, Visceral pain, G protein-coupled receptors, Ion channels, Hypnosis

List of abbreviations

MOR	μ Opioid receptor
DOR	δ Opioid receptor
KOR	κ Opioid receptor
APN	Aminopeptidase N
CNS	Central nervous system

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ClC	Chloride ion channels
CFTR	Cystic fibrosis transmembrane conductance regulator
CC	Chronic constipation
CIC	Chronic idiopathic constipation
IBS-C	Constipation-predominant irritable bowel syndrome
DPP IV	Dipeptidyl peptidase IV
ECS	Endocannabinoid system
EOS	Endogenous opioid system
GI	Gastrointestinal
GC-C	Guanylate cyclase C
HEK cells	Human embryonic kidney cells
EC cells	Enterochromaffin cells
5-HT	Serotonin
SERT	Serotonin-selective reuptake transporter
SCBM	Spontaneous complete bowel movement
TPH1/2	Tryptophan hydroxylase 1/2
5-HT2B	Type 2B serotonin receptor
5-HT3	Type 3 serotonin receptor
5-HT4	Type 4 serotonin receptor

Introduction

Irritable bowel syndrome (IBS) is a complex and multifactorial disease with multiple molecular mechanisms involved in its pathophysiology. Consequently, the exact mechanism responsible for the development of IBS remains unrevealed what significantly hinders the search for the new medications. Nevertheless meaningful efforts have been put on the development of drugs that secure fundamental therapeutic goals of the treatment of IBS, such as improvement of unbearable symptoms accompanied with augmentation of patients quality of life. Intensive research in this field lead to the development of several treatment options tailored to the specific groups of patients based on the type of IBS or gender (please see below for more details). Since IBS is not accompanied with any known organic changes in the gut, and none of these treatment options includes invasive procedures, the IBS patients must rely solely on the pharmacotherapy and lifestyle modification. Of note, the present-day prospect of anti-IBS therapies as well as drugs available on the market undergoes constant variations with some compounds being withdrawn and other ones entering it in a relatively short time span.

In this chapter we provide an overview on the pharmacological targets for small-molecule anti-IBS drugs including serotonin receptors, chloride ion channels, guanylate cyclase C (GC-C), endogenous opioid system (EOS), cystic fibrosis transmembrane conductance regulator (CFTR) and somatostatin-2 receptors (Fig. 1). We also discuss the virtues and drawbacks of the most commonly prescribed medications. Moreover, we introduce selected complementary and alternative medicine (CAM) methods that have been proven effective in clinical tests.

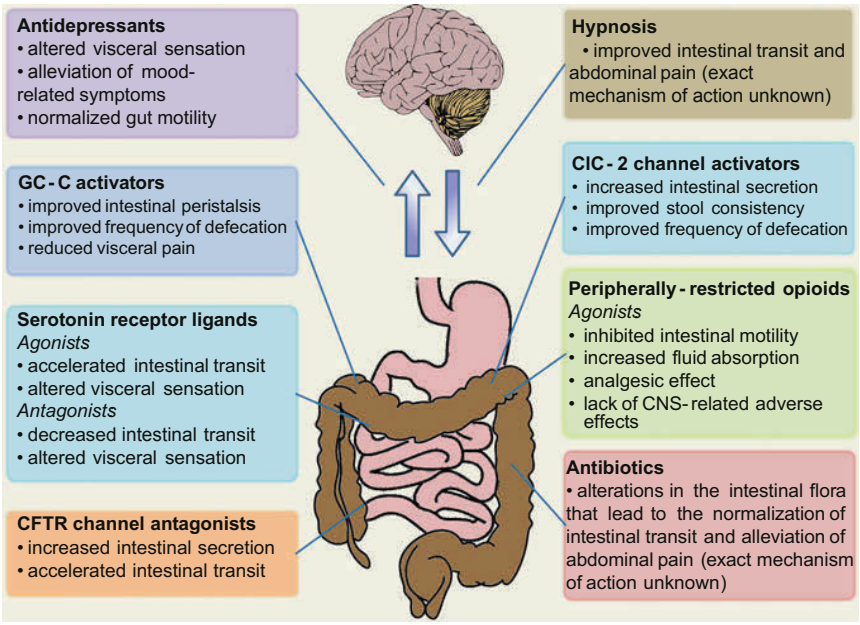

Fig. 1: An overview on pharmacological targets for clinically validated anti-IBS drugs/interventions. *ClC-2* type 2 chloride ion channels; *CFTR* cystic fibrosis transmembrane conductance regulator; *CNS* central nervous system; *GC-C* Guanylate cyclase C

Pharmacological Targets

Serotonin System in the Gastrointestinal Tract

Serotonin, which is a derivative of the exogenous amino acid tryptophan is synthesized and stored in the enteric enterochromaffin (EC) cells located in the intestinal mucosa. In the human gastrointestinal (GI) tract EC cells are the most abundant in the duodenum and rectum and the scarcest in the ileum. On the other hand activated mast cells may also contribute to the synthesis and secretion of serotonin. The concentration of serotonin is relatively low in the duodenum and ileum (1.4 and 0.6 nmol/mg protein, respectively) and gradually rises in the colon reaching 45 nmol/mg protein in the rectum [1]. The synthesis of serotonin in the gut requires tryptophan hydroxylase 1 (TPH1), which is a rate limiting enzyme in this process [2]. In neurons serotonin is synthesized by an isoform of tryptophan hydroxylase, TPH2 [3]. Additionally Moreover, the availability of serotonin in the GI tract is locally regulated by the serotonin-selective reuptake transporter (SERT) which removes it from the interstitial space following the release by EC cells. SERT is expressed by all epithelial cells of the intestinal mucosa [2]. Noteworthy, the expression of SERT is decreased in the gut of IBS patients [4].

Serotonin receptors are distributed on enteric neurons, extrinsic nerve fibers, smooth muscle cells, goblet cells and enterocytes [2]. They can exert excitatory and/or inhibitory activities

depending on the receptor type. Serotonin secreted by the EC cells mediates various GI functions including those involved in the pathophysiology of IBS such as peristalsis, electrolyte secretion and absorption, vasodilatation, as well as perception of pain (for comprehensive review, see Mawe et al. [2]). Moreover, it has been shown that the plasma 5-HT concentration correlates with colonic motility under both fasting and fed conditions [1]. Hence, perhaps not surprisingly, serotonin system has been recognized as one of the most promising targets for anti-IBS drugs and stimulation of serotonin receptors has been clinically validated for the treatment of disorders manifested by disturbed intestinal motility and pain.

Chloride Ion Channel 2 in the Gastrointestinal Tract

Chloride ion channels (ClC) constitute an evolutionarily well-conserved family of voltage-gated channels that are structurally unrelated to the other known voltage-gated channels. To date several types of ClC have been identified, including ClC-0, ClC-1, ClC-2, ClC-4 and ClC-5 [5]. CICs are involved in the regulation of the excitability of neurones, smooth muscle cells, cell volume control and transepithelial salt transport.

Chloride ion channel-2 is a member of the ClC family that is ubiquitously expressed in mammalian tissues and has been found in both small and large intestinal epithelial cells as well as on GI parietal cells [6]. In the physiological membrane conditions the channel is closed; however, it may be activated by hyperpolarisation, cell swelling as well as acidic extracellular pH [5]. Chloride secretion is responsible for maintenance of mucosal hydration throughout the GI tract, and chloride transport is also pivotal in the regulation of fluid secretion into the intestinal lumen [6]. Activation of ClC-2 enables translocation of chloride ions across the membrane followed by the release of sodium and water into the gut lumen. The influx of fluid into the intestine promotes GI motility and increases the colonic transit together with the number of spontaneous bowel movements. The surplus of water is absorbed by the colonic epithelial tissue what limits the emergence of diarrhea [6]. Taken together, ClC-2 has been validated as a target for the treatment of chronic idiopathic constipation as well as constipation-predominant IBS (IBS-C) [7].

Guanylate Cyclase-C in the Gastrointestinal Tract

Guanylate cyclase-C is a transmembrane enzyme, belonging to the protein family synthesizing one of the most common and important secondary messengers—cyclic guanosine monophosphate (cGMP) [8]. There are seven members of the GC family (GC-A–G); however, only GC-C has been validated as a pharmacological target for the treatment of GI pathologies. The endogenous activators of GC-C include peptides, guanylin and uroguanylin which play important function in the maintenance of gut homeostasis. Moreover, GC-C is known as a target protein for heat-stable enterotoxins produced by numerous enteric pathogens that colonize intestines, including Escherichia coli, Citrobacter freundii, Vibrio cholerae and Yersinia enterocolitica [8, 9]. GC-C is expressed on the brush border of intestinal cells along the small and large intestine. Its expression is regulated by intestine-specific transcription factor Cdx2 and is higher in the crypt of the colonic mucosa compared to the crypt of the small intestine [10, 11].

Activation of GC-C leads to the increase of the intracellular level of cGMP, what causes activation of the cGMP-dependent protein kinase II (PKG II). PKG II by phosphorylation of cystic fibrosis transmembrane conductance regulator (CFTR) ion channel induces secretion of chloride and HCO_3-into the intestinal lumen. Moreover, cGMP reduces absorption of Na^+ ions by Na^+/H^+ exchanger [11]. All these events lead to the accumulation of osmotically active molecules in the intestines what causes massive influx of water and increased excretion [12]. The pro-excretory properties of GC-C activators have been exploited in the development of synthetic GC-C agonists that are used in the treatment of functional GI disorders manifested by chronic constipation, such as IBS-C [8, 13, 14].

Cystic Fibrosis Transmembrane Conductance Regulator in the Gastrointestinal Tract

Cystic fibrosis transmembrane conductance regulator is a cyclic AMP (cAMP)-regulated ion channel that transfers chloride and thiocyanate ions through the membrane of various types of epithelial cells. It consists of two transmembrane domains linked by the R domain whose phosphorylation by the protein kinase A (PKA) leads to the opening of the gate for the ions [15]. The expression of CFTR alters throughout the GI tract. The lowest level is observed in the mucosal epithelium of the stomach. In the ileum the expression is relatively high and exhibits decreasing gradient along the crypt axis [16]. Furthermore, a small subpopulation of the cells of yet unrevealed function has been shown to express CFTR in the duodenum and jejunum [16]. In the colon the expression of CFTR is the highest in the base of the crypts and resembles the pattern occurring in the small intestine [16]. In the physiological conditions CFTR is responsible for the proper production of the mucus, secretion of fluids into the intestinal lumen and has a strong impact on GI motility and excretion. Knock out of CFTR gene impairs the intestinal transit and lowers the volume of fluids in the gut [17]. On the other hand, CFTR upregulates some of the genes associated with the GI inflammation and stimulates accumulation of mast cells in the intestinal smooth muscle tissue [18]. In line, cystic fibrosis patients (possessing mutation on the CFTR gene) reveal prolonged intestinal transit compared to healthy controls [18].

Cystic fibrosis transmembrane conductance regulator is one of the most important factors involved in the proper formation of the intestinal mucus, which constitutes a niche for the growth of intestinal microbiota. Thus, perhaps not surprisingly, loss of CFTR is associated with significant decreases in GI bacterial community richness, evenness and diversity as well as reduced abundance of protective species, including a multitude of Lactobacillales members [19].

The properties and functions of CFTR made it an attractive target for the treatment of disorders accompanied with deregulated motility and abdominal pain.

Endogenous Opioid System in the Gastrointestinal Tract

Endogenous opioid system (EOS) consists of three main types of opioid receptors, namely μ, κ and Δ (MOR, KOR and DOR respectively). Their respective endogenous ligands, endorphins, dynorphins and enkephalins as well as enzymatic machinery dedicated to their degradation, including various proteases [e.g. aminopeptidase N (APN) and dipeptidyl peptidase IV

(DPP IV)] [20]. Opioid receptors are widely distributed in the human body. All opioid receptor subtypes have been localized in the gastrointestinal tract of many mammalian organisms. In human body the highest concentration of MOR in the human body has been detected in the myenteric and submucosal plexuses, on immune cells in the lamina propria and ileal longitudinal muscle. DOR was detected in the enteric ganglia and fibers of esophagus, duodenum, ileum, cecum as well as in the proximal, and distal colon. KORs were localized on the myenteric and submucosal neurons, smooth muscle fibres as well as mucosa in rats [21]. Furthermore, opioid receptors were also found in high amounts on lymphocytes and macrophages, which suggest their involvement in the modulation of function of these cells [22]. EOS is crucially involved in numerous physiological processes, including pain signaling in the central and the peripheral nervous system, and respiration.

In the GI tract opioid receptors play a major role in the regulation of GI transit, secretion and immune responses. The major effects of opioid receptor agonists in the GI tract are reduction of intestinal contractility and impairment of peristalsis caused by blockade of neurotransmitter release [22]. Moreover opioids promote water and electrolyte absorption thus decreasing the volume of intestinal content and frequency of excretion. On the other hand, Moreover, both natural and synthetic opioid agonists exhibit potent analgesic effects and decrease abdominal pain in both physiological and pathophysiological conditions [23–25]. To date, several EOS-targeting compounds reached the market and found a place in the clinical treatment of GI-related conditions (e.g. loperamide, alvimopan, oxycodone, racecadotril; for comprehensive review please see Mosinska et al. [21]).

Pharmacological Treatment of Diarrhea-Predominant IBS (IBS-D)

Alosetron

Alosetron is a 5-HT3 receptor antagonist is effective for the treatment of IBS-D in women. It is a therapeutic agent with a limited use and is available only for severe and unresponsive to other agents IBS-D cases. It improves pain and discomfort as well as stool frequency and urgency [7, 26]. Alosetron was approved by the U.S. Food and Drug Administration (FDA) in 2000, after a seven month review process. However, eight months later it was removed from the market following reports of serious complications, such as severe constipation and ischemic colitis that, in several cases, lead to a surgery. In 2002 FDA reconsidered the case of alosetron and reintroduced it to the market under a risk management plan with a lower recommended starting dose of 0.5 mg twice daily [7]. In 2005 and 2007 Chang et al. [27] and Krause et al. [28] respectively, have shown the effectiveness of alosetron in the treatment of IBS-D both in men (n = 662) and women (n = 705) reporting low incidence of serious adverse events. The recent 9-year evaluation of trends in alosetron postmarketing safety under the risk management program indicate that incidence of ischemic colitis and constipation remain rare and stable, at approximately 1 case/1000 patient-years [29]. The indications for alosetron in women with severe IBS-D include: (i) chronic IBS symptoms (generally lasting 6 months or longer), (ii) the absence of anatomic or biochemical

abnormalities of the GI tract excluded, (iii) disability or restriction of daily activities due to IBS and (iv) no adequate response to conventional therapy.

Ramosetron

Ramosetron is a potent and selective 5-HT3 receptor antagonist, which has been initially developed for the treatment of nausea and vomiting [30]. Clinical studies showed that ramosetron is effective against IBS-D. In a double-blind, placebo-controlled, parallel-group study of 418 male and female patients with IBS-D ramosetron increased the monthly responder rates of IBS symptoms compared to placebo [31]. In another 12-week randomized controlled trial of 539 patients, a positive response to treatment was reported by 47 % [32]. Furthermore, the drug was active after oral administration. A long-term efficacy for overall improvement of IBS symptoms was also demonstrated. Seven % of patients reported adverse events after ramosetron treatment; however, no serious adverse events (severe constipation, ischemic colitis), were reported for long-term treatment with ramosetron [33]. Ramosetron is only licensed for use in Japan and selected Southeast Asian countries (e.g. India).

Loperamide

Loperamide is a synthetic peripherally-restricted MOR agonist, which does not cross the blood-brain barrier. It decreases gastric emptying, slows peristalsis, delays intestinal transit and relaxes the segmental colonic smooth muscles. On the other hand it increases fluid absorption and inhibits intestinal secretion of electrolytes [34]. In IBS-D loperamide combats diarrhea and reduces stool frequency; however, it has only limited effect on abdominal pain. Clinical features of loperamide are well-established, the drug is safe and effective hence it is often recommended as a first-line therapy for functional GI disorders accompanied with diarrhea in adults. At high doses loperamide may induce constipation; therefore, the treatment starts with a relatively low dose (approx. 2 mg) and then it is titrated up or down based on the symptoms [7, 34]. Clinical studies demonstrated that loperamide is well tolerated in a 5-week therapy [35].

Trimebutine

Trimebutine (used in the form of trimebutine maleate) is a weak agonist of peripheral MOR, KOR and DOR receptors, which also exhibit antimuscarinic properties [36]. Trimebutine accelerates gastric emptying, induces premature phase III of the migrating motor complex in the intestine and modulates the contractile activity of the colon [37]. Clinically, trimebutine has been shown to alleviate both acute and chronic abdominal pain in patients with IBS and it may also be used in children with abdominal pain. Recently, Karabulutu et al. [36] evaluated the effect of trimebutine versus non-medication in 345 children and adolescents demonstrating the effectiveness (94.9 % patients in trimebutine group experienced significant relief) [36]. The indications for trimebutine include: (i) IBS, (ii) abdominal pain and abdominal cramping and (iii) dyspepsia. It may be administered in multiple doses per day with the maximal total daily dose of 600 mg.

Eluxadoline

Eluxadoline is a peripherally-restricted mixed MOR agonist and DOR antagonist approved by FDA in May 2015 [34, 38]. In 2013 a phase II clinical trial (n = 807) demonstrated the effectiveness of eluxadoline versus placebo against global IBS-D symptoms [39]. Patients receiving a drug were significantly more likely to meet the U.S. FDA response end point during the full 12 weeks of the study than those receiving placebo. Eluxadoline was well tolerated with a low incidence of constipation. Phase III trials (n = 2428 patients in total) confirmed these results and showed that treatment with eluxadoline (75 or 100 mg twice daily) lead to simultaneous improvement in abdominal pain and stool consistency on the same day for ≥50 % of days over weeks 1–12 and 1–26 of the study (for more details please see Nee et al. [34]). On the other hand a nonsignificant improvement in worst abdominal pain scores in those who received eluxadoline compared to placebo was observed. Common adverse effects in the two phase III clinical trials were nausea, headache, nasopharyngitis, abdominal pain and constipation but rates of discontinuation due to constipation were low (approx. 1.5 %) for both eluxadoline and placebo [40]. Known contraindications to the treatment with eluxadoline include: (i) biliary duct obstruction, or sphincter of Oddi disease or dysfunction, (ii) alcohol abuse or addiction, or patients who drink more than three alcoholic beverages per day, (iii) a history of pancreatitis or structural diseases of the pancreas, including known or suspected pancreatic duct obstruction, (iv) a history of chronic or severe constipation or known or suspected mechanical gastrointestinal obstruction.

Rifaximin

Rifaximin is another drug for IBS-D approved by FDA in 2015. It is a nonabsorbable, semisynthetic antibiotic belonging to the rifamycin family. The use of antibiotics for the treatment of IBS emerged from the observation that gut microflora differs between IBS and general population. Furthermore epidemiological data reveal that up to 31 % of IBS cases are caused by an episode of gastroenteritis [34]. Rifaximin targets the β-subunit of bacterial RNA polymerase which is responsible for the transcription process [41]. It does not affect the overall composition of the microbiota but appear to influence mainly potentially detrimental species such as *Clostridium* sp. and increases the presence of some species, such as Faecalibacterium prausnitzii [42].

Clinical trials suggest that the drug can reduce global IBS symptoms, improve bloating, abdominal pain, and stool consistency in patients with non-constipated IBS [43]. While other anti-IBS therapies require daily administration to maintain their efficacy, 2-week rifaximin treatment can achieve symptom improvement that persists up to 12 weeks post-treatment [44]. However, in the clinical trial it has been shown that 64 % of patients who underwent a 2-week therapy with rifaximin (550 mg) develop a relapse in the 18 weeks follow up hence FDA recommends a 14-day therapy with rifaximin at the dose of 550 mg (orally), three times a day. In case of the recurrence of the symptoms therapy may be repeated for another 14 days. Rifaximin is well-tolerated both after single and repeated treatments with a side effect profile comparable to that of placebo. The most common adverse events caused by rifaximin are headache, upper respiratory infection, nausea, nasopharyngitis, diarrhea and abdominal pain.

Crofelemer

Crofelemer is a plant-derived drug originating from Croton lechleri, which belongs to the proanthocyanidin family. It was approved by FDA for the treatment of diarrhea associated with anti-HIV drugs [45]. It simultaneously targets two distinct channels, CFTR and calcium-activated chloride channel, both responsible for chloride and fluid secretion in the GI tract. Although it has been shown that crofelemer did not produce significant improvement in stool consistency, stool frequency, urgency and adequate relief it increased the number of pain-free days in female IBS-D patients after 1 and 3 month therapy and was well tolerated [46]. Further studies evaluating the analgesic potential action of this drug are needed to draw a clear conclusion on its therapeutic potential.

Antidepressants

Antidepressants are commonly used in IBS-D. There are many plethora of evidences for point to the link between mood-related disorders and functional GI diseases. Emotional fluctuations that often occur in distressed patients correlate with IBS symptoms. Moreover, IBS patients are more likely to develop psychiatric disorders (depression, anxiety) and dementia [47, 48].

The bidirectional communication between the brain and the gut, so called brain-gut axis, may be exploited therapeutically in IBS patients. Some of the tricyclic antidepressants, selective serotonin re-uptake inhibitors and serotonin-norepinephrine reuptake inhibitors have already been employed in the treatment of IBS and proved effective in symptom relief via mood stabilization, modulation of pain perception and amelioration of GI motility and secretion. A recent meta-analysis confirmed the efficacy of antidepressants, including tricyclic antidepressants, in the treatment of IBS symptoms [49]. In a randomized, double-blind, placebo controlled study low dose amitriptyline (10 mg) successfully ameliorated IBS-D symptoms [50]. Fifty out of 54 patients completed an intention-to-treat study; 68 % of those receiving amitriptyline had a complete response defined as a loss of all symptoms over a 2 month trial period compared to only 28 % of the controls. Adverse effects were similar between the two groups.

Pharmacological Treatment of Constipation-Predominant Irritable Bowel Syndrome (IBS-C)

Polyethylene Glycol (PEG) 3350

The first-line therapy for patients suffering from IBS-C involves laxatives and dietary fibers. Although this approach may effectively and safely combat slowed intestinal transit and constipation, it does not alleviate pain symptoms [51]. The effect of PEG 3350 plus electrolytes (PEG+E) on IBS-C has been tested in a randomized, double-blind, placebo controlled study by Chapman et al. [52]. One hundred thirty four patients received the treatment or placebo for 28 days. PGE+E was superior than placebo as assessed by spontaneous bowel movements (the primary endpoint), responder rates, stool consistency, and straining. There was no difference between PGE+E versus placebo in the mean severity score for abdominal discomfort/pain. PEG+E constitutes a well

tolerable and effective treatment that should be considered suitable for use as a first-line treatment in functional GI disorders manifested by chronic constipation.

Tegaserod

Tegaserod is a partial 5-HT4 receptor agonist that reduces visceral sensitivity and stimulates the secretion of chloride from epithelial cells. It has been approved by FDA in 2002 and subsequently withdrawn from the market in 2007 due to possible adverse cardiovascular effects (heart attack and stroke) [26]. The putative adverse events caused by tegaserod most likely result from its non-selective binding to other serotonin receptors, such as 5-HT1, 5-HT2a and 5-HT2b [53]. FDA had been criticized for this decision and ultimately reconsidered it and allowed for reintroduction of tegaserod under an investigational new drug protocol for IBS-C and chronic idiopathic constipation in women younger than 55 who are not at risk for certain cardiovascular events [53, 54]. The effect of tegaserod on IBS-C in women has been evaluated in a large (n = 661) randomized, controlled trial [55]. It provided significant improvement and satisfactory relief of IBS symptoms over 4 weeks of treatment in 43.3 % of IBS-C patients. The most frequent adverse events leading to study discontinuation in tegaserod-treated patients were diarrhea (1.5 %) and abdominal pain (0.9 %). Although long-term safety of tegaserod was investigated in a prospective study suggesting that treatment was safe over a 12-month period tegaserod was not approved for use in the EU due to the opinion that its benefits does not outweigh its risks [56].

Prucalopride

Prucalopride, which belongs to benzofurans, is a selective agonist of 5-HT4 receptor that exhibits prokinetic effect in the GI tract. It stimulates colonic peristalsis, which provides the main propulsive force for defecation. On the contrary to other 5-HT4, it does not induce cardiovascular adverse events, which may be attributed to its high selectivity over other types of 5-HT receptors and ion channels. Clinical trials with prucalopride (1974 patients in total; both men and women) demonstrated a significant increase in the proportion of patients achieving at least three spontaneous complete bowel movements (SCBMs) per week compared with placebo [57–59]. Response rates ranged from 24 to 28 % with 4 mg prucalopride, and 9.6–12 % with placebo. Clinically relevant improvement was also demonstrated in other measures, including satisfaction with bowel function, perception of the severity of constipation as well as quality of life. It should be also underlined that prucalopride is not effective in children with functional constipation, as showed by Mugie et al. [60]. Regardless of the patient's age, prucalopride is well tolerated with no impact on the cardiovascular system [26]. The most frequently reported adverse events include headache, abdominal pain, nausea and diarrhea. Prucalopride has been approved in Europe for both men and women; however, it has not been allowed for sale in the USA.

Linaclotide

Linaclotide is a 14 amino acid peptide agonist of GC-C which has been approved by FDA for the treatment of IBS-C in 2012 and to date is considered as a first-in-class drug by majority of gastroenterologists. It is characterized by low bioavailability (approx. 0.1 %), what enables local action in the intestines. Linaclotide activates GC-C and causes an increase in the level of intracellular cGMP with concomitant upregulation of HCO_3-and chloride ions what results in an increased secretion and acceleration of intestinal transit [8]. Clinical data demonstrated that linaclotide improves severity of abdominal pain as well as bowel movements in IBS-C patients (for more details please see Jarmuz et al. [8]). Phase I trial showed that linaclotide provides relief and is well tolerated in 42 patients [61]. Rao et al. [62] reported the effects of 12-week treatment with linaclotide in IBS-C patients (n = 800). One-third of patients receiving linaclotide reached the FDA-recommended primary endpoint (improvement of ≥30 % from baseline in the average of the daily worst abdominal pain score on a standardized scale and an increase of at least 1 CSBM from baseline in the same week for at least 6 of first 12 weeks of treatment). During the withdrawal period patients receiving linaclotide experienced sustained decrease of abdominal pain while placebo-treated patients had a gradual increase of the pain score. In another clinical study linaclotide administered orally improved global IBS-C symptoms during 26-week therapy [63]. In line with the previous studies linaclotide induced significant relief in approx. one-third of the patients. Abdominal discomfort, fullness, cramping and bloating were also significantly improved. The most common adverse effect, which leads to discontinuation of the medication with linaclotide is diarrhea, occurring in approximately 5 % of patients [64].

Lubiprostone

Lubiprostone (approved by FDA in 2008 to treat IBS-C) is a bicyclic fatty acid derived from prostaglandin E1 that activates ClC-2 chloride channels located on the apical area of GI epithelial cells. It is poorly absorbed from the gut what facilitates its local activity in the GI tract [65]. Although it is widely accepted that lubiprostone acts via apical CIC-2 channels, recently some novel insights into its mechanism of action have been demonstrated. It was shown that lubiprostone, not only activates apical CIC-2 channels but also induces the internalization of basolateral ClC-2 into the cytoplasm with concomitant trafficking of CFTR and chloride/hydrogen carbonate exchanger PAT-1 to the apical membrane [66]. At the molecular level events triggered by lubiprostone leads to the increased luminal secretion of chloride and decreased absorption of this ion by basolateral CIC-2 channels. These events soften the stool, increase motility, and promote SCBMs.

In clinical trials lubiprostone was shown to improve SCBMs frequency after 1 week of therapy. Of note, some of the patients (approx. 55 %) experienced a relief in the first day of the treatment. Improved stool consistency, straining, and constipation severity, as well as patient-reported assessments of treatment effectiveness, were also reported [67–69]. The most common adverse events of lubiprostone are nausea, diarrhea, headache and abdominal distention.

Box 1. Anti-IBS drugs in the nutshell.

Drug	Key information
IBS-D	
Alosetron	• 5-HT_3 receptor antagonist is effective for the treatment of IBS-D in women • Indications include: (i) chronic IBS symptoms (generally lasting 6 months or longer), (ii) the absence of anatomic or biochemical abnormalities of the GI tract, (iii) disability or restriction of daily activities due to IBS and (iv) no adequate response to conventional therapy
Ramosetron	• Licensed for use only in Japan and selected Southeast Asian countries (e.g. India)
Loperamide	• At high doses loperamide may induce constipation • Treatment starts with a relatively low dose (approx. 2 mg) and then it is titrated up or down based on the symptoms
Trimebutine	• Indications include: (i) IBS, (ii) abdominal pain and abdominal cramping and (iii) dyspepsia • May be administered in multiple doses per day with the maximal total daily dose of 600 mg
Eluxadoline	• Contraindications to the treatment include: (i) biliary duct obstruction, or sphincter of Oddi disease or dysfunction, (ii) alcohol abuse or addiction, or patients who drink more than three alcoholic beverages per day, (iii) a history of pancreatitis or structural diseases of the pancreas, including known or suspected pancreatic duct obstruction, (iv) a history of chronic or severe constipation or known or suspected mechanical gastrointestinal obstruction
Rifaximin	• Recommended is a 14 day therapy with the dose of 550 mg (orally), three times a day • Therapy may be repeated for another 14 days • The most common adverse events are headache, upper respiratory infection, nausea, nasopharyngitis, diarrhea and abdominal pain
IBS-C	
Polyethylene glycol 3350+ electrolytes	• Well tolerable and effective treatment that should be considered suitable for use as a first-line treatment in functional GI disorders manifested by chronic constipation
Tegaserod	• Long-term safety of tegaserod was investigated in a prospective study suggesting that treatment was safe over a 12-month period • Not approved for use in the EU due to the opinion that its benefits do not outweigh its risks
Prucalopride	• The most frequently reported adverse events include headache, abdominal pain, nausea and diarrhea • Approved in Europe for both men and women; however, it has not been allowed for sale in the USA
Lubiprostone	• Recommended dose is 8 μg twice daily; however, this dose might be increased if the symptoms do not improve • Contraindicated in patients exhibiting chronic diarrhea, bowel obstruction, or IBS-D and is not approved for the use in children

The recommended dose of lubiprostone is 8 μg twice daily; however, this dose might be increased if the symptoms do not improve [70]. Of note, some of the patients experience significant relief in all symptoms only after 1 month of the treatment what has to be taken into consideration by specialists planning therapy. Lubiprostone is contraindicated in patients exhibiting chronic diarrhea, bowel obstruction, or IBS-D and is not approved for the use in children.

Conclusions and Future Perspectives

Significant improvement of patient's quality of life, which is an ultimate goal of all anti-IBS therapies, can be only achieved if the drug/intervention used satisfies several clearly defined conditions. On top of all, a sufficient efficacy and acceptable safety in subjects with IBS is required. Furthermore, selection of a medicine should take into account patients lifestyle, other medicines that are possibly used in the same time and all other contraindications. These issues may particularly affect patient's adherence to medication. To enhance the compliance and satisfaction of the patient, improvement of all symptoms, including diarrhea and/or constipation as well as abdominal pain should be secured by one a single drug. Moreover, reliable estimation of possible drug-related adverse events, such as nausea or headache is critical for proper selection of the drug(s).

Noteworthy, the race for novel anti-IBS medications is always on and patients can be reassured that several novel, superior compounds will enter the market in the next few years (please see Mosinska et al. [71] and Deiana et al. [72] for detailed information on experimental drugs).

As shown in this chapter, a significant number of highly effective and safe synthetic and semi-synthetic drugs is currently available on the market for all types of IBS, often tailored to the needs of particular groups of patients. However, it has to be underlined that there is also a significant group of non-responders who struggle to find an appropriate method of treatment. These people often reach to the complementary and alternative therapies that, as proven clinically, may also provide a long-awaited relief. There are several herbal preparations that may provide at least transient relief, such as peppermint oil capsules (for detailed information please see [73, 74]). Moreover, acupuncture, which is commonly used in China, has emerged as a new potential anti-IBS therapy. However, based on the available data which is often contradictory, it is difficult to state a firm conclusion on its effectiveness and clinical relevance [75–77]. One of the most intriguing forms of therapies is hypnosis, which has been evaluated in large clinical trials (n = 1000) demonstrating its safety and potency in refractory IBS [78]. The mechanism of this method is still unexplained; however, it holds a great promise for many IBS sufferers who do not experience sufficient relief with a standard therapy [79].

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3

Current guidelines for colonoscopy

Nallely Saldana-Ruiz, Andreas M. Kaiser

Abbreviations

ACS	American Cancer Society
ACG	American College of Gastroenterology
AGA	American Gastroenterology Association
ASCRS	American Society of Colon and Rectal Surgeons
ASGE	American Society of Gastrointestinal Endoscopy
CRC	Colorectal cancer
CRP	C-reactive protein
FIT	Fecal immunochemical testing
FOBT	Fecal occult blood testing
FAP/AFAP	Familial adenomatous polyposis/attenuated FAP
HNPCC	Lynch syndrome, hereditary nonpolyposis colon cancer
IBD	Inflammatory bowel disease
MAP	MUTYH-associated polyposis
WBC	White blood cells

Key Points

- Colorectal cancer (CRC) is the most common malignancy in the gastrointestinal tract and develops in 4.5% of the average risk in the U.S. population. CRC can develop as sporadic cancer without any known gene mutation, result from known genetic mutations, or be superimposed on chronic inflammatory bowel disease.
- Cancer-specific survival at 5 years for all tumor stages is 65% with an indirect correlation between tumor stage and prognosis.

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- Development of sporadic colorectal cancer is a slow process that takes 7–10 years to progress through a number of genetic steps from normal mucosa through precursor lesions (polyps) to an invasive and metastasizing cancer. This long interval provides us with an opportunity to intervene by screening for and eliminate precancerous lesions.
- Diagnostic colonoscopy is done as part of a workup for specific symptoms such as a positive fecal occult blood test, chronic anemia, or gross rectal bleeding.
- Screening programs aim at reducing the incidence of CRC by removing precursor lesions and to improve cancer survival by detecting cancer at an earlier stage

Introduction

Colorectal cancer (CRC) is the most common malignancy in the gastrointestinal tract. Over a lifetime, it affects 1 in 22 individuals (4.5%) of the general population in Western civilizations including the United States. Worldwide, however, there is a much larger geographical variation, with a crude incidence of 6.5/7.7 cases per 100,000 females/males in less developed areas as opposed to 48.3/36.6 in more developed regions. Since the mid-1980s, there has been a steady decrease in overall incidence in the United States, whereby some subgroups such as patients younger than 50 or African-American males in fact showed an increase or remained unchanged. According to the American Cancer Society despite the overall decline in incidence and mortality, CRC remains the third most frequently diagnosed cancer in both the U.S. men (lung/prostate) and women (breast/lung) and accounts for the third most common fraction of cancer death (behind lung, prostate/breast) [1]. In gender-neutral absolute numbers, colorectal cancer ranks fourth in annual cancer incidence (behind breast, lung, and prostate, respectively, excluding skin cancers) and second in cancer mortality (behind lung cancer) [1]. An estimate for 2016 of the incidence in the United States projects 95,270 new colon cancer and 39,220 new rectal cancer cases (total 134,490 cases); furthermore, 49,190 people are anticipated to succumb to colorectal cancer in 2016 [1].

The majorities of CRC cases are sporadic cancers and typically arise within a polyp. Adenomatous and serrated polyps are two subtypes that possess the potential to transform into a cancer through a series of gene mutations ("adenoma-carcinoma sequence"). The prevalence of polyps is an age-dependent phenomenon that increases from 11% at age 40–49 to 15% at age 50–59 [2]. In fact, up to 45–50% of asymptomatic average-risk individuals who undergo screening are found to have at least one polyp, of which about half shows an adenomatous (90–95%) or serrated (5–10%) pathology. This epidemiology translates into an estimated cancer risk of 1 in 5 polyps ultimately transforming into a cancer. Moreover, early detection is key as cancer-specific survival at 5 years is 65% for all tumor stages together, but it is directly correlated to the tumor stage with 90% for local (stages I/II), 71% for loco-regional (stage III), and 13% for distant metastatic disease (stage IV), respectively [1, 3].

Concept of CRC Screening and Surveillance vs. Diagnostic Workup

Since clinical symptoms are almost always late signs of colorectal cancer and hence not reliable for early risk or disease detection and since earlier tumor stages are associated with better

cancer-specific outcomes, risk-adjusted screening programs have been developed and are supported by all major professional organizations (ACS, ACG, AGA, ASCRS, ASGE) with minor variations only [4–8]. The term screening in a strict sense is reserved to the testing of asymptomatic average-risk individuals.

If there is an underlying high-risk constellation or clinical symptoms are present (such as positive fecal occult blood test, noticeable bleeding, anemia, change in bowel habits, etc.), not screening but surveillance or appropriate age-adjusted diagnostic workup should be initiated [6]. Below the age of 40 without additional risk factors, a flexible sigmoidoscopy (or even less) may be sufficient, but a full colon evaluation is recommended for clinical symptoms above the age of 40, or if there are additional findings or suspicion to suggest more proximal pathology.

Screening efforts aim (a) at decreasing the burden of colorectal cancer by removing precancerous lesions, and (b) at reducing cancer mortality by detection of early rather than advanced disease [7, 9]. Effective screening is founded on the understanding that the multistep adenoma-carcinoma sequence may take up to 7–10 years from the first molecular change to a clinically manifest cancer; it should also take into consideration an individual's genetic and disease or age-dependent risk profile for the development of colorectal cancer.

Common screening tools fall into one of three categories: (a) complete or partial direct mucosal visualization (colonoscopy, flexible sigmoidoscopy), (b) indirect structural visualization by radiological imaging (surrogate tests), or (c) indirect nonstructural testing by stool analysis for fecal occult blood (guaiac-based FOBT versus immunochemical testing FIT) or fecal DNA (surrogate tests). For the procedural evaluations, most centers offer their patients to use conscious sedation or monitored anesthesia care (MAC). It is important to state that in order to optimize visualization and increase accuracy of the evaluation, all direct and indirect structural tests alike require a complete and thorough bowel preparation, which is among the most significant obstacles for patients to agree to screening. All circumstances taken together, these tests impose a relevant burden as the patients likely will miss 1–2 days of work and require the utilization of a chaperone for transportation after the intervention.

There is broad consensus among societies and organizations of medical professionals involved in developing screening guidelines that direct tests to detect cancer and adenomatous polyps should be preferred over the indirect tests where resources are available and if the individuals are amenable [7]. In populations where the required infrastructure is lacking, as well as in patients who are either unwilling and/or unable to undergo one of the structural tests or the necessary dietary and bowel cleansing preparation before, the use of stool-based colorectal cancer screening tests are an acceptable alternative.

In the United States, colonoscopy is recognized as the most effective screening tool and has become common practice with an estimated more than ten million procedures performed annually [9]. The advantages of the procedure are obvious as it allows for direct mucosal inspection of the entire colon and also provides opportunity for biopsy sampling for further evaluation as well as for definitive therapeutic interventions by polypectomy in the case of precancerous lesions or early stage cancers [9]. Data from the National Polyp Study, as well as other reports, have demonstrated that colonoscopy with polypectomy is able to reduce the incidence of polyps by 76–90% and the CRC mortality by 53% [10, 11].

Indications for Colonoscopy

In order to achieve good penetration of the target screening population while also remaining cost effective, it is of utmost importance to distinguish between screening of asymptomatic individuals and diagnostic workup for their appropriate use in regard to onset and duration of screening and frequency of repeat exams (Table 1).

Risk Categories

Approximately, 65–75% of the population are considered to be low or average risk, i.e., there are no identifiable risk factors including, a lack of first-degree relatives with CRC or advanced adenomata (Table 2). Another 20–30% are at an increased risk of CRC, based on having one first-degree relative with an age of less than 60 years or two or more first-degree relatives of any age with CRC or advanced polyps, or a respective personal history; there are also a number of ethnicities who have been associated with an increased risk of CRC, including African-Americans and Ashkenazi Jews [4]. Additionally, 6–8% of the population are linked to a high-risk constellation for developing CRC based on the presence of genetic mutations/syndromes such as familial adenomatous polyposis (FAP) or its attenuated form (AFAP), Lynch syndrome (HNPCC), or MUTYH-associated polyposis (MAP), or based on the presence of chronic inflammatory bowel disease (IBD) [12].

Time for the First Screening

In the asymptomatic average-risk individual, it is recommended to start screening colonoscopy at age 50, and if negative to repeat it every 10 years (Table 3). Data from larger cohort studies suggest

Table 1: Distinction between and criteria for screening versus diagnostic colonoscopy.

Setting	Parameters
Screening	Absence of symptoms
	Defined risk categories (Table 2)
	Establishing the time for the first screening (Table 3)
	Quality assessment parameters for each test in general and in individual patient (Table 4)
	Establishing the appropriate repeat intervals depending on (Table 5): • Basic risk profile • Quality of the test performance • Individual findings
Diagnostic workup	Symptom characterization
	Age
	Presence of age-independent risk factors
	Defining the appropriate role of other tests beyond colonoscopy

Table 2: Risk categories for the development of colorectal cancer.

Category	Fraction of population (%)	Lifetime risk of CRC	Details
Average risk	65–75	4.5%	• No personal risk factors
			• Negative family history
Increased risk	20–30	10–20% (?)	• CRC or advanced adenoma in one first-degree relative with age ≤ 60 years or ≥ two first-degree relatives of any ages
			• Personal history of curative resection of CRC
			• Personal history of large adenomatous polyp (> 1 cm) or multiple colorectal polyps of any size
			• Personal history of sessile serrated adenomas (proximal to sigmoid colon)
			• African-American ethnicity, Ashkenazi Jews
High risk	6–8	Nearly 100% by age 45	• FAP
		70%	• Attenuated FAP (AFAP)
		60–80%	• Lynch syndrome (HNPCC)
		Nearly 100% by age 65	• MUTYH-associated polyposis (MAP)
		10–20%	• IBD

CRC colorectal cancer, *FAP* familial adenomatous polyposis, *IBD* inflammatory bowel disease, *HNPCC* hereditary nonpolyposis colorectal cancer, *MUTYH* (*aka MYH*) MutY Homolog of E.coli gene

that the first colonoscopy was associated with the overall greatest benefit in risk reduction, and that an earlier start of general screening (e.g., at age 40) was of only limited value.

However, it has been postulated by some of the professional societies to start routine screening earlier in some subgroups and ethnicities that were associated with an overall increased risk or have shown no or an insufficient decrease of CRC incidence rates over the past decades. Among these groups are African-Americans who are recommended to start screening at the age of 45 years [4]. Moreover, if there is a positive family history involving, in particular, first-degree relatives, and no known genetic mutation is identifiable, the first screening colonoscopy should be recommended to start at age of 40 or 10–15 years before the age at diagnosis of the youngest family member with CRC or advanced adenoma (whichever comes first).

Recommendations for high-risk categories include not only a much earlier start, but due to the accelerated adenoma-carcinoma sequence, much shorter intervals, more frequent repeat exams, and potentially screening for extra-colonic pathology. The specifics are also outlined in Table 3 and depend on the nature of the risk (e.g., genetic syndrome versus IBD) [12]. Preferably, the gene carrier status in families with known genetic syndromes (FAP, Lynch, MAP) should be established by genetic testing rather than "screening" for the presence of polyps. Patients with established clinical or genetic diagnosis of FAP have traditionally been recommended to start

Table 3: Indications for screening based on risk constellation.

	Start	Interval to subsequent colonoscopy (if no pathological findings)
Average risk		
• No personal/family risk factors	Age 50 years	Every 10 years
Increased risk		
• African-American ethnicity, Ashkenazi Jews, and other subgroups	Age 45 years	(5-) 10
• Personal history of CRC	Clearing colonoscopy within 6 months of surgical resection	1/3/5 years
• Personal history of large adenomatous polyp (>1 cm), multiple colorectal polyps of any size, or sessile serrated adenomas (proximal to sigmoid colon)	–	1/3/5 years
• Family history of CRC in FDR <60 years	Age 40 years or 10 years before the youngest affected immediate family member	Every 5 years
• Family history of CRC in any 2 or more family member(s) age <60 years	Age 40 years or 10 years before the youngest affected immediate family member	Every 5 years
• Family history of CRC in FDR(s) >60 years	Age 50 years	Every 10 years
High risk		
• FAP	Age 14	Annual with flexible sigmoidoscopy or colonoscopy until proctocolectomy @age 16–25
• FAP, status post IPAA/Kock pouch	1 year after surgery	Annual pouchoscopy and monitoring of ATZ
• Lynch syndrome/HNPCC	Age 20–25 years, or 10 years before youngest affected family member	Every 1–2 years
• Chronic IBD (UC, Crohn)	7–8 years post onset	Every 1–2 years
• IBD, status post IPAA/Kock pouch	1 year after surgery	Every 1–3 years

FDR first-degree relative, *ATZ* anal transitional zone, *FAP* familial adenomatous polyposis, *UC* ulcerative colitis, *IBD* inflammatory bowel disease, *IPAA* ileal pouch anal anastomosis, *CRC* colorectal cancer

screening at age of 10–12 years with annual flexible sigmoidoscopy. In reality however, there is no nonsurgical, pharmacological, or endoscopic intervention that could obviate the necessity for a prophylactic surgical resection (typically proctocolectomy) which should be planned for an appropriate time between ages 16 and 25. Particularly with wide availability of genetic testing, it is therefore our recommendation that these patients wait with "screening" until they reach the age of 14, as those 2–4 additional years allow these young patient to mature and get an opportunity

to understand and participate in the process of screening rather than being traumatized. The risk of this delay is negligible as a proctocolectomy is almost never needed before the age of 14. The purpose of flexible sigmoidoscopy or colonoscopy in FAP is less to prevent CRC but to get a relative growth profile and establish the right timing for the inevitable surgery.

In contrast, Lynch syndrome (HNPCC) has a more variable phenotype. Patients with a clinical or genetic confirmation of a carrier status are recommended to begin colonoscopy screening at age 20–25 years or 10 years before the youngest family member with CRC or advanced polyps and to subsequently continue every 1 or 2 years.

Quality Assessment Parameters

The efficacy of colonoscopy as a screening tool has been linked to a number of quality parameters that involve: (a) the endoscopist, (b) the patient and the bowel preparation, and (c) potentially some technological aspects (see Table 4) [13, 14]. The clinically most relevant though unpractical parameter would be the detection rate of interval cancers. Hence, the most important surrogate parameter appears to be the overall adenoma detection rate. Other similar parameters such as polyp detection rate (which includes hyperplastic polyps), the overall cecal intubation rate with photo documentation, and the average withdrawal time (typically greater than 6 min) have been used as quality benchmarks even though strong supportive evidence is lacking. Unquestionably, visibility is highly dependent on the completeness of the bowel cleansing. An adequate bowel preparation is critical for the accuracy and cost-effectiveness of colorectal cancer screening while inadequate cleansing should trigger an earlier reexamination [15].

Follow-up Surveillance and Repeat Intervals

After a previous polypectomy or colon resection for CRC, the aim of repeat colonoscopies is to detect and remove adenomata that were potentially missed on the initial exam as well as metachronous new adenomata with advanced pathologic features [16]. Defining the exact length of recommended interval depends on the number of factors to not only include the previously mentioned overall risk categories but also the individual findings (Table 5). In particular, the number of detected and removed adenomatous or serrated polyps, the completeness of the previous removal, the size of lesions, and the presence or absences of unfavorable features (e.g., high-grade dysplasia) have to be taken into account. Furthermore, the time interval may need to be shortened depending on the quality of the previous examination, e.g., if it was complete or the bowel cleansing and visibility were inadequate.

If there were only a limited number of small adenomata (tubular adenoma), a 5- to even 10-year interval is sufficient. A shorter interval of 3 years would be recommended if there were more advanced or multiple polyps (≥ 3), including sessile serrated adenomata proximal to sigmoid colon. In patients who were found to have numerous adenomata (including serrated adenoma), a malignant adenomatous polyp with high-grade dysplasia or focal adenocarcinoma (cancerous polyp), large sessile polyps including sessile serrated adenomata, incomplete removal of polyps,

Table 4: Colonoscopy quality parameters.

Accepted quality parameters	**Benchmark**
Withdrawal time (WT)	≥6 min
Cecal intubation rate (with photo documentation)	≥95%
Adenoma detection rate (ADR) in average risk screening colonoscopy	≥ 25% in men, ≥ 15% in women
Alternate or unquantified parameters	*Detail*
Polyp detection rate (PDR), including nonadenomatous polyps (hyperplastic polyps)	35%
Detection rate of proximal sessile serrated adenomata/polyps (SSA/SSP)	>4.5%
Miss rate	<6–12%
Quality of bowel cleansing	Scored by various instruments: (e.g., Boston bowel prep scale 0–9, based on sum of assessments in 3 segments, 0=unprepped, 3=perfect)
Incidence of interval cancer within 3–5 years	<2–9%

Table 5: Impact of pathological findings on subsequent surveillance intervals.

Pertinent findings on index colonoscopy	**Interval to subsequent colonoscopy**
Small hyperplastic polyps in distal rectosigmoid	10 years
1–2 small tubular adenomas <1 cm with low-grade dysplasia	5–10 years
3–10 adenomas, or 1 adenoma >1 cm, or any adenoma with villous features/ high-grade dysplasia	3 years
More than 10 adenomas completely removed in a single examination	1–2 years
Sessile adenomata removed in piecemeal	<6 months
Polyps in Lynch syndrome	1–2 years

or whose colonoscopy was incomplete or otherwise unsatisfactory, an interval of a few months may have to be recommended (unless a surgical resection is carried out). No adjustment to the screening schedule of 10 years is needed if there were only hyperplastic polyps with typically distal distribution in the rectum and sigmoid colon. Patients with proximal serrated adenomata/polyps or with hyperplastic polyposis syndrome are exceptions from that.

For patients undergoing a curative resection for a colorectal cancer or advanced polyps, there should be a full colonic evaluation to rule out synchronous lesions. If the circumstances did not allow for preoperative clearance of the entire colon (e.g., emergency, obstruction), a full examination should be recommended within 6 months of the surgery. Subsequently, patients with

sporadic cancers require surveillance of their colon to rule out true anastomotic recurrence (<2% risk for colon, 5–20% for rectum); to detect and remove adenomata that have subsequently developed or were missed on the initial examination. Surveillance after CRC is to be planned after 1 year, then after 3 years, and subsequently every 5 years if everything looks normal. In case of pertinent findings as stated earlier, a tighter schedule would be entertained. CRC patients with high-risk constellations (particularly Lynch syndrome) who have only undergone segmental resections mandate continued annual surveillance of the residual.

Contraindications to Colonoscopy

Contraindications are defined by the factors related to either: (a) the condition of the colon, (b) the patient's overall condition, or (c) denial of consent. In general, an intervention is contraindicated when the risks to the patient's health or life outweigh the potential benefits. Absolute contraindications to perform a colonoscopy include toxic megacolon, fulminant colitis, or a known free or concealed colonic perforation; furthermore, the list includes ASA IV/V, hemodynamic instability, or severe coagulopathy such as disseminated intravascular coagulation (DIC). Relative contraindications are situations in which the risk of the procedure (bleeding; perforation; extrinsic organ injury, e.g., to spleen or aortic aneurysm) or of the conscious sedation/anesthesia is substantially increased. Nonetheless, it may on occasion still be deemed appropriate to proceed with at least a limited evaluation if the information that may be acquired would have a crucial impact on further treatment and management decisions. Routine screening is never indicated in pregnancy. Specific situations in pregnancy or management of patients on medications (platelet inhibitors, anticoagulation) are being discussed later.

Effectiveness

Analysis of the effectiveness of colonoscopy is difficult and can be based on a number of different factors, including: (a) the immediate procedural success and miss rates as well as accuracy and safety profile on an individual basis; (b) the population-based impact on CRC incidence and mortality; (c) the cost-effectiveness as measured, for example, by the number of gained patient years per invested direct and indirect dollar amount in comparison to other screening tools and interventions, or to no interventions at all.

Even if there are likely other contributing factors, the simple observation of decreasing CRC incidence and mortality since introduction of routine use of colonoscopies seems to provide convincing evidence for its effectiveness and justification of its broad use. It is not easy, however, to draft high-quality prospective, randomized controlled trials over several decades. The implementation of the National Polyp Study in the 1970s has, along with other large cohort studies, provided a flood of long-term data that demonstrate a lasting impact of interventions and polypectomies. Early reports of 76–90% reduction in colorectal cancer incidence have been recently supplemented with an observed long-term decrease of CRC mortality by 53% [10, 11, 17].

Undoubtedly, colonoscopy has remained and solidified its current role as the gold standard for detection and prevention of colorectal cancer. This remains true despite an imperfect score card. There is substantial inconvenience and the low, but not negligible, risk of side effects and complications associated with the procedure. Furthermore, colonoscopy has an estimated miss rate of approximately 6–12% for large adenomas (adenomas with a size greater than or equal to 10 mm) and a miss rate of 5% for colon cancer [9]. Lastly, while the population-wide screening rates have improved in the United States, 40% of Americans aged 50–75 years are still not being screened, and our set goals remain below the recommendations of our screening guidelines [18–20].

Complications

Problems and complications may result from the preparation, sedation, or occur during the actual procedure phase but signs and symptoms thereof may be delayed [21]. A high index of suspicion, early recognition, and prompt intervention are key to minimizing the morbidity and mortality associated with any major complication. Not surprisingly, pure screening procedures have the lowest risk of complications followed by diagnostic and interventional colonoscopies (e.g., polypectomy); both age and comorbid conditions increased the risk for adverse events [22].

Hemorrhage and Perforation

The two most serious complications are bleeding and perforation. The former is typically associated with endoscopic interventions, while the latter may be due to both, interventions or the mechanics of scope advancement and insufflation. The reported risk of colonic perforation increases with age and with the presence of diverticular disease and ranges from 0.01% to 0.2% of examined patients [21, 23]. In a random five-percent sample of Medicare beneficiaries with colonoscopies compared with a matched control group without colonoscopy, the unadjusted risk of perforation or bleeding increased from 0.1 to 0.6 and from 1.8 to 6.4 per 1000 procedures, respectively [22]. The unadjusted risk for gastrointestinal bleeding was more than four times higher in the polypectomy group than the screening alone group without polypectomy (8.7 vs. 2.1 per 1000 procedures, respectively) [22].

Mortality

The ultimate complication of death in relation to colonoscopy is rare but not negligible. It may be difficult to distinguish in larger databases whether the mortality was truly related to the intervention as such or more the result of a severe underlying disease and comorbidities. In a 2010 review of colonoscopy complications based on prospective studies and retrospective analyses of large clinical or administrative databases, there were 128 deaths reported among 371,099 colonoscopies, for an unweighted pooled death rate of 0.03% [21].

Abdominal Pain or Discomfort

Up to one-third of patients report at least one minor, transient gastrointestinal symptom after colonoscopy. The most commonly reported adverse effects of colonoscopy include bloating (25%) and abdominal pain or discomfort in 5% to 11% [24]. Avoidance of endoscope looping and minimized air insufflation help to reduce these symptoms during and after the procedure. Carbon dioxide compared with standard air insufflation accelerates the postinsufflation recovery [24].

Postpolypectomy Syndrome

After interventional colonoscopy with submucosal or transmural injection (e.g., endoscopic mucosal resection, tattooing) and/or application of electrocautery (e.g., hot-snare polypectomy), patients may develop localized abdominal pain and tenderness, occasionally associated with an increase in inflammatory parameters (WBC, CRP), but show no evidence for a perforation. Postpolypectomy electrocoagulation syndrome (PPES) is poorly quantitated with a wide range of reported incidences from 3 per 100,000 (0.003%) to 1 in 1000 (0.1%) [21]. It is thought to be the result of collateral transmural energy spread through the bowel wall which leads to a localized peritoneal reaction. Treatment is conservative and ranges from watch and wait to administration of antibiotics, which results in resolution of symptoms within a few days.

Gas Explosion

Explosive complications related to the use of cautery during colonoscopy are uncommon but can have dramatic consequences. A 2007 review reported 9 cases, each resulting in colonic perforation and, in one case, death [25]. The combination of hydrogen or methane gas at combustible levels, oxygen, and electrosurgical energy form the risk triangle for explosions. The lack of an adequate anterograde cleansing, use of nonabsorbable or incompletely absorbable carbohydrate preparations (such as mannitol, lactulose, or sorbitol), or the use of enemas-only cleansing (e.g., for flexible sigmoidoscopy) has been associated with an increased risk [26]. Electrocautery should not be performed during routine flexible sigmoidoscopy after enema preparation [26].

Management of Anticoagulants and Platelet Inhibitors

An increasing number of patients presenting for colonoscopy are being treated with antithrombotic agents (anticoagulants, platelet inhibitors) for a variety of conditions. The American Society of Gastrointestinal Endoscopy (ASGE) recently released extensive updated guidelines for the management of antithrombotic agents for patients undergoing endoscopy [27]. In essence, the individual circumstances have to be analyzed to determine (a) the indication, the urgency, and the bleeding risk of the procedure (screening only = low risk, intervention including polypectomy=high risk), (b) the type of antithrombotic treatment and medications, and (c) the risk of thromboembolic events if one or all of these medications were paused. For example, when

the anticoagulation was interrupted in patients with atrial fibrillation, the risk of a periprocedural thromboembolic events and stroke within 30 days was low with 0.7% and 0.3% respectively [28]. On the other hand, the respective risk is very high if there is a mechanical heart valve or a recent status postpercutaneous coronary intervention. Careful interdisciplinary communication and discussion are critical to optimize outcomes.

Ideally, maintenance anticoagulation with warfarin or newer direct thrombin or factor Xa inhibitors (e.g., dabigatran, rivaroxaban) should be paused 5–7 days and 2–3 days before the colonoscopy, respectively, and bridged with subcutaneous injections of unfractionated heparin or low-molecular-weight heparin. Depending on the extent of procedural intervention, the baseline medications may be resumed after 0–5 days. Routine antiplatelet agents for general prophylaxis should be discontinued 7–10 days prior to the procedure and again depending on the degree of intervention can be resumed right away if no polypectomy was done, or after 3–5 days if one was performed. In case of a more critical need for single or dual antiplatelet agents or a nonelective procedure, it might be acceptable to proceed with continued medications for low-risk procedures, and to either postpone noncritical polypectomies or assure more careful hemostasis including application of clips to the polypectomy site. Dual antiplatelet therapy is common after cardiovascular interventions, particularly after placement of bare metal stents or drug-eluting stents; it is generally advisable to postpone elective procedures 1–12 months if clinically acceptable or to limit colonoscopy to diagnostic efforts only, even if some pathology were to be identified.

Colonoscopy During Pregnancy

There is never an indication for a pure colon screening during pregnancy. However, a need may arise for a diagnostic or therapeutic colonoscopy in that period. As with any intervention, the use of colonoscopy is contraindicated in situations where the risks to the patient or the fetus outweigh the expected benefits of the colonoscopy. While it is generally considered safe to perform a needed colonoscopy after the first trimester of pregnancy, it should be determined whether the indication is of such urgency that it cannot be postponed until after delivery [29]. Occasionally, however, a woman's condition is of such great concern that only the use of colonoscopy would have a reasonable chance to lead to an immediate resolution of the patient's ailment or establishing a needed diagnosis. Under such circumstances, the inherent procedural and sedation risks to the patient and the unborn fetus would be acceptable [29].

IBD—Screening and follow-up Pouchoscopies

Chronic inflammatory bowel disease poses a high risk for development of CRC. Routine surveillance with systematic biopsies is therefore recommended to start no later than 7–8 years after onset of the disease, in order to monitor for dysplasia—a cancer precursor. Restorative proctocolectomy eliminates the majority of the disease and the majority of the cancer risk [30]. However, there is a residual risk of cancer formation within the anal transitional zone cuff (even if a mucosectomy has been performed) and in any surgically constructed small bowel reservoir (ileo-anal

pouch, Kock pouch) [31]. It is therefore recommended to perform surveillance of the pouch and the ATZ cuff every 1–3 years by means of a flexible pouchoscopy and random biopsies.

Colorectal Screening for Elderly

While there is a general broad consensus about the age of when to initiate CRC screening and surveillance, there remains significant controversy and silence about when to end it. As previously noted, this question does not or only to a lesser degree apply to the indications for a diagnostic workup for respective clinical symptoms, which are generally an accepted reason to perform a colonoscopy even in patients of advanced age and have been associated with a high yield of advanced neoplasms in 26–30% [32]. However, in absence of symptoms the potential screening benefits of prolonging cancer-free survival have to be weighed against the risks, the lower estimated gain in life expectancy (compared to younger individuals), and the cost of prophylactic screening for cancer in any patient subgroup. In the elderly population (as defined by an age above 75–80 years), the patient's overall performance status and non-CRC life expectancy have a much higher impact and should be taken into consideration [32–34]. A strict limitation based on a rigid age threshold would result in underuse of appropriate screening efforts in fit older individuals; at the same time, it would carry the potential of overusing it in otherwise less healthy younger individuals with limited life expectancy [35]. Unfortunately, elderly patients have been commonly excluded from participation in high-quality, randomized trials including colorectal cancer screening trials that aim at studying the efficacy of the screening colonoscopy. As such, the current screening colonoscopy recommendations have largely failed to address the impact of comorbidities, functional status, and life expectancy in general and particularly in the elderly [34].

Pearls and Pitfalls

- The start age and screening intervals recommended for the use of screening colonoscopies are patient dependent and rely largely on the patient population and associated underlying risk factors. Critical population characteristics and risk factors include:
  - Age (dependent on family history, race, and known genetic predisposition)
  - Family history (history of CRC and known genetic predispositions)
  - Personal medical history (including genetic predispositions, underlying inflammatory bowel disease, findings on prior screening colonoscopies).
- Appropriate preparation prior to the screening colonoscopy is critical for a clinically meaningful examination; this preparation includes the adoption of an appropriate diet and the completion of a recommended bowel-cleansing regimen.
- Colonoscopy guidelines for the purpose of identifying early disease in asymptomatic patients (screening), have no role in defining the appropriate use of colonoscopies with alternate roles (diagnostic or therapeutic colonoscopies) for identifying and treating pathology in the symptomatic patient.

- In the elderly, the role of screening colonoscopies has not been sufficiently defined but should be determined on an individual basis on criteria that include other factors than age only.
- In pregnant women, there is no role for screening colonoscopies. Inevitable diagnostic or therapeutic interventions must be undertaken with caution and clinical judgment of each individual patient case; evaluating the benefits and risks of the procedure for the mother and the unborn fetus.

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‘Clinicians versus clinicians versus managers’ or a new patient centred culture that eradicates ‘them and us’?

Jill Aylott, Prasad Godbole, Derek Burke

Doctors in the NHS are often singled out and blamed for individual behaviour that is sometimes labelled ‘difficult’ ‘obstructive’ ‘resistant to change’ and ‘downright awkward’. In an English NHS system that is highly managed by a majority of non-clinicians at an NHS Trust Board level and controlled by politicians in terms of priorities and budget, an individual doctor’s behaviour might better be understood within social identity theory (SIT) [1] as a normative response to an increasingly antagonistic context within the English NHS. SIT is a psychological theory that argues that a person’s concept of ‘self’ comes from the groups to which the person belongs and that they will seek to identify with others who are also associated with this same group to help form a positive social identity, which will result in feelings of high esteem and positive wellbeing. Within hospitals, specialisms and sub-specialisms of medical and surgical practice creates highly skilled doctors and surgeons who work within increasingly highly specialised areas. Such a high level of specialism will require even closer attention to team working within health care to provide patients with a more holistic and patient centred service. However, in reality there might well be tensions between the objectives of team working and collective leadership and the motivation of individual specialists who seek to preserve their professional identity and the skills associated within their professional role. While clinicians seek to preserve their identity within their clinical role, they may not wish to participate in sharing medical/professional practice, which is suited both to their own skills and the skills of their colleagues, but will be defined separately within their own Royal Colleges’ ‘scope of practice’. This is a challenge for organisations who require more

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teamwork and sharing of practice, as services are transformed into new, more patient centred integrated care models.

This chapter will explore how doctors develop a positive self identity through their Royal Colleges 'scope of practice' and how the employing organisation or the wider context of healthcare practice seeks to challenge this scope of practice when disciplinary boundaries come under pressure as a result of staffing shortages in medicine, nursing and allied health professions [2]. Within this context there is very little self-determination [3–6] of doctors, (which is a critical condition for doctors to remain motivated and engaged), when the development of knowledge is constrained by a managerialist agenda [2, 7]. We will explore a specific case study of two medical specialities, Vascular Surgery and Interventional Radiology whose 'scope of practice' overlaps and argue for the introduction of (1) a quality improvement competency based programme for all clinicians and non-clinicians in healthcare and (2) the introduction of an organisational Quality Excellence award such as the European Foundation for Quality Excellence (EFQM). We argue that a QI competency framework combined with the EFQM could help to facilitate the development of team working across medical, clinical and non-clinical staff and focus all efforts to provide a high level of excellence in patient centred care. Such a focus on patient centred care will serve to focus the efforts of all team members emphasising an 'integrated model of care'.

Our case study will explore how executive hospital leadership in the United States have developed new initiatives to 'integrate' surgical and radiology skills with a 'new' medical role in Vascular services. This project was successful in achieving an integrated social identity of vascular surgery and radiology which generated effective team working to deliver a quality service for patients. We go one step further and argue that to sustain collaborative working practices and to support effective team working, healthcare organisations should engage with the Quality Excellence model (EFQM), (Australian Quality Award or Baldrige Quality Award) which embeds the needs of its customers, patients and end users as being the primary focus for the business of healthcare, driving more demand for shared and overlapping multi-professional 'hybrid' roles.

We conclude with a recommendation that a healthcare organisation's leadership strategy should actively concern itself with the development of a patient centred quality improvement culture, that provides the rationale for the development of clinical and non-clinical competence. If such a step is not undertaken, then Social Identity Theory (SIT) explains that deep divisions will occur in the workforce and professionals will continue to become defensive and territorial about their own 'scope of practice'. The hospital executive board needs to act in a facilitative role to broker a more harmonious, happy and positive medical, clinical and non-clinical workforce.

Each of the Medical Royal Colleges or colleges of Nursing, physiotherapy and other professions in healthcare, are defined by a 'scope of practice' which sets out the legal and professional scope of practice of a given profession. Royal College specialties are further sub specialised. So for example the Royal College of Surgeons has separate register requirements for competence in general surgery and vascular surgery and the Royal College of Nursing is sub specialised to parts of the register for adult, child, mental health and learning disability nursing. A scope of practice will inform 'credentialing' which is a verification of the experience and expertise of a scope of practice and also documents personal interest and willingness to provide medical or nursing care within this 'scope of practice'. This is used as a process to establish a contract between providers

and commissioned work and is part of a process to award payment by private insurance companies for private healthcare. Credentialing is no longer just of interest or relevance to private insurance companies, but is increasingly relevant to doctors, nurses and the allied health professions working in healthcare who have to undergo revalidation every 3–5 years and who need to secure personal and professional indemnity insurance. While doctors currently go through a revalidation process it was a recommendation of the inquiry in the Mid Staffordshire Hospital inquiry [8] that nurses will also have to undertake this process of professional revalidation in the UK in the future.

Social Identity Theory argues that the person's concept of self comes from the groups to which the person belongs. The person will have multiple selves and identities with their affiliated groups. There is also a psychological process of us aligning ourselves to the 'ingroup' and identifying the groups we don't belong to as the 'outgroups'. There are three processes that develop the in/out group thinking:

- Social Categorisation—we categorise people in order to understand and identify them. In relation to the scope of practice of a professional group, we begin to know what categories we belong to and understand things about ourselves, defining and explaining appropriate behaviour according to the group we belong to. We can belong to several groups at the same time.
- Social Identification—we adopt the identity of the group that we belong to and act in ways that we understand and perceive we need to act in. In relation to the scope of practice of a profession, we develop an emotional significance to that identification and our self-esteem will depend on it.
- Social Comparison—after we have categorised ourselves within a group and identify ourselves as being members of that group, we tend to compare our group (the ingroup) against other groups (the outgroups). To maintain self-esteem we will compare our group favourably against other ones. A group will tend to view members of competing groups negatively to increase self-esteem.

Social Identity Theory is always evidenced within a given context and with healthcare employing many different professional clinical roles and non-clinical roles, there will be significant opportunities to observe the effects of SIT. Studies have illustrated that extreme hostility can be induced by putting people into groups and then manipulating intergroup relations [9, 10]. Where groups exist in competition, where one's gain is other's loss—members will feel and act negatively towards each other. The theory calls against blaming individuals who respond to such arbitrary groupings and proposes that minimal conditions are necessary and sufficient to produce negativity towards outgroups. Studies have shown that the mere act of dividing people into groups can create antagonism. We define ourselves through the groups to which we belong. Social identities are much more than self perceptions: they also have value and emotional significances. To the extent that we define ourselves in terms of the group membership, our sense of self-esteem attaches to the fate of the group (and hence the fate of a fellow group members is pertinent to our own) [9]. The social nature of the bond is primary rather than secondary and we identify with others through our common link to a leader. This could explain how clinicians will feel a closer sense of connection to their Royal College with a secondary connection to the corporate values of the organisation. We are bound together through our joint sense of belonging to the same category as our primary purpose.

Case Study: Vascular Surgeons and Interventional Radiologists

In the past, most vascular procedures were performed by vascular surgeons through large incisions that required hospitalisation with prolonged recuperation. Over the last few years advances in technology have seen the growth of endovascular procedures that are performed through a small tube placed in the artery. The removal of blockages in the artery or vein becomes a less invasive process for the patient and after the endovascular procedure, the patient recovers quickly and hospitalisation is unlikely to be required. The rapid development of endovascular techniques, while having a significant impact on both the diagnosis and treatment of patients with vascular disease, has at the same time also created conflict between the two main clinical specialists involved: interventional radiologists and vascular surgeons. The demand for endovascular techniques in the future will make up to 40–70% [11] with possibly 90% in the future of vascular procedures being less invasive, as safer treatment modalities have evolved [11]. Scope of practice will change and evolve over time, but registering changes or advances in 'scope of practice' services the legal and credentialing framework, it does not guarantee patients that a professional is a safe and competent practitioner. Canada has recognised that a surgeon will change their scope of practice over time and provides guidance for this, however it also adds: "*the performance of innovative techniques or procedures within the context of a speciality or family of medicine, while new may not constitute a change of practice*".

It could be argued that the growth of endovascular surgery fits within this definition as it is the use of a particular technique that offers the vascular surgeon a wider range of skills to utilise in his/her intervention with patients. However, in 2010, in the UK, consultant radiologists developed a sub-specialty of radiology called 'interventional radiology' a new role created to provide this intervention within vascular services which had a major impact on both the professions of vascular surgeons and radiologists. Although IR was officially given subspecialty status by the GMC in 2010—radiologists have been performing these procedures since these procedures were conceived by Charles Dotter and presented in his talk at the Czechoslovak Radiological Congress in 1963 [12]. While there are now attempts to understand the procedure as integrated 'vascular interventional radiology (VIR)' the Royal Colleges continue to serve to represent the separate social identities of the separate medical profession of radiologists and vascular surgeons.

Healthcare employing organisations have an important role to play in the facilitation of new and developed 'hybrid' roles that will deliver high quality of care to patients. The development of integrated service models, which are defined by clinical and non-clinical competencies will bring both vascular surgeons and interventional radiologists to the table to develop new service specifications of joint and collaborative team working. SIT could help to facilitate an understanding of the challenges and the tensions that could be encountered along the way. Working from a 'them' and 'us' position towards a people centred service for patients has been successful elsewhere [11, 13].

The lack of uniformity in credentialing criteria for the performance of endovascular procedures adds to the complexity of the problem and there have been calls to modify the training programmes most closely focused on vascular disease, vascular surgery and interventional radiology [11, 13]. The delivery of endovascular services differ substantially [11] and mini fellowships of 3 months in endovascular techniques are not seen as adequate for physicians with limited

experience. It is recommended that any training programme solution must seek to 'up skill' all vascular surgeons to become proficient in endovascular techniques and for interventional radiologists to require broad clinical training in order to adequately and safely apply these new endovascular techniques. One such initiative is a 1-year integrated fellowship for interventional radiologists and vascular surgeons where the evaluation found that the fellows support, like and recommend further integration of their roles. The fellowships were found to be mutually beneficial to both disciplines [11].

The case study of the emergence of endovascular procedures across two medical specialties scope of practice, highlights the tensions that can arise with the changing nature of medical practice with advances in technology and innovation. SIT illustrates the difficult and complex adjustment that is required of self-esteem of doctors in this fast changing healthcare context. What is considered by one Royal College as 'performance of innovative techniques or procedures within the context of a specialty or family of medicine (such as vascular services) may be seen by another Royal College as a 'technique' or 'speciality' belonging to their own specialty's 'scope of practice'. In such situations employing organisations need to take a lead to develop integrated service models, where new skills are acquired by vascular surgeons and interventional radiologists and a team approach is facilitated. Only when this is achieved will the goal of offering high quality patient centred health procedures, within a team based culture, with less invasive procedures be delivered to patients.

The Quality Excellence Framework (EFQM Excellence Model) is a total quality framework [14] widely applied to healthcare in Italy [15] Holland [16] and Germany [17] with its American equivalent the Malcolm Baldrige award or the Australian Excellence award in Australia. The EFQM has nine dimensions which are grouped into five enablers and four results. The enablers describe how staff can improve: leadership, policy, strategy, people, partnerships and resources and processes, while the results cover what the staff achieve: customer (patient feedback and satisfaction) people and society and key performance results. The model works primarily as a self-assessment tool which helps to prioritise improvements. The staff achieve a rating which is either a stage three, four or five level rating dependent on an external assessment and this process can support the integrated care model and support a competency approach with its balanced measures of processes and results (Fig. 1).

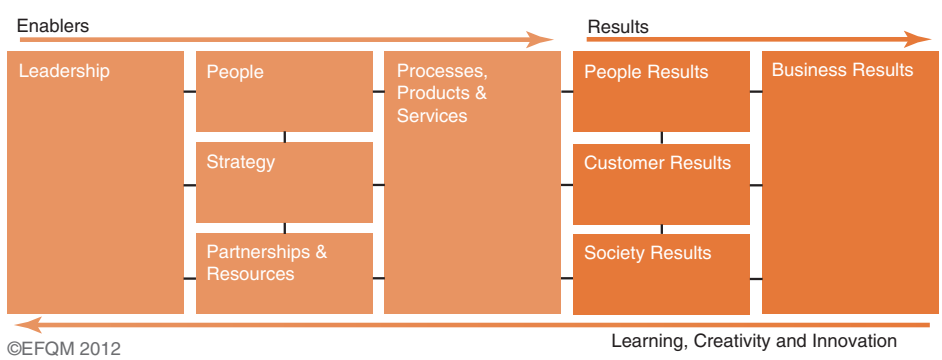

Fig. 1: The EFQM excellence model.

The EFQM excellence model can stimulate greater accountability and support better performance results which ultimately improves patient quality in accessibility, safety, effectiveness, appropriateness and service efficiency [15]. With a UK shortage of consultant radiologists and 44% of NHS trusts (93 out of 156) not offering interventional radiologists around the clock [18], the Excellence model could help provide a healthcare quality governance tool to identify specific action for upskilling and enabling a new hybrid role in endovascular services to achieve quality improvement. This would focus more effort into a new 'dual' hybrid role to meet the needs of patients instead of focusing on the development of uni-discipline specialties. As an improvement tool the Excellence model can connect and align healthcare governance and organisational structures and processes to increase quality across the healthcare system [15]. In an area such as endovascular services that is continuing to evolve across medical specialties, a more objective system wide improvement tool is required to keep a focus on the aspiration of excellence for patients.

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5

Learning to work together through talk: continuing professional development in medicine

Walter Eppich, Jan-Joost Rethans, Pim W. Teunissen, Tim Dornan

Learning to Work Together Through Talk

Becoming a physician is a lengthy process. The trajectory begins after secondary school, may include a general university degree before entering 4–6 years of medical school, and ends with some form of structured graduate training program. The latter can last from 3 to more than 10 years, after which physicians must continue to learn throughout their professional lives. They need not only to stay abreast of the evidence that informs practice, but also to translate evidence into action within the social context of clinical environments. In discussing how all of this might progress, this chapter has three main sections. In the first one, we focus on learning from work when becoming a doctor and explore an emerging framework for practice-based learning in healthcare. We highlight the essential role of 'talk' as a mediator of learning and how it informs communication practices. We address limitations of learning from work, including social structures that promote communication breakdowns. In the second section, we outline the current state of formal continuing professional development (CPD) in medicine, the stated goal of which is to maintain or further develop physicians' competence. In doing so, we highlight the paradox

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between: (a) how CPD is currently organized around activities that promote decontextualized knowledge and skill acquisition, and (b) the evolving understanding that learning and participation in authentic workplace activities are inextricably linked. We explore the limitations of formal CPD by addressing the primary factor that threatens patient safety: breakdowns in communication among healthcare professionals. Since current CPD models foreground individual competence, the competence of healthcare teams—and patient care—likely suffer. In the final section, we explore recent developments in healthcare education discourse relevant to clinical practice since collaboration and communication across professional and disciplinary boundaries are prerequisites for safe patient care. We then envision a world in which workplace learning plays a central role in certified CPD, and how foregrounding talk as a medium for collaboration and learning can enhance practice.

Section I: Becoming a Doctor

Medicine is one of many health professions. Undergraduate medical education consists of mostly uni-professional training programs, which are accredited by governmental and/or local medical regulatory bodies. These training curricula are not the focus of this chapter; see "Educating Physicians: A Call for Reform of Medical School and Residency" for an overview (Cooke, Irby, and O'Brien, 2010). After undergraduate medical studies, medical students emerge as doctors and enter the second phase of clinical training, or graduate medical education, termed 'residency'. After residency, doctors become independent practitioners (Cooke et al., 2010). In primary care settings, as well as in hospitals, they work in teams usually composed of several fully-trained doctors and a complement of nurses and other providers. In teaching hospitals, teams might also include a number of doctors in training (i.e. residents) and perhaps undergraduate medical students if the institution is affiliated with a medical school. A newly qualified doctor might enter a 1- or 2-year period of foundational training in a broad area such as internal medicine or surgery with the aim of pursuing focused training in general practice, internal medicine, obstetrics and gynaecology, surgery, paediatrics, or emergency medicine. Not infrequently, physicians pursue further specialized training to master the nuances of a specific area within their specialty (Cooke et al., 2010). Examples include:

- Internal medicine: e.g. endocrinology, cardiology, gastroenterology
- Surgery: e.g. colorectal surgery, heart surgery, neurosurgery
- Paediatrics: e.g. cardiology, critical care, neonatology, emergency medicine

Practising Medicine Requires More Than Acquiring Knowledge

We can apply two metaphors of learning to doctors' education: 'learning as acquisition' and 'learning as participation' (Sfard, 1998). Medical education requires learners to command large amounts of codified propositional knowledge. A 'knowledge as competence' discourse emphasizes knowledge mastery as an indicator of competence (Hodges, 2006) and foregrounds formal classroom learning, embodied by the metaphor 'learning as acquisition' (Sfard, 1998). Although learning

from clinical practice alongside more experienced clinicians in a classic apprenticeship model (Dornan, 2005; Swanwick, 2005) is a time-honored form of physician training, recent trends towards the 'learning as participation' metaphor explicitly recognize the social nature of healthcare (Sfard, 1998). Lave and Wenger (1991) popularized the notion of learning by engaging in situated social activity in 'communities of practice'. Medical learners, thus, prepare for independent practice not only through acquiring knowledge by reading books or attending lectures, but by gaining access to healthcare communities—through legitimate peripheral participation—in order to work and learn with and from others, and consequently develop their professional identities (Lave and Wenger, 1991; Dornan, Boshuizen, King, and Scherpbier, 2007; Teunissen et al., 2007). There is, accordingly, a movement to promote earlier clinical experiences within undergraduate medical curricula (Diemers et al., 2007; Dornan and Bundy, 2004; Dornan, Littlewood et al., 2006; Littlewood et al., 2005).

In contrast to formal curricula focused on knowledge acquisition, Eraut (2004) outlines four categories of work-based learning: (a) participation in group activities; (b) working with others; (c) assuming challenging tasks; and (d) working with clients [or patients], all of which apply to healthcare. Eraut (2000) also proposes various forms of non-formal learning at work, including: (a) unconscious *implicit learning* that may never reach awareness, such as how to interpret social cues, (b) conscious *reactive learning* that is spontaneous and responds to emergent learning opportunities, such as unexpected changes in patients' conditions, and (c) *deliberative learning*, which involves actively reviewing past events and experiences and planning for future learning, as, for example, when debriefing after clinical events. As he notes, learning at work is mostly invisible and, thus, easily taken for granted (Eraut, 2004). Hence, the resulting knowledge is acquired without awareness and remains tacit (Eraut, 2000; Reber, 1989). Billett (2001c), however, views the differentiation between formal and informal learning critically since it suggests a situational determinism that de-emphasizes the role of human agency in the constructive processes of thinking-acting-learning. To the contrary, workplaces are characterized by participatory practices (Billett, 2004) that afford opportunities for individuals to engage in work activities (Billett, 2001b) within a guided learning workplace curriculum (Billett, 1996, 2000; Dornan, Arno, Hadfield, Scherpbier, and Boshuizen, 2006). Despite tendencies to emphasize formalized components of medical education, recognition that the social nature of clinical work environments affords both tacit *and* explicit learning has refocused clinical training on authentic patient care experiences.

Learning to Practise Medicine Involves Participating in Patient Care

Sociocultural learning theories stress the importance of both context and social interactions within those contexts as prerequisites for individual and collective learning (Brown, Collins, and Duguid, 1989; Durning and Artino, 2011; Eraut, 2007; Lave and Wenger, 1991; Yardley, Teunissen, and Dornan, 2012) and highlight learning by doing, or experience-based learning (Ashley, Rhodes, Sari-Kouzel, Mukherjee, and Dornan, 2009; Dornan et al., 2007; Teunissen et al., 2007). Features of curricula, such as predetermined learning objectives on the one hand and, on the other hand, social interactions between medical learners and nurses, doctors, patients, and peers

while engaged in supported participation in authentic environments, combine to promote competence and a sense of readiness for practice (Dornan et al., 2007). Importantly, feeling invited to participate and engage with a team is essential to initiate and maintain meaningful participation (Sheehan, Wilkinson, and Billett, 2005).

Indeed, Teunissen (2015) claims that the key strength of learning from practice is that it enables people to learn how to perform, think, and interact in ways appropriate for their specific work setting. Further, health care settings are particularly challenging as workplace learning environments since not only are they highly contextual, they are also structured primarily for patient care rather than learning. In exploring this tension, he outlines an empirically-based framework for practice-based learning in healthcare workplaces (Teunissen, 2015). In conceptualizing those who participate in healthcare, including patients, as learners, he also views learning as a process of constructing meaning that is both situated in specific contexts at individual and social levels. Learning may be visible if it leads to changes in future behaviour, making it easier to describe and study. However, learning often represents reinforcing or slightly modifying existing knowledge or behaviours, making it difficult to recognize or observe. The utility of Teunissen's experiences-trajectories-reifications (ETR) framework is to explore how individual and collective effects contribute to acting and learning in workplaces (Teunissen, 2015). First, learners engage in acts within specific situations embedded in social and cultural systems, select and make sense of information, and then adapt their behavior, which leads to personal *experiences*. They can be helped in this process when clinical teachers maximize the affordances of workplaces, support learning, and help create meaning from participation in clinical work activities (Bleakley, Bligh, and Browne, 2011). Of course, different learners will experience situations—and draw meaning from them—differently, because of their unique personal histories. These collections and combinations of personal experiences lead to *trajectories* over time—for multiple individuals, whose trajectories intertwine as their professional and social identities evolve. Indeed, Teunissen also asserts that because many aspects of individuals' experiences and trajectories are shared with others, norms and conventions develop, hierarchies are established and exercised, and specific tools are invented, and a shared understanding of the situational requirements for performance emerges (Teunissen, 2015). Examples of these *reifications* are standard operating procedures, practice guidelines, tools, ways of talking, and structured communication strategies. Given the importance of talk and communication in healthcare workplaces for both learning and patient care, we will give these aspects special attention.

Talk Is Central to Learning from Clinical Practice

Learning from work can be seen as a by-product of engaging in work activities through social interactions with patients and other members of healthcare teams, highlighting the important role of talk in learning (Edmondson, 2012; Steven, Wenger, Boshuizen, Scherpbier, and Dornan, 2014). Both formal and informal opportunities to engage in conversation, including interactions over coffee with more experienced clinicians, contribute in important ways that promote learning and encourage professional thinking (Sheehan et al., 2005). Indeed, "learning to talk", represents the

shift in modern societies away from "manual work to discourse work" (Scheeres, 2003, p. 332) in which talking has become one of the main components of the work (Iedema and Scheeres, 2003). Thus, although talk has always played a role in the work of healthcare, rather than a supporting role, we argue here that talk, as discourse, now plays a central role since it is a core activity in learning and in caring for patients.

Oral case presentations are a prominent example of healthcare talk through which medical students legitimately participate in patient care. During oral presentations, medical learners verbally summarize and present information gathered through interviewing patients/families, examining patients, and—importantly—interpret what it means in terms of diagnosis and/or management. In general, giving an oral case presentation to colleagues represents a fundamental communication skill for *all* physicians, not only to report key findings of patient assessments and diagnostic evaluations, but also to demonstrate an ability to process, prioritize, and synthesize information, formulate possible diagnoses, and outline steps in patient management. *The key is to include only what is relevant to the listener in a given setting.* Haber and colleagues used rhetorical analysis to explore how medical students learn oral case presentation skills (Haber and Lingard, 2001). Students struggle to tailor presentations to the context, in contrast to more experienced physicians who view the rhetoric of their presentations as fluid and dependent on patient, time, and situational factors (Haber and Lingard, 2001). In short, physicians *must* master oral case presentations. Lingard and colleagues (2003) note that socialization involves learning to speak like other community members, both learning to talk *with* and *about* patients (Lingard, Schryer, Garwood, and Spafford, 2003). Indeed, professional identities are "constructed and co-constructed through talk" (p. 40) (Monrouxe, 2010). In addition to demonstrating an ability to synthesize and integrate patient information, medical students shape their professional identifies though oral case presentations, particularly in learning to deal with and convey uncertainty (Lingard, Garwood, Schryer, and Spafford, 2003). For example, students observe more experienced doctors using modal auxiliaries (e.g. can, could, may, might must, shall, etc.) and adverbs (e.g. perhaps, maybe, etc.) in oral case presentations to manage uncertainty in a skilful manner (Lingard, Garwood, et al., 2003). Thus, oral case presentations represent a textual form of talk that comprises a significant form of work for many physicians, one that has important implications for both learning and patient care in all career phases.

The discourse of clinical teaching is, like case presentations, an important example of talk in medicine for which learning is an explicit goal. Supervising or attending physicians are more experienced and fully qualified doctors who oversee medical trainees and are ultimately accountable for patients' care. These more senior physicians often use questions to assess trainee competence during oral case presentations (Kennedy and Lingard, 2007). For example, supervising physicians often pose clarifying questions to support their own understanding of the case. In addition, three other forms of question help assess trainee competence: (a) case-related probing questions to explore the trainee's understanding of diagnostic decision-making or management plans, (b) knowledge-related probing questions to assess medical knowledge, and (c) challenging

questions to test the trainee's assumptions of shared knowledge that emerge during case presentations. Thus, oral presentations reflect a "regular discursive meeting place" (p. S14) for medical trainees and supervising physicians that play an important role in how trainees develop and demonstrate evolving competence and thus earn progressive autonomy (Kennedy and Lingard, 2007). Further, a critical discourse analysis explored descriptions that both medical students and physician supervisors provided about their moments of interaction supplemented by follow-up student debriefing interviews (van der Zwet, de la Croix, et al., 2014). The authors identified various discourses within the Question-Answer dynamic between physician supervisors and medical learners. These included discourses related to a 'power game', 'distance' and 'equality and reciprocity' between educators and learners. Importantly, this analysis revealed affordances of student-doctor relationships conceptualized as 'developmental spaces' that generate positive learning momentum for students and doctors and 'developmental vacuums', which stifle learning. Another study examining the audio diaries of seven general practitioners (GPs) during a 10-week-long clinical placement uncovered trajectories of developing relationships through evolution of dialogue (van der Zwet, Dornan, Teunissen, de Jonge, and Scherpbier, 2014). Doctors in the study used dialogue to define and shape their discourses of good medical practice, both influencing *and* depending on students' learning trajectories.

Supervising physicians often view their questioning practices as activities that serve both teaching *and* patient care. However, Goldszmidt and colleagues (2012) found that supervisors' interruptions to pose questions or make teaching points led to detours from the standard case presentation format that disrupt critical information sharing (Goldszmidt, Aziz, and Lingard, 2012). There is also a form of questioning known in medical circles as 'pimping', which is a slang term (Kost and Chen, 2015) referring to the practice of posing a rapid series of ever-more difficult questions (Brancati, 1989) in a manner that can be interpreted as intimidating or even humiliating to junior medical trainees (Martin and Wells, 2014). In 'pimping' we see an example of the 'power game' (van der Zwet, de la Croix, et al., 2014), which is, ultimately, pedagogically unproductive. Indeed, as a manifestation of inherent hierarchical structures within healthcare, 'pimping' may have negative impacts on medical students and junior doctors, such as fostering future disrespectful behaviour (as a doctor) towards nurses, trainees, colleagues, and patients (Leape et al., 2012). And, yet, both senior surgeons and resident physicians said that intimidation and harassment could have legitimate educational value (Musselman, MacRae, Reznick, and Lingard, 2005).

Talk plays a central a role in learning, identity formation, and socialization of doctors(-to-be) as well as being a core mechanism of patient care. The dialogical nature of interactions within healthcare teams and with patients has numerous positive benefits and in many ways reflects the shift to 'discourse work' seen in other professions. Given the complexity of healthcare settings in which it occurs, however, talk also has the potential to amplify less favourable social structures and practices that impede learning and patient care. These insights highlight the need to understand the positive and negative impact of talk in clinical practice so that we can better design strategies to improve communication for patient care *and* learning.

Shortcomings of Practice-Based Learning in Medicine: When Communication Breaks Down, Learning Breaks Down

The achievements of modern healthcare are, unfortunately, accompanied by errors that have the potential to harm patients. A majority of them result from breakdowns in communication, which we are only beginning to understand. These relate to a number of factors, including authority gradients and power differentials (Cosby and Croskerry, 2004; Nugus, Greenfield, Travaglia, Westbrook, and Braithwaite, 2010), conflict (Janss, Rispens, Segers, and Jehn, 2012), incomplete information sharing (Manser, 2011; Maughan, Lei, and Cydulka, 2011), and failures to speak up about questions or concerns (Okuyama, Wagner, and Bijnen, 2014; Rainer, 2015). Team communication in operating rooms (ORs), for example, was characterized by 'high-tension' events that impacted whole teams including trainees (Lingard, Reznick, Espin, Regehr, and DeVito, 2002) and led trainees either to disengage from the communication or mimic their senior colleagues whose behaviour contributed to the tension. Thirty percent of over 400 communication events in ORs reflected communication failures, which compromised patient safety (Lingard et al., 2004). These failures included not sharing information at all or giving inaccurate information, failing to take account of important contextual issues, and communication without clear purpose. Effects included delays, inefficiency, patient inconvenience, procedural error, and tension.

Accurate information sharing is particularly important at times of transition of care, such as patient handoffs or handovers, which are highly contextualized forms of oral case presentations. A handoff is the verbal exchange of information between health professionals when responsibility for patient care changes hands (Cohen and Hilligoss, 2010). This verbal communication occurs in person or by phone and is called handover or handoff—both are interchangeable terms. An example would be a physician or team of providers handing over care of patients at the end of a shift to a new physician or team before leaving the hospital, thus passing the baton of accountability. Handoffs are also essential when patients are transferred from one area of a hospital to another, such transfer from intensive care units to hospital wards when life-threatening illness has improved. Factors that predict handoff quality include conveying clear, reliable, and salient information, developing shared understanding, and having a supportive working atmosphere (Manser, Foster, Gisin, Jaeckel, and Ummenhofer, 2010). An effective handoff includes a clear assessment of a patient's status and anticipated problems (Manser, Foster, Flin, and Patey, 2013) with the goal of co-constructing a shared understanding of the patient (Cohen, Hilligoss, and Kajdacsy-Balla Amaral, 2012). In surveys, however, residents in emergency medicine report receiving little training in effective handoff practices, increasing the likelihood of communication errors; standardized handoff tools are rarely used (Kessler, Scott, et al., 2014; Kessler, Shakeel, et al., 2014). There are several essential needs: enhancing our conceptual understanding of handoff communication (Beach et al. 2012; Patterson and Wears, 2009, 2010) and then developing comprehensive strategies to promote effective communication (Cheung et al., 2010).

In high-risk settings of emergency departments (EDs), despite the best intentions, information can be erroneous or omitted altogether when one physician hands over patients to another at change of shift (Maughan et al., 2011). In addition to within-unit handoffs, which are generally

planned and involve team members from the same unit who know each other, between-unit handoffs require particular negotiation and coordination skills, such as when patients require hospital admission from the ED to the ward for ongoing care. Patient admission handoffs are more complex due to differences between health professions in their orientations towards illness and treatment, unequal power distribution, and lack of established relationships (Hilligoss and Cohen, 2013; Nugus et al., 2010). During handoff from ED doctors to inpatient teams, a particularly crass discourse is 'selling' patients; in other words, to persuade the inpatient surgical or medical teams to accept patients for hospital admission by minimizing and/or embellishing aspects of their cases (Nugus, Bridges, and Braithwaite, 2009). The goal is procuring inpatient beds expeditiously in order to maintain the flow of patients out of EDs (Nugus et al., 2011), especially when waiting rooms are full of patients still needing care. Selling patients is but one of four metaphors for handoffs between doctors in EDs, who are hospital gatekeepers, and physicians who care for patients after admission. Three others (Hilligoss, 2014) are:

1. Sports and games: handoffs as competition
2. Packaging: handoffs as expectation matching
3. Teamwork and conversation: handoffs as collaboration

These metaphors highlight that handoffs represent more than just information transmission. Handoffs are social interactions in which conversation partners co-construct meaning in the heat of clinical care (Cohen et al., 2012; Patterson and Wears, 2010). This explains why simple technical fixes such as handoff tools to structure information exchange are insufficient to prevent communication breakdowns. Importantly, the social nature of such dialogues develops professional identity (Burford, 2012) and a tribe mentality (Weller, Boyd, and Cumin, 2014). There is an interesting relationship, moreover, between those dialogues and the media through which they take place. In-person compared with telephone conversations, for example, are differently shaped by their social contexts in ways that are familiar to all physicians but currently ill-understood by researchers (Henn et al., 2012).

An insidious and pervasive communication deficit is a failure to 'speak up', or raise concerns to colleagues or supervisors (Okuyama et al., 2014); in other words giving 'voice' (Morrison, 2011) to information, ideas, and opinions (Van Dyne, Ang, and Botero, 2003). In contrast to communication lapses that represent honest mistakes (Reason, 2000), not speaking up and giving voice to concerns represent deliberate choices to remain silent (Maxfield, Grenny, Lavandero, and Groah, 2011) about poor and unsafe patient care or deficient actions by healthcare team members. Factors influencing whether or not providers speak up include (Okuyama et al., 2014): (a) being motivated by a perceived risk to patients depending on how clear the clinical situation appears and what needs to happen; (b) contextual factors such as relationships among team members, attitudes of leaders/supervisors, and organizational support; (c) individual factors such as confidence in skills and education and feelings of responsibility toward patients; (d) feeling that speaking up will make a difference, and (e) the perceived impact of speaking up, for example, fear of reprisals or being made to feel incompetent. The ability to ask questions, express concerns or admit mistakes—thus taking risks—is part of learning (Edmondson, 1999). An important counterpart to trainees feeling empowered to speak up is supervisors being sensitive to unease in colleagues, such

as nursing staff, and creating spaces where concerns can be voiced (Edmondson, 2012). Being able to speak up is related to the climate of learning environments (Boor, Van Der Vleuten, Teunissen, Scherpbier, and Scheele, 2011) and the approachability of clinical supervisors (Boor et al., 2008), which influence willingness to seek support when help is needed (Kennedy, Regehr, Baker, and Lingard, 2009) and ask for feedback (Bok et al., 2013; Teunissen et al., 2009). When viewed through a lens of 'feeling safe to speak up', the harassment and intimidation that is regarded as legitimate and of educational value in surgery (Musselman et al., 2005), 'pimping' by clinical supervisors (Brancati, 1989; Kost and Chen, 2015), 'tense' communication in ORs (Lingard, Reznick, Espin, et al., 2002), and witnessing rude behavior (Flin, 2010; Porath and Erez, 2009) are threats to learning and safe practice because they inhibit a workplace culture of speaking up. These factors influence the internal tension providers face when faced with choosing 'voice' over 'silence' (Eppich, 2015).

As an example of how social milieus contribute to communication breakdowns, we explore some factors that impacted the activation of rapid response teams (RRTs) in four Australian hospitals (Kitto, Marshall, et al., 2014). RRTs are comprised of physicians and nurses who provide expert support to colleagues when a patient's clinical status deteriorates. In one-third of patients whose clinical status warranted RRT activation, issues of hierarchy between treating physicians and nurses, discrepant perceptions about who makes ultimate decisions, and barriers to interprofessional communication prevented RRTs from being called (Kitto, Marshall, et al., 2014). The opposite also occurred: nurses activated RRTs as 'work arounds' to compensate for breakdowns in collaboration with doctors. Together, those two types of shortcomings represent collective incompetence (Kitto, Marshall, et al., 2014). Unfortunately, however, the dominant discourse of competence is an individualistic one, which deflects attention from relational issues like power dynamics or inability to adapt collaborative strategies to new or changing situations (Lingard, 2012).

To summarise, this section shows that learning to become a doctor is more than just acquiring knowledge. Learning and doing are part of the same process (Teunissen, 2015), and participating in authentic patient care within the social context of healthcare teams is essential for learning. Shared activities in these social contexts are structured through verbal and non-verbal communication (Lingard, Reznick, DeVito, and Espin, 2002) enacted during work activities. Thus, talk is the vehicle to co-construct the meaning of shared experiences and is central to learning from practice. Now that we have explored the role of talk in learning, we turn our attention to the current state of continuing professional development.

Section II: The Current State of Continuing Professional Development

After completing residency and subspecialty training, doctors become independent licensed practitioners alongside nurses and other health professionals. Doctors must, however, participate in educational programs for the rest of their careers. Continuing professional development (CPD) helps them acquire and maintain specialty-specific knowledge and skills, which meet the needs of their patients (Peck, McCall, McLaren, and Rotem, 2000). Participation in approved programs of CPD allows them to remain licensed (Sole et al., 2014), maintain their specialty certification

(Campbell and Parboosingh, 2013; Hawkins, Lipner, Ham, Wagner, and Holmboe, 2013; Holmboe, 2013), and be 'revalidated' as practitioners who are fit for purpose (Archer and de Bere, 2013).

The United Kingdom's General Medical Council (GMC) defines CPD in this way:

> CPD is any learning outside of undergraduate education or postgraduate training that helps [physicians] maintain and improve [their] performance. It covers the development of…knowledge, skills, attitudes and behaviors across all areas of…professional practice. It includes both formal and informal learning activities. p. 7 (GMC, 2012).

Traditionally, CPD focuses on the maintenance and development of medical knowledge and skills that are specific to an individual doctor's specialty practice (Davis, Davis, and Bloch, 2008; O'Neil and Addrizzo-Harris, 2009; Peck et al., 2000) and takes various forms (Davis et al., 1999; Mazmanian, Davis, and Galbraith, 2009). Unfortunately, however, it targets relatively low order cognitive skills of remembering and understanding (Legare et al., 2015) rather than behaviour change, which is more likely to impact clinical practice. CPD is largely decontextualized from workplaces, thus divorcing learning from the social context of clinical practice and minimizing the complexity of the learning experience (Bleakley et al., 2011). 'Knowing in practice', which is an essential element of vocational expertise (Billett, 2001a), plays only a secondary role in CPD.

Likewise, interprofessional and multidisciplinary working, which is ubiquitous in clinical workplaces, is largely ignored by contemporary CPD. Current frameworks privilege individual over collective accomplishment because they are profession-specific, constrained by regulatory bodies (Barr, 2009) and removed from the talks between different health workers, which is necessary for safe, effective patient care. While the metaphor of 'learning as acquisition' (Sfard, 1998) has at least some place, traditional CPD foregrounds 'acquisition' over 'participation' disproportionately. The work of Lingard (2012), which contrasts individualist and collectivist discourses of medical competence, supports that interpretation. The individualist discourse views competence as a construct which individuals acquire and possess, is context-free, and represents a state to be achieved. In the collectivist discourse, competence evolves from participation in authentic situations, is situated across networks of persons and artefacts, and manifests in interconnected behaviours occurring within time and space (Lingard, 2012). Lingard notes that "competent individuals can come together to form an incompetent team" (p. 44). Therefore, individualistic CPD is not well aligned with patients' needs (Kitto et al., 2013; Rowland and Kitto, 2014). It does little to combat tribal conflict between providers from different disciplines, whose values and cultural norms diverge (Weller et al., 2014). It seems reasonable to conclude that siloed initial and ongoing health professions education (Kohn, Corrigan, and Donaldson, 2000) contributes to collective incompetence.

Collective incompetence is a serious problem because, according to the 2000 United States (U.S.)-based Institute of Medicine (IOM) Report *To Err is Human* (Kohn et al., 2000), over 70 % of medical errors are caused by communication breakdowns within healthcare teams. Medical errors are a leading cause of death, estimated at 210,000–400,000 deaths/year in 2013 in the U.S. (James, 2013). Communication within and amongst healthcare teams is a critical medium for enacting knowledge and forms the basis for teamwork (Salas, Cooke, and Rosen, 2008),

interprofessional collaboration and learning (Hammick, Olckers, and Campion-Smith, 2009) and safe patient care. Communication breakdowns involve verbal, non-verbal, and written communication during patient handoffs, communication with patients, and failures to speak up with concerns (Sutcliffe, Lewton, and Rosenthal, 2004).

Interprofessional education (IPE), enacted "when members (or students) of two or more health and/or social care professions engage in interactive learning activities to improve collaboration and/or the delivery of care" (p. xiv) (Reeves, Lewin, Espin, and Zwarenstein, 2010), is one potential antidote to collective incompetence. But it is, at best, a partial solution. IPE, continuing education, and workplace learning intersect (Kitto, Goldman, Schmitt, and Olson, 2014) as do quality improvement, patient safety, and continuing education (Kitto et al., 2015). In contrast to uni-professional, off-the-job education, work is *the* primary medium for learning interprofessional collaboration and communication. The next section explores how physicians and other healthcare professionals can enhance their clinical practice by the way they work, talk, and learn together around the central task of giving patients high quality care.

Section III: Aligning Workplace Learning, CPD, and Improved Care Quality

We now envision a world in which workplace learning plays a central role in certified CPD, and enhances practice through quality improvement. We focus on three examples of fundamental structural changes, which support collective team learning and enhance communicative practice. Each example exemplifies Teunissen's (2015) ETR framework by representing concrete experiences and trajectories of activities, shared between individuals and groups over time. Each structural change focuses on a mechanism for steering the talk of practice through reifications, which promote collective learning and are inextricably linked to patient care. In each instance, learning also benefited patients. These examples include: (a) interdisciplinary and family-centred rounds (b) patient handoffs in a children's hospital, and (c) use of checklists in surgery and for central venous catheter insertion.

Improving Patient Care Through Enhanced Interdisciplinary Collaboration on Ward Rounds

When patients are admitted to hospital, a team of physicians, nurses, and other allied health professionals cares for them. Each day, physicians review patients' status and responses to treatment, and modify care plans during what is known as a 'ward round'. It is in this setting that medical learners give oral presentations about their patients in order to inform the team about patients' status and contribute to plan care. Given the sheer number of providers involved, there is great potential for miscommunication. Indeed, doctors and nurses may not communicate clearly with each other or even agree about the care plan (O'Leary, Thompson, et al., 2010). In response to these findings, O'Leary and colleagues re-engineered ward rounds into structured interdisciplinary rounds (SIDR) on both units with medical trainees (O'Leary et al., 2010) and those units

without trainees (O'Leary et al., 2011). They standardised where and when SIDRs took place, who participated, and how long rounds lasted. Nurses' perceptions of collaboration and teamwork subsequently improved. Importantly, key safety measures got better (O'Leary et al., 2011): patients hospitalized on units with medical trainees had significantly lower rates of preventable adverse events. In a subsequent study, preparing physicians and nurses to share leadership within SIDRs improved teamwork and communication, as measured by a Safety Attitudes Questionnaire (O'Leary et al., 2014). Stein and colleagues (2015) built on this work and reorganized the workflow of a hospital ward to create what they call an accountable care unit. In doing so, they integrated: (a) unit-based teams, (b) structured interdisciplinary bedside rounds, (c) unit-level performance reporting, and (d) unit-level nurse and physician co-leadership. Similar to the work by O'Leary and colleagues (2014), Stein and team (2015) structured rounds to include interdisciplinary input and shared leadership structures. Dissimilar was the location of rounds themselves; Stein and team conducted rounds *at the bedside* with a standard communication protocol that also engaged the patient. All participants prepared in advance to promote efficient and accurate information exchange. A preset choreography allowed each actor to play their role, from unit charge nurse, bedside nurse, junior physician, medical students, to allied health professionals. The protocol included daily review of a quality safety checklist. Health professionals, patients and families all reviewed the plan of care together to ensure shared understanding. Importantly, restructuring the hospital ward into an accountable care unit enhanced communication and work climate whilst reducing unadjusted mortality rates by half (from 2.3 to 1.1 %). Examples of family-centred rounds exist also in paediatrics (Muething, Kotagal, Schoettker, Gonzalez del Rey, and DeWitt, 2007). These innovations worked in part because they brought together interprofessional teams in both time *and* space, which served to facilitate the talk of collaborative clinical practice and harmonize patient care.

Improving Patient Handoffs

Given the variable size, weight, and developmental stage of sick and injured children (Luten et al., 2002), paediatric units are at particularly high-risk of communication errors (Kohn et al., 2000). Some attempts to standardize handoffs, focusing solely on information transfer, have not yielded the expected benefits (Cohen et al., 2012) but more comprehensively designed handoffs have been successful. Starmer and colleagues (2012) developed a mnemonic to standardize verbal handoffs called I-PASS, whose elements were:

- I: Illness severity in terms of patient stability or potential for deterioration
- P: Patient summary of key events, ongoing assessment/plan
- A: Action list of key to-do items
- S: Situation awareness and contingency planning
- S: Synthesis by receiver to summarize key elements, ask questions, restate key to-do items

Beyond clear and accurate information transfer, this model encourages providers to process what they have heard, repeat back key elements, and speak up with questions or concerns. This process helps them understand what to anticipate and what tasks they must complete. In other

words, *this form of handoff provides a space for co-constructing meaning*. Rates of medical error and preventable adverse events in hospitalized children fell significantly after the handoff tool was implemented, which also comprised training and structured changes to where handoffs occurred and who attended them (Starmer et al., 2013). The training included workshops, simulation exercises, faculty development tools, and materials to influence institutional culture. It addressed individual, organizational, and contextual factors linked to both care processes and patient outcomes (Starmer, O'Toole, et al. 2014; Starmer, Spector, et al. 2014). Involvement of nine hospitals in the research provided a multi-centre view of how improved resident handoff could reduce medical errors, preventable adverse events, and communication failures (Starmer, O'Toole, et al. 2014; Starmer, Spector, et al. 2014). In 10,740 patient admissions, the rates of medical error and preventable adverse events decreased significantly without increasing the time required to complete handoffs. These results show how structured processes can shape social and organization culture, shift the discourse of a high-risk event, and improve patient outcomes. Similarly, adapting standardized handoff approaches to local practice in 23 children's hospitals significantly reduced handoff failures (Bigham et al., 2014), highlighting how important it is to contextualize such interventions to institutional cultures. Shared understanding among 'sender' and 'receiver' during ED patient handoffs and structuring the input of nurses provide space for dialogue is gaining traction (Gopwani, Brown, Quinn, Dorosz, and Chamberlain, 2015).

Maximizing the Potential of Using Safety Checklists

The use of checklists also improves patient safety. For example, a surgery safety checklist implemented in hospitals in many different countries reduced rates of death and complications significantly (Haynes et al., 2009), although social factors such as the collaborative competence of individual teams (Kitto and Grant, 2014) influence uptake and effectiveness. Similar contextual issues (Dixon-Woods, Bosk, Aveling, Goeschel, and Pronovost, 2011; Dixon-Woods, Leslie, Tarrant, and Bion, 2013) affect the uptake of measures to reduce the rate of potentially lethal bloodstream infections (Pronovost, 2008; Pronovost et al., 2006) associated with insertion of long catheters into the veins of the neck or upper chest in patients in intensive care units to administer medications and fluids. As Bosk and colleagues (2009) note, it is a mistake to view checklists as simple technical solutions for complex sociocultural problems. Indeed, use of checklists may have unintended consequences when implemented in a top-down fashion. Building checklists for interprofessional contexts requires understanding of the politics and complex local power structures as well as cultural and relational factors of stakeholder groups (Kitto, 2010). We conclude that both handoff tools and checklists are powerful mechanisms to improve communication and practice-based learning if they are designed and implemented with local context and social factors in mind.

Common Themes Relevant for Workplace Learning, Quality Improvement, and CPD

The positive patient outcomes demonstrated in quality improvement initiatives linked to interdisciplinary rounds, handoffs, and the effective use of checklists highlight several key themes of

practice-based learning. These include collective competence (Lingard, 2012), intersubjectivity (Billett, 2014; Teunissen, 2014) and reciprocal interdependence (Edmondson, 2012). Talk links these themes because it intertwines learning and working within the social fabric of workplaces. Collective competence involves making collective sense of workplace events, developing and using a collective knowledge base, and cultivating a sense of interdependency (Boreham, 2004). Thus, groups negotiate competence collectively through work and talk (Lingard, 2012). Viewing effective clinical practice through the lens of collective competence, it becomes clear that quality improvement work brings trainees and practicing clinicians together and nurtures meaningful collaboration and communication by focusing on patient outcomes achieved by the collective rather than on the competence of individuals. When teams have successfully implemented interdisciplinary rounds, an important component of their intervention has been co-leadership by physicians and nurses (O'Leary et al., 2014; Stein et al., 2015), which mitigated the tradition of dominance by doctors and made space for truly interprofessional care (Bleakley, 2013a). They shifted "multi-professionalism to interprofessionalism" (p. 461) (Bleakley, Boyden, Hobbs, Walsh, and Allard, 2006) and co-promoted collaborative learning and patient-centeredness (Bleakley et al., 2011). Although entailing communication between physicians only, the effective practices orchestrated by Starmer and colleagues (2012, 2013; Starmer, O'Toole, et al. 2014; Starmer, Spector, et al. 2014) reframed handoffs as collective events that integrated socio-cultural and adaptive elements of healthcare environments. When checklists are implemented as part of a care bundle, they promote dialogue by opening channels of communication that make health workers collectively responsible for outcomes.

The term intersubjectivity means that people working together share common understanding (Billett, 2014). This understanding involves sensing what others intend, think, and feel as well as imagining what impact their actions may have on those around them. Interactions are fundamental for creating shared realities (Teunissen, 2014). Further, intersubjectivity helps explain how members of established healthcare teams understand and make sense of individual preferences and idiosyncrasies. This makes constant negotiation for routine tasks unnecessary while reserving it for grappling with non-routine or novel problems (Sheehan et al., 2005). One can envision high degrees of intersubjectivity on medical wards with nurse-physician co-leadership and processes that promote collaboration. Billett (2014) highlights that intersubjectivity itself can be viewed as a desirable learning outcome among interprofessional teams.

Edmondson (2012) advocates reciprocal interdependence, which denotes a shared understanding that professionals cannot work and learn without each other. This notion is at the very core of interprofessional practice. Specifically, she states that healthcare is at times so complex that processes must constantly adapt to the unique needs of patients, providers, and workplace contexts. As all of these are in constant flux, providers need to work together to promote collective learning on a daily basis. Edmondson's conceptual model uses the term 'teaming' to highlight the behaviours rather than the people (Edmondson, 2012). Notions of complexity (Lingard et al., 2012) and team working (Bleakley, 2006) as 'liquid' and 'fluid' (Bleakley, 2013c) support this approach. Individuals coming together to solve collective problems should engage in 'teaming

behaviours' to 'organize-to-learn' rather than 'learning to execute' (Edmondson, 2012). Those behaviours include:

- Explicitly framing activities as learning opportunities
- Making it safe to learn
- Learning from failure
- Spanning occupational and cultural boundaries

These behaviours are enacted through the discourse of workplaces; specifically, by asking questions, sharing information, seeking help, talking about mistakes, and seeking feedback. Leaders in Edmondson's 'teaming' model—lead nurses and doctors—frame their own roles in the process by espousing reciprocal interdependence and acknowledging their own fallibility in the service of psychological safety. Feeling safe to learn means feeling safe to disagree, to question, to be wrong (Edmondson, 2012), which is not typical of clinical practice. Indeed, even when we feel safe, we still engage in self-censorship and often remain silent, which inhibits knowledge sharing and group learning (Detert and Edmondson, 2011). Although we have focused on talk here, silence is discourse too (Lingard, 2013), especially when it comes to 'speaking up' and giving voice to ideas or concerns (Milliken and Morrison, 2003; Van Dyne et al., 2003; Eppich, 2015). The teaming behaviours outlined by Edmondson promote discourses of collective competence, intersubjectivity, and reciprocal interdependence. We now discuss ways forward by exploring how to enhance productive discourse in clinical practice to address communication breakdowns.

Use of Simulation to Promote Productive Discourse

The 2000 Institute of Medicine report recommended team training in simulated settings (Kohn et al., 2000), which promoted simulation-based education (Eppich et al., 2013). The team training literature, in general (Weaver et al., 2010) and simulation-based team training (SBTT) in particular (Weaver et al., 2010) is beginning to show that simulation is effective in domains such as obstetrics (Draycott et al., 2008). This work has supported the expanded use of SBTT to promote teamwork and interprofessional collaboration (Tofil et al., 2014). More robust needs assessment is required to ensure that simulation-based experiences align with the demands of clinical practices that depend upon interprofessional communication and collaboration (Eppich, Howard, Vozenilek, and Curran, 2011). Recent trends emphasize the importance of an interprofessional approach (Hammick, Olckers, and Campion-Smith, 2009; Thistlethwaite, 2012; WHO, 2010). We see potential for learners in team and interprofessional simulations to engage in types of talk that promote collaboration and team-working and the forms of communication that comprise substantive elements of the work (Iedema and Scheeres, 2003; Scheeres, 2003). Exploring simulation experiences in post-event debriefings (Cheng et al., 2014; Eppich and Cheng, 2015; Fanning and Gaba, 2007) prepares health care providers to reflect on critical events in clinical settings (Kessler, Cheng, and Mullan, 2014), which has been beneficial in paediatric intensive care units (Wolfe et al., 2014). Voices are emerging that call for the greater integration of simulation-based strategies in the educational paradigm of clinical practice (O'Leary and Woods, Woods, 2014; Weller et al., 2014), while ensuring that sufficient theory guides practice and integrates simulation within

existing curriculum (Bleakley et al., 2011). So although healthcare simulation holds promise, it is not a panacea. How to best design and implement simulation-based activities during medical school and clinical training needs further study.

Aligning Simulation and Workplace Learning

It has been suggested that "learning by simulation can become a simulation of learning" (p. 606) and that simulation may, in some instances, no longer accurately reflect actual clinical practice (Bligh and Bleakley, 2006). These authors call for greater dialogue between practitioners in work-based learning and simulation-based learning, noting that advocates of work-based learning may glean important lessons from strategies simulation educators use to structure learning environments, integrate scaffolding, and facilitate feedback (Bligh and Bleakley, 2006). Team research could usefully address concerns about complexity including the need to study interprofessional teams in clinical settings during patient care (Salas et al., 2008). A pressing research agenda is to explore how healthcare providers learn collaborative practice and the personal and situational factors that influence this capability (Thistlethwaite, 2012).

Mechanisms to incorporate sociological factors such as hierarchy, power relations, professional identity, and interprofessional conflict (Kitto, Gruen, and Smith, 2009; Lingard, Reznick, DeVito, et al., 2002) in interprofessional team simulations are relatively underexplored. Some authors point out that current approaches to SBTT focus primarily on enhancing individuals' team orientation, and propose increased emphasis on collaboration, negotiation, and communication skills (Sharma, Boet, Kitto, and Reeves, 2011). One strategy to align simulation with workplace learning is to rely less on resource-intensive simulations using computer controlled manikins and expand the use of simulated patient methodologies. The latter approach uses real people trained to mimic patient conditions to recreate clinical events (Cleland, Abe, and Rethans, 2009). Using such trained people to serve as unannounced or 'incognito' simulated patients in real primary care practice (Rethans, Gorter, Bokken, and Morrison, 2007) and for phone consultations (Derkx, Rethans, Maiburg, Winkens, and Knottnerus, 2009) demonstrates promise. Unobtrusive data collection in actual clinical practice can serve as a starting point for simulation scenario building and inform subsequent feedback/debriefing. More targeted work is needed in this area; and it seems particularly promising to align the needs of practitioners and their patients with an educational strategy to improve discursive practice.

Summary

In outlining learners' paths towards becoming doctors, this chapter has highlighted the essential role of discourse in learning, identity formation, and patient care. Shared understanding and co-construction of clinical experiences—and learning—are mediated through talk. We have argued that most forms of CPD, which focus on the 'learning as acquisition' rather than the 'learning as participation' paradigm, are divorced from authentic clinical practice. We have provided examples of structures that strengthen collective learning processes--the space, the actors, the

talk—and steer the discourse of practice in productive directions. Although adding structure may reduce agency (Teunissen, 2015), it likely augments learning from practice. We suggest that patient-focused quality improvement projects and simulations aligned to workplace needs could meet requirements for continuous professional development are both measurable and linked to authentic practice. Future work could usefully further explore how steering the talk of practice can promote learning.

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Abbreviated Prescribing Information Polyethylene glycol (Macrogol 3350), Sodium Chloride, Sodium Hydrogen Carbonate & Potassium Chloride Concentrate for Oral Solution **Cremapeg. COMPOSITION:** Each 25 ml of solution contains: Polyethylene glycol 3350 USP 13.125 gm, Sodium Chloride IP 0.3507 gm, Sodium Hydrogen Carbonate IP 0.1785 gm, Potassium Chloride IP 0.0466 gm. **INDICATIONS:** Cremapeg is indicated for bowel cleansing prior to colonoscopy. **DOSAGE AND ADMINISTRATION:** Dosage recommendation for Bowel cleansing prior to colonoscopy - Each Cremapeg 200 ml bottle, supplied as liquid concentrate, must be reconstituted with water to reach a final volume of 1 litre before its use; it is not for direct ingestion. Four bottles of Cremapeg 200 ml liquid concentrate reconstituted with water to reach a final volume of 4 litres would be needed to achieve adequate bowel cleansing prior to colonoscopy. **Administration: Adults:** 4-litre PEG preparation can be consumed as 2 litres solution on the day before and 2 litres of the solution on the morning of colonoscopy or all 4 litres of solution on the morning of colonoscopy for same afternoon procedures as recommended by the physician. Drink 240 ml of the solution (8 Oz.) every 10 minutes till all the solution is consumed or rectal effluent is clear. **USE IN PREGNANCY AND LACTATION:** It is not known whether Cremapeg can cause harm when administered to a pregnant/lactating woman. Cremapeg should be given to a pregnant/lactating woman only if clearly needed. **CONTRAINDICATIONS:** Gastrointestinal (GI) obstruction, ileus, or gastric retention, Bowel perforation, Toxic colitis or toxic megacolon, Known allergy or hypersensitivity to any component of the formulation. **WARNINGS AND PRECAUTIONS:** Cautiously used is patients with serious Fluid and Serum Chemistry Abnormalities, cardiac Arrhythmias, Seizures, renal Impairment, Colonic Mucosal Ulcerations and Ischemic Colitis. **ADVERSE REACTIONS:** Nausea, abdominal fullness and bloating are the most common adverse reactions to administration of Cremapeg. Abdominal cramps, vomiting and anal irritation occur less frequently. These adverse reactions are transient and usually subside rapidly. **DRUG INTERACTIONS:** Use caution when prescribing Cremapeg for patients who are using medications that increase the risk for fluid and electrolyte disturbances or may increase the risk of adverse events of seizure, arrhythmias, and prolonged QT in the setting of fluid and electrolyte abnormalities. Oral medication administrated within 1 hour of the start of the Cremapeg solution may be flushed from the GIT and not absorbed. Issued on: 3rd January 2018. Source: Prepared based on full prescribing information, version 1.0, dated: 3rd January 2018. For full prescribing information, please contact: Medical Sciences Division, Abbott India Limited, Floor 17, Godrej BKC, Plot No. C – 68, BKC, Near MCA Club, Bandra (E), Mumbai – 400 051.

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