Gastrointestinal Endoscopy-Associated Infections: Update on an Emerging Issue

Article *in* Digestive Diseases and Sciences · May 2022

DOI: 10.1007/s10620-022-07441-8

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INVITED REVIEW

Gastrointestinal Endoscopy-Associated Infections: Update on an Emerging Issue

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Received: 10 October 2021 / Accepted: 7 February 2022

Abstract

Over 17.7 million gastrointestinal (GI) endoscopic procedures are performed annually, contributing to 68% of all endoscopic procedures in the United States. Usually, endoscopic procedures are low risk, but adverse events may occur, including cardiopulmonary complications, bleeding, perforation, pancreatitis, cholangitis, and infection. Infections after the GI endoscopies most commonly result from the patient's endogenous gut flora. Although many studies have reported infection after GI endoscopic procedures, a true estimate of the incidence rate of post-endoscopy infection is lacking. In addition, the infection profile and causative organisms have evolved over time. In recent times, multi-drug-resistant microorganisms have emerged as a cause of outbreaks of endoscope-associated infections (EAI). In addition, lapses in endoscope reprocessing have been reported, with some but not all outbreaks in recent times. This systematic review summarizes the demographical, clinical, and management data of EAI events reported in the literature. A total of 117 articles were included in the systematic review, with the majority reported from North America and Western Europe. The composite infection rate was calculated to be 0.2% following GI endoscopic procedures, 0.8% following ERCP, 0.123% following non-ERCP upper GI endoscopic procedures, and 0.073% following lower GI endoscopic procedures. *Pseudomonas aeruginosa* was the most common culprit organism, followed by other Enterobacteriaceae groups of organisms and Gram-positive cocci. We have also elaborated different prevention methods such as antimicrobial prophylaxis, adequate sterilization methods for reprocessing endoscopes, periodic surveillance, and current evidence supporting their utilization. Finally, we discuss disposable endoscopes, which could be an alternative to reprocessing to minimize the chances of EAIs with their effects on the environmental and financial situation.

Keywords Contamination · Infections · Endoscopic retrograde cholangiopancreatography · Infection · Duodenoscopy · Transmission · Endoscopy, colonoscopy · Antibiotic prophyalxis · Esophagogastroduodenoscopy

Introduction

Ever since gastrointestinal (GI) endoscopy was first introduced in 1868 [1], the field has undergone rapid development in the evolution of techniques and their implementation in clinical practice. Technological advancement has widened the diagnostic and therapeutic scope of endoscopy in the field of gastroenterology. An estimated 15 million colonoscopies and 7 million esophagogastroduodenoscopies (EGD) are performed annually in the United States (US). In addition, endoscopic retrograde cholangiopancreatography (ERCP) procedures [2], flexible sigmoidoscopies, and endoscopic ultrasound (EUS) procedures add to another one million GI endoscopies approximately [3]. Moreover, outpatient GI endoscopic procedures contributed toward a healthcare expenditure of $32.4 billion in 2012, with $12.3 billion associated with upper GI endoscopies and $19.3 billion related to colonoscopies [4]. Colonoscopies alone accounted for about 1.03% of Medicare expenditure in 2015 [5]. These estimates include spending accrued from the procedure as well as from post-procedural complications such as infections, bleeding, and others.

Post-endoscopy infections have long been acknowledged as a complication associated with endoscopic interventions [6]; however, comprehensive information on the incidence

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Published online: 09 March 2022

of infections following GI endoscopic procedures is lacking. Most of the available data about endoscopy-associated infections (EAI) is related to duodeonoscope, mainly related to elevators [7, 8]. Only a few original research articles have addressed the prevalence of EAI and contamination rates related to other types of endoscopes. Moreover, the infection profile and causative organisms have continuously evolved over time. Specifically, there are limited data on the temporal trend of post-endoscopic infection events. The current evidence on the prophylactic measures to prevent these infections is also rapidly evolving, lacking consensus on adequate preventive measures.

This review systematically summarizes the incidence of cross-infection following various GI endoscopic procedures, including ERCP and other upper and lower GI endoscopic procedures. Finally, we have also elaborated on the pathogens associated with the endoscopic cross-infections, with control strategies to mitigate these infections.

Methods

A comprehensive systematic review of the literature was performed for studies reporting EAIs after any GI endoscopic procedures from PubMed, Google Scholar, Cochrane, Web of Science, Scopus, and Embase databases from inception to October 2020. The search strategy included the following MeSH terms or keywords: "endoscope" or "endoscopic retrograde cholangiopancreatography" or "ERCP" or "esophagoscope" or "duodenoscope" or "gastroscope" or "jejunoscopy" or "enteroscopy" or "colonoscope" or "endoscopic ultrasound" and "infection". The initial search yielded 1708 results, from which, after removing duplicate studies, we screened out 1554 articles based on our exclusion criteria (case reports, literature review, systematic reviews, summary recommendations, and policy documents, mentioning endoscope contamination without any information on patient's infection, unavailability of full-text, language other than English). We also manually searched primary literature from review articles addressing infections arising as a result of the endoscopies, which yielded another 37 articles. These articles were also screened as above. Thus, the number of studies that were finally included was 118 (Fig. 1). All the included studies mentioned clinically and microbiologically confirmed infection as their complication event following the endoscopic procedure, with the source of infection both exogenous as well as endogenous gut flora.

Epidemiology of EAI

The overall composite cross-infection rate was calculated to be 0.2% (5616 cross-infection events out of 2,798,989 procedures). The EAIs were categorized into the following groups based on the type of endoscopic procedures: infections associated with ERCP (Table 1 [9–38]), infections related to upper GI endoscopic procedures other than ERCP (Table 2 [2, 25, 39–57]), and infections related to lower GI procedures (Table 3 [2, 58–63]). While Table 3 contains all the infection events reported in the literature databases, Tables 1 and 2 include data over the last decade (2011–2020). The remaining data (from inception till 2010) are reported in Supplementary Tables 1 and 2. In addition, a composite post-endoscopy infection rate was calculated from 71 studies reporting the total number of patients undergoing an endoscopic procedure (denominator) and the total number of infections following such procedures (numerator). This included 51 studies reporting infection rates after ERCP, 16 studies reporting infections after non-ERCP upper GI endoscopic procedures, and four studies reporting infection rate after lower GI endoscopic procedures. This low rate could be because of the underrecognition and underreporting of the cross-infections, especially from developing countries.

Figure 2 summarizes the geographical distribution of all studies reporting infections after ERCP procedures (green dots), non-ERCP upper GI endoscopic procedures (red dots), and lower GI endoscopic procedures (black dots). Post-procedural infectious adverse events are more common following ERCP and upper GI procedures. The highest number of infections are reported from North America, including the USA and Canada, and Western European countries. This skewed geographical distribution is likely due to reporting bias since stringent surveillance of infection, and strict quality control measures are possible in the developed nations due to the availability of resources and funding.

Data from the studies between 2011 and 2020 that reported infections following ERCP are summarized in Table 1. A total of 88 studies reported post-ERCP infections, out of which data from 51 studies were used to calculate the composite post-ERCP infection rate. Following ERCP procedures, the composite infection rate was estimated to be 0.8% (3452 out of 433,414 procedures). Sepsis and cholangitis were the two most common infections reported after ERCP, together contributing to over 77% of post-ERCP infections (2419 out of 3115 total post-ERCP infection events). Pancreatitis, Clostridium difficile infection, surgical site infections, intra-abdominal abscess formation, and bacterial peritonitis were also rarely reported following ERCP. In recent years, colonization following ERCP procedures by multi-drug-resistant organisms (MDRO), i.e., organisms with resistance to more than one different class of antibiotics [64], was also reported. In addition, endoscopic interventions such as sphincterotomy were linked to infectious complications [65, 66]. The infection complications can arise from both the endoscope as well as endoscope accessories that come in contact with the GI mucosa [67].

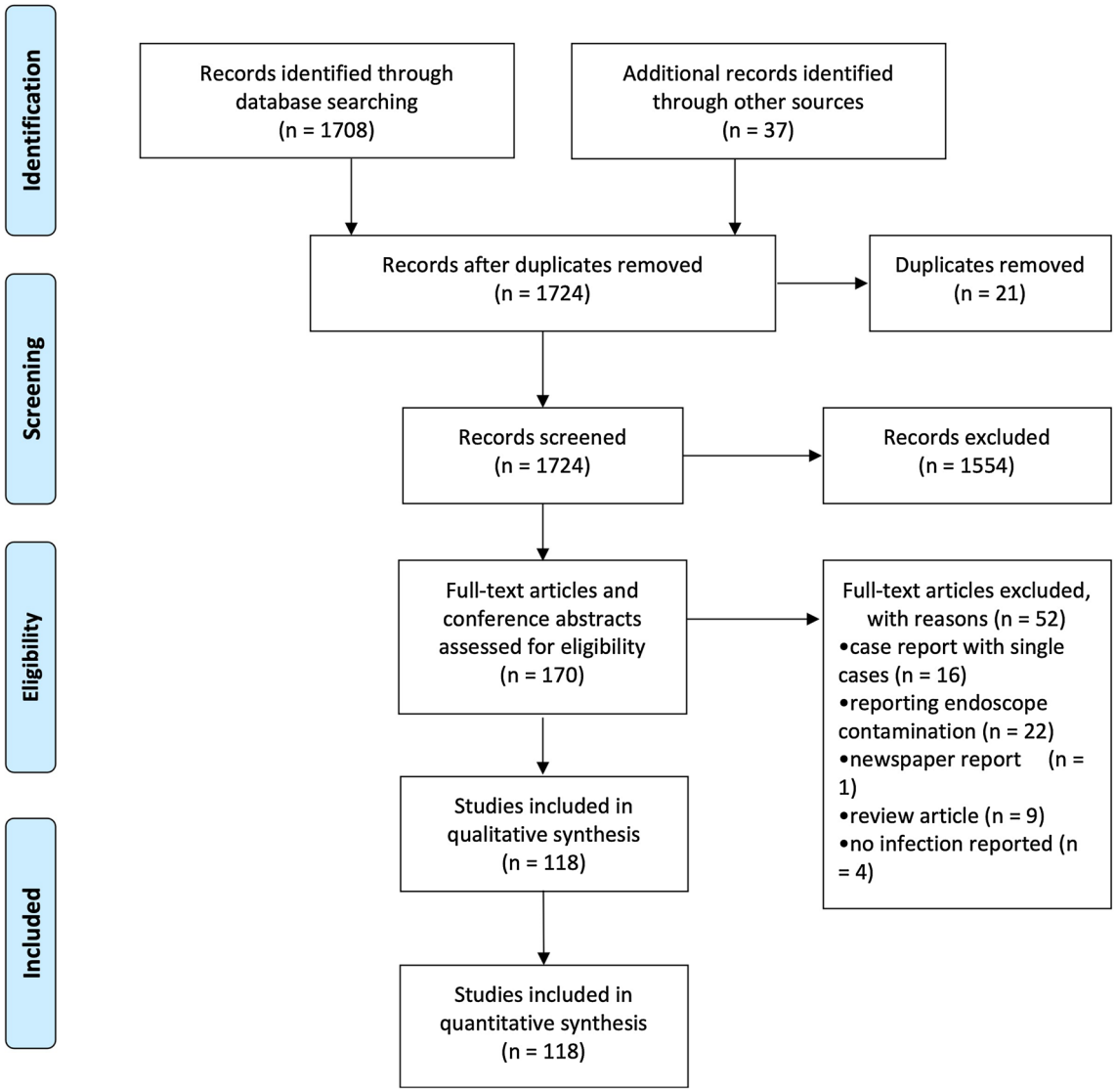

Fig. 1 Selection of studies based on the inclusion and exclusion criteria

Table 2 shows the infectious events after non-ERCP upper GI endoscopic procedures reported between 2011 and 2020. These infections were most commonly reported after duodenoscopies followed by gastroscopies, rarely after EUS and esophageal dilatation procedures. Sepsis, i.e., a positive blood culture without any other obvious identifiable source of infection, cholangitis, and gastroenteritis are the most common infectious complications following non-ERCP upper GI endoscopy, together contributing to 89% of EAIs. Colonization with MDRO was reported in 32 out of 1787 EAIs following such procedures. Rarely, these interventions have resulted in surgical site infections, peripancreatic abscess, gall bladder empyema, cyst infection, and post-procedure pneumonia. Very rare cases of Hepatitis B virus (HBV) transmission after upper gastrointestinal endoscopic interventions have been reported in the literature, while no cases of HIV transmission are reported [68–70]. Although a total of 29 studies reported infections after non-ERCP upper GI endoscopic procedures, the composite infection rate of 0.123% (1083 out of 876,263 procedures) was calculated from 16 studies reporting infection rates.

Table 3 summarizes the infections reported in patients who underwent lower GI procedures (colonoscopies and sigmoidoscopies). Gastroenteritis, septicemia, and Hepatitis C virus (HCV) infections following lower GI endoscopic procedures have been reported. The composite infection rate of 0.073% (1081 out of 1,488,779 procedures) was calculated from three studies reporting infection rates following lower GI endoscopic procedures.

Table 1 ERCP associated infections reported in 2011–2020

Year	Place	Microorganism	No. of patients	Infection profile
2020 [9]	Rotterdam, Netherlands	N/A	21	N/A
2020 [10]	Charleston, SC, USA	N/A	804	BSI, acute cholangitis
2020 [21]	Pittsburgh, PA, USA	N/A	44	Cholangitis, cholecystitis
2020 [32]	New Brunswick, NJ, USA	N/A	1288	BSI
2019 [33]	Montreal, Canada	*Klebsiella spp, Escherichia coli, Enterobacter spp, Enterococcus spp.*	44	BSI
2019 [34]	Norman, OK, USA	N/A	300	N/A
2019 [35]	Boston, MA, USA	N/A	17	SSI, intra-abdominal abscess
2019 [36]	Rotterdam, Netherlands	MDR *Klebsiella pneumoniae*	24	BSI, colonization
2018 [37]	Richmond, VA, USA	Klebsiella pneumoniae, Clostridium difficile	4	BSI, CDI
2017 [38]	Minneapolis, MN, USA	N/A	13	Surgical site infection
2017 [11]	Istanbul, Turkey	N/A	11	Pancreatitis
2017 [12]	Houston, TX	N/A	23	Cholangitis, BSI
2017 [13]	Glasgow, UK	*Salmonella enteritidis*	4	N/A
2017 [14]	Beijing, China	*Escherichia coli and Enterococcus fecium*	62	biliary tract infection, BSI
2017 [15]	Hartford, CT, USA	MDR *Escherichia coli*	32	None
2017 [16]	Boston, MA, USA	MDR *Escherichia coli*	28	N/A
2016 [17]	Stanford, CA, USA	N/A	10	BSI
2016 [18]	Scottsdale, AZ, USA	MDR *Enterobactereriaceae*	2	N/A
2016 [19]	New Hyde Park, NY, USA	N/A	106	Bacterial peritonitis
2015 [20]	Sichuan, China	Elizabethkingia meningoseptica and Escherichia coli	20	Cholangitis, BSI, colonization
2015 [22]	Seattle, WA, USA	MDR *Escherichia coli*	32	N/A
2015 [23]	Rotterdam, Netherlands	MDR *Pseudomonas aeruginosa*	22	N/A
2015 [24]	Milwaukee, WI, USA	MDR *Escherichia coli*	3	N/A
2015 [25]	Seattle, WA, USA	MDR *Escherichia coli*	7	N/A
2015 [26]	Pittsburg, PA, USA	*Klebsiella pneumoniae*	37	N/A
2014 [27]	Pittsburgh, PA, USA	MDR *Enterobacteriaceae*	13	N/A
2013 [28]	Seoul, South Korea	MDR Gram negative organisms	70	BSI
2013 [25]	Rochester, MN, USA	N/A	16	Cholangitis
2012 [29]	Nürnberg, Germany	N/A	46	N/A
2012 [30]	Tallahassee, FL, USA	MDR *Klebsiella pneumoniae*	10	Blood, bile, urine infection
2011 [31]	Genoa, Italy	MDR *Acinetobacter baumannii*	2	N/A

N/A not available, MDRO multi drug-resistant organism, SSI surgical site infection, MDR multi drug-resistant, BSI blood stream infection, CDI clostridium difficile infection

Microbial Profile

EAIs are either exogenous, i.e., associated with contaminated instruments, or endogenous, i.e., infections resulting from the patient's own gut flora [7]. Depending on the source, endogenous infections can be either polymicrobial or monomicrobial, while exogenous infections are mostly monomicrobial. For example, past studies have shown that the blood cultures' yield from septic patients were mostly monomicrobial, while the culture of bile aspirated from the pancreato-biliary tract was often polymicrobial [20, 71, 72]. However, the latter infections resulted in severe sepsis, cholangitis, and gangrenous cholecystitis.

Sometimes the bacteria form a layer of extracellular matrix called "biofilm" whereby the microbial cells adhere, giving rise to the persistence of infectious foci within the instruments [46, 73]. The biofilm formation provides bacteria a niche to protect from the microbicidal action of disinfectants, including cross-protection to different microorganisms [74]. Biofilms that form in endoscopes over repeated cycles of hydrated and dehydrated phases are called "build-up biofilms", which are a cause of persistent contamination of endoscopes, particularly in the difficult to clean small diameter channels [75, 76]. Wet storage, in particular, can lead to the formation of biofilms in the endoscope channels, despite adequate disinfection [75]. Studies have shown that the luminal surface of air–water

Table 2 Upper GI endoscopy (non-ERCP) associated infections reported in 2011–2020

Year	Place	Microorganism	No. of patients	Infection profile
2020 [49]	USA, Canada, Brazil	N/A	28	SSI, cholangitis
2020 [51]	Rotterdam, Netherlands	Multiple organisms	20	N/A
2020 [52]	Rome, Italy	MDR *Pseudomonas aeruginosa*, *Klebsiella pneumoniae* and *Escherichia coli*	N/A	N/A
2019 [53]	Foggia, Italy	N/A	5	Cyst infection
2019 [54]	Beijing, China	N/A	37	N/A
2018 [55]	Nantes, France	MDR *Klebsiella pneumoniae*	5	N/A
2017 [56]	Paris, France	MDR *Enterobacteriaceae*	29	N/A
2017 [57]	Malatya, Turkey	MDR *Pseudomonas aeruginosa*	8	Peripancreatic abscess, BSI, cholangitis, empyema gall bladder, pancreatitis
2017 [39]	Los Angeles, CA, USA	MDR *Klebsiella pneumoniae*	17	BSI, colonization
2017 [2]	Baltimore, MD, USA	*Escherichia coli, Clostridium difficile Staphylococci*	1539	Gastroenteritis, BSI
2017 [40]	Woodstock, ON, Canada	*Salmonella enteritidis*	3	Gastroenteritis
2016 [41]	Shenyang, China	N/A	7	N/A
2016 [42]	Minneapolis, MN, USA	MDR *Enterobacteriaceae*	5	Abdominal pain, nausea, and weakness
2016 [43]	Los Angeles, CA, USA	MDR *Enterobacteriaceae*	15	Colonization
2015 [44]	Paris, France	MDR *Klebsiella pneumoniae*	13	N/A
2015 [45]	Berlin, Germany	MDR *Klebsiella pneumonia*	6	N/A
2015 [46]	Hangzhou, China	*Pseudomonas aeruginosa*	3	BSI
2014 [47]	New York, NY, USA	HCV	2	N/A
2014 [25]	Illinois, USA	MDR *Escherichia coli*	39	N/A
2013 [48]	Reims, France	MDR *Pseudomonas aeruginosa*	4	Pneumonia
2013 [50]	Changhua, Taiwan	*Acinetobacter baumannii*	2	N/A

N/A not available, SSI surgical site infection, MDR multidrug-resistant, HCV Hepatitis C virus, BSI bloodstream infection,

Table 3 Lower GI endoscopy associated infections

Year	Location	Organism	Procedure	No. of patient	Infection profile
2018 [2]	USA	*Escherichia coli*, *Klebsiella pneumoniae*, *Clostridium difficile*, *Pseudomonas*, *Staphylococcus*, *Streptococcus*, other GNB, anaerobes, HPV	Colonoscopy	662	Gastroenteritis, anorectal abscess, peritonitis, septicemia, respiratory infections, genitourinary infection, endocarditis, CNS infection
2017 [58]	Kaohsiung, Taiwan	N/A	Colonoscopy and sigmoidoscopy	411	N/A
1997 [59–61]	Vandoeuvre les nancy, France	HCV	Colonoscopy	2	Hepatitis
1991[62]	Leeds, UK	*Escherichia Coli*	Colonoscopy	2	Septicemia
1987 [63]	Oklahoma City, OK, USA	*Salmonella newport*	Colonoscopy	8	Gastroenteritis

N/A not available, CNS central nervous system, HPV human papillomavirus, HCV Hepatitis C virus, GNB gram-negative bacilli

junction channels of new endoscopes gets contaminated with biofilms within 30 and 60 days of clinical use [77]. The best method to prevent the formation of biofilms is by drying the endoscopes thoroughly prior to storage. Automated drying and storage cabinet provides better dryness of both internal channel surfaces as well as outer surfaces as compared to standard storage cabinets [78].

Historically, *P. aeruginosa* is the most commonly reported organism in patients with EAIs, demonstrated by the blood and bile cultures from septic patients [24, 39, 50,

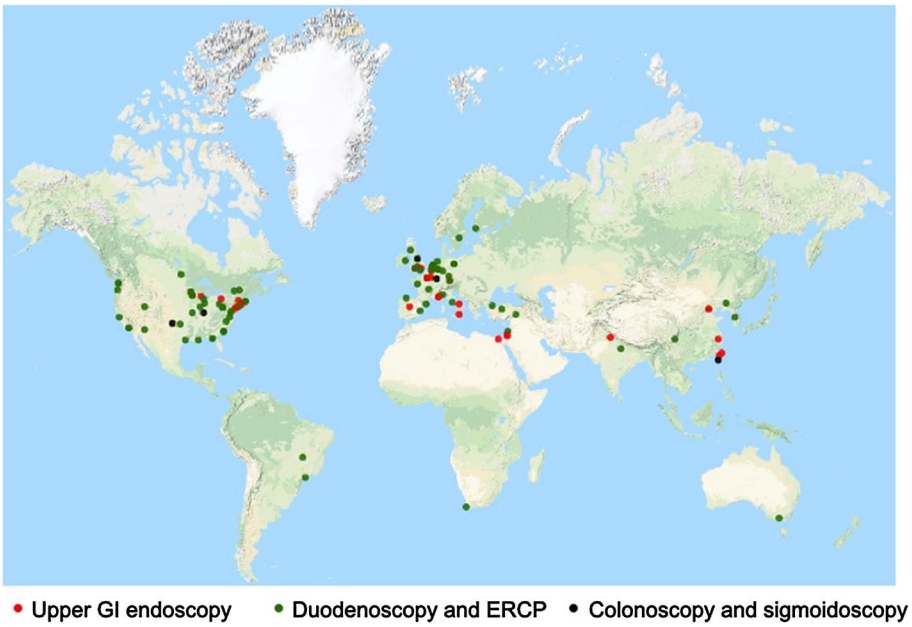

Fig. 2 Worldwide distribution of EAIs from inception until 2020

79, 80]. Overall, 387 cases of EAIs were reported across 23 articles from 14 countries attributed to *Pseudomonas aeruginosa*. *Pseudomonas* accounts for 6.21% of total EAIs. *Salmonella spp* were isolated from 30 cases between 1980 and 1990, with another 7 cases were recently reported in 2017 [13, 59]. All of these patients developed gastroenteritis as a manifestation of *Salmonella* cross-infection. Nevertheless, *Pseudomonas aeruginosa* and *Salmonella* infections after endoscopies have declined over the years due to improved sterilization and reprocessing techniques. Other bacteria that have often been reported with EAI include *Escherichia coli (E. coli)* [2, 14, 22], *Klebsiella pneumoniae* [37], and other members of the Enterobacteriaceae family of bacteria [52], *Staphylococcus aureus* [2], *Streptococci*, and *Enterococci* [14]. Rare incidences of cross-infection caused by *Campylobacter pylori* [61], *H. pylori* [81, 82], *Acinetobacter* [50], *Elizabethkingia meningoseptica* [83], and *Clostridium difficile difficile* [2, 37] have also been described in the literature. Although primarily bacterial, endoscope-associated fungal [84] and viral infections [47, 59, 61, 85, 86] have also been described, with 18 cases of HCV transmission out of a total of 6232 patients of EAI.

The MDROs have emerged as an important cause of EAIs in recent years, with 458 total cases of EAIs resulting from such organisms, thereby contributing to 7.35% of all reported EAIs. The first outbreak of MDR *Pseudomonas aeruginosa* sepsis associated with ERCP was reported in 2004 [25, 39, 80]. Later several reports of MDRO-related EAIs were described in the literature, including MDR *E. coli* [22], MDR *Klebsiella* [36], and MDR *Pseudomonas* [87]. The increasing incidence of MDRO associated EAIs could be due to the expanding use of antibiotics. Extended-spectrum beta-lactamase (ESBL) producing *K. pneumoniae* [42, 88], *Pseudomonas aeruginosa* [28, 48] as well as other beta-lactamases such as AmpC producing organisms [25] have been implicated in EAI. Moreover, EAIs associated with Carbapenem-resistant organisms have also been described in recent years. Organisms producing several different classes of carbapenemase have been reported in EAIs, such as New Delhi metallo-beta-lactamase (NDM)-1 producing *E. coli* [24, 89–92], *K. pneumoniae* carbapenemase (KPC) producing *E. coli* [93], and *K. pneumoniae* [44, 94, 95], Verona integron-encoded metallo-beta-lactamase (VIM) producing *Pseudomonas aeruginosa* [23], OXA-48 producing *Klebsiella pneumoniae* [45], OXA-204 producing Enterobacteriaceae [56]. Several other infection incidences by unclassified carbapenemase-producing organisms have also been reported, such as Carbapenem-resistant *Klebsiella* [39, 52, 55, 95–97] and other members of Enterobacteriaceae [20, 50, 98].

The infection profile by MDRO is similar to other EAI, with bloodstream infections (BSI) and cholangitis being the most common clinical presentation. Some of these infections have led to the colonization of the host by MDRO without causing any significant clinical manifestations [36, 43, 93, 99]. However, such colonization by MDRO may pose a threat to cause infections in the future with limited treatment options. The contaminated instruments were implicated as the source of cross-infection despite adequate reprocessing techniques in most cases caused by MDRO. This has led to duodenoscope recalls [100] and prompted regulating bodies and professional societies to update their guidelines on endoscope reprocessing [101].

Prevention Strategies

Infection prevention in endoscopy has been a focus of research for many years. Antimicrobial prophylaxis, adherence to adequate endoscope disinfection procedures, improved screening techniques for detection of endoscope contamination, and the use of disposable endoscopes are a few strategies that have been widely proposed and studied for the prevention of infection after GI endoscopy. We discuss each of these prevention methods and review the current evidence-based recommendations.

Antimicrobial Prophylaxis

Antimicrobial prophylaxis for EAI prevention has been studied in the context of ERCP. The most common post-ERCP EAI include cholangitis and cholecystitis and systemic infections like BSI and endocarditis (Table 1). However, the utility of antibiotics to prevent such infections has remained controversial. Some earlier studies reported antibiotic prophylaxis to be minimally protective against post-ERCP bacteremia and cholangitis, especially in complicated cholestasis cases. However, several studies found that antibiotics have not been useful for preventing EAIs after ERCP [20, 50, 71, 102] or reducing the length of hospital stay [99]. It was also not beneficial in reducing cholangitis and bacteremia after therapeutic ERCP in biliary obstruction or in patients with cancer [12, 103, 104]. A meta-analysis confirmed that prophylactic antibiotics were irrelevant in preventing clinically significant infections [102]. Thus, earlier recommendations endorsing the use of antibiotic prophylaxis for preventing post-ERCP infections in patients with a high risk of endocarditis, bile duct obstruction, or pancreatic pseudocyst [50] have been replaced in favor of recent evidence against the use of such prophylaxis [105].

Antibiotic prophylaxis to prevent infection in other endoscopic procedures like colonoscopy and EUS procedures has not been very well studied. A recent meta-analysis has found that antimicrobial prophylaxis given before or after endoscopic mucosal resection or endoscopic submucosal dissection of colorectal lesions is beneficial in preventing infection in such patients [106]. However, the amount of evidence was low, with only three randomized trials and one retrospective study. Although earlier recommended before EUS-FNA of cystic lesions, lack of benefit of using antibiotics has precluded their use [102, 107]. Nevertheless, some contrary evidence suggests antibiotic prophylaxis may be useful in EUS procedures [108]. There is, therefore, a need for prospective randomized controlled trials (RCT) to arrive at a definite conclusion.

ERCP interventions for post-liver transplant stricture were associated with a higher rate of infections in a retrospective study [20]. Therefore, current guidelines by the ASGE standard of practice committee recommend using antimicrobial prophylaxis for liver transplant recipients undergoing ERCP [109]. However, recent studies have shown that antibiotic prophylaxis is not particularly beneficial in preventing post-ERCP infections in post-liver transplants [37], challenging the previous evidence.

Disinfection Methods for Reprocessing Endoscopes

Considering that GI endoscopes are semi-critical instruments, i.e., they come in contact with non-intact skin or mucous membranes without penetration, the Centre for Disease Control and Prevention (CDC) [110] and the Food and Drug Administration (FDA) [105] recommend meticulous cleaning followed by high-level disinfection (HLD). However, invasive endoscopic interventions such as papillotomy, endoscopic necrosectomy, and ampullectomy raise the concern of EAI because of a breach in the natural mucosal barrier. Therefore, these procedures demand revisiting the Spaulding classification of semi-critical instruments for GI endoscopes [111]. In addition, a recent review has shown that the overall contamination rate of endoscopes after a procedure varies between 7.7 and 34.6%, while that of duodenoscopes and echoendoscopes varies between 0.697 and 60% [112].

Endoscope accessories such as biopsy forceps, snares, sphincterotomes commonly breach the GI mucosa and therefore are classified as critical devices requiring sterilization prior to reuse [113]. Single-use biopsy forceps could get contaminated during passage through the accessory channel of reprocessed endoscopes, thereby highlighting the need for adequate sterilization of endoscopes, including accessory channels. Soaking in 2% glutaraldehyde for 20 min could eliminate this contamination [114, 115]. Data on endoscopic accessories linked to transmission of infection are limited. A study from Egypt has shown that the reuse of biopsy forceps during colonoscopy leads to increased risks of HCV transmission to patients [67].

Similarly, few cases of transmission of *Campylobacter jejuni* gastritis [116, 117] and *Trichosporon asahii* esophagitis [84] have been linked to improper sterilization of biopsy forceps during UGIE. Further, *Salmonella* Newport gastroenteritis [63] and HCV transmission [118] have also been associated with non-sterilized biopsy forceps during colonoscopy and sigmoidoscopy. These examples signify the need for strict and thorough sterilization of all mucosa breaching accessories. Although specific recommendations about using single-use disposable tissue biopsy forceps or sterilized reusable accessories are limited [119], an individualized approach to eliminate endoscopic-related infections should be considered.

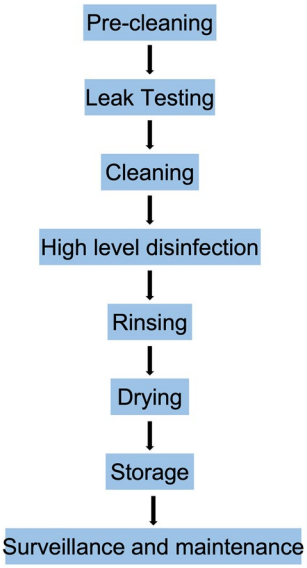

Fig. 3 Steps of endoscope reprocessing

The steps of a typical reprocessing cycle of an endoscope (Fig. 3) include precleaning, leak testing, manual cleaning, rinsing after cleaning, visual inspection, HLD, rinsing after HLD, and drying (Table 4) [110]. Pre-cleaning reduces bioburden by preventing drying of debris to the endoscope exterior as well as the channel interior [7]. Cleaning should specifically address the elevator part since it has been incriminated in several outbreaks [23, 36]. The importance of meticulous cleaning of the working channels by manual brushing has been highlighted by the British Society of Gastroenterology (BSG) [120] and the Canadian Association of Gastroenterology [121]. Difficult to reach areas can be targeted by ultrasonic cleaners to dislodge debris [110]. HLD, as per the manufacturer's guidelines, should be performed either manually or in an automated endoscope reprocessor (AER) after removing superficial debris. In light of recent outbreaks with MDRO, the Gastroenterological Society of Australia (GESA) endorsed AER to prevent infections by CRE [122]. The instruments are then rinsed, and the channels flushed with sterile water to remove residual disinfectants and later dried using 75% alcohol [120] or 70–80% isopropyl alcohol [110] and dry air. Drying is essential to prevent contamination of the reprocessed endoscopes with water-borne pathogens such as *Pseudomonas*. GESA recommends using dedicated cabinets with forced air drying capability to store reprocessed endoscopes, which ensure removing any water or disinfectant remnants and minimizing infections with CRE [122].

Several EAI outbreaks have been reported recently, despite adherence to adequate disinfection strategies [24, 105]. These incidences raise questions about the adequacy of the endoscope disinfection methods. Furthermore, the efficacy of manual cleaning and disinfection is operator-dependent. Therefore, the FDA suggested multiple additional measures in 2015 to reduce endoscope contamination rates. These measures include repeat HLD, low-temperature sterilization using either ethylene oxide or liquid chemical sterilant, and surveillance cultures, besides regular processing. Unfortunately, heat sterilization methods such as autoclaving are not feasible with endoscopes. Sterilization by ethylene oxide and frequent surveillance of endoscope cultures have been found to reduce transmission of infection by MDRO [60, 123]. However, none of these methods have been proven to completely eliminate the risks of disease transmission.

Endoscopic Surveillance Methods for Minimizing Cross-Contamination

An effective surveillance method helps to correctly ascertain the contamination risk. Several organizations and professional bodies, such as the CDC, the American Society for Gastrointestinal Endoscopy (ASGE), the European Society of Gastrointestinal Endoscopy (ESGE), BSG, and GESA, have provided recommendations for surveillance and auditing of reprocessed endoscopes. While the CDC and ASGE do not recommend routine testing for surveillance purposes, GESA, ESGE, and BSG recommend periodic sampling and testing of endoscopes. Recommendations from different organizations regarding sampling sites and frequency are aptly summarized by Shin et al. [124].

Table 4 Different steps of endoscope reprocessing

Step	Definition
Preclean	Immediate washing of the endoscope exterior and flushing of the channels to prevent the drying of debris stuck to the endoscope, thereby reducing a bulk of bioburden
Clean	Manually or automatic process to ensure that no visible debris (organic and inorganic material) are present. Cleaning steps include soaking in detergents, wiping and brushing the exteriors as well as flushing of the channel interiors
Disinfection	A process of eliminating most pathogenic microorganism, except bacterial spores. HLD as per manufacturer's guidelines is done, either manually or in an automated endoscope reprocessor (AER). Disinfectants used are Hydrogen Peroxide (7.5%), Peracetic Acid (0.2%), Glutaraldehyde (≥ 2.0%), OPA (0.55%), Hydrogen Peroxide/Peracetic Acid (7.35%/0.23%)
Sterilization	The process of making something completely free from bacteria or other living microorganisms, including spores

ESGE guidelines suggest the quantitative culture of the effluent collected after flushing the endoscope channels with 20 mL of sterile saline, with a cut-off of 20 colony forming units (CFU) per mL. They recommend such surveillance cultures of reprocessed microscopes at an interval of fewer than 3 months. However, the longer turnaround time and inability to detect viral contaminants have led to the development of alternate screening strategies such as bioburden assays, ATP bioluminescence, and molecular biology assays. Bioburden assays help detect the presence and amount of residual bioburden and organic matter on the surface or within channels of the endoscopes remaining after proper manual cleaning and before HLD. Sterile water flushing or swabs collected from the surface or channels are used as samples. The available commercials kits such as ScopeCheck (Valisafe™ America, Tampa, FL, USA) and EndoCheck™ and ChannelCheck™ (Health Mark Industries, Fraser, MI, USA) can produce results within 10–90 s. The threshold for adequate cleaning was determined to be protein < 6.4 μg/cm^2, hemoglobin < 2.2 μg/cm^2, and carbohydrate < 1.2 μg/cm^2 [25]. Bioluminescence assays allow detecting ATPs present in the cells and microorganisms remnants after the initial cleaning by detecting relative light units (RLU) generated in the chemical reaction of luciferin, luciferase, and ATP. ATP bioluminescence levels of less than 200 RLUs are proposed and validated as a cut-off to ensure adequate disinfection [125]. With the development of commercial kits with rapid turnaround time, this method has emerged as a reliable method for the surveillance of endoscope reprocessing in recent times [126].

With the advancement of technology, molecular diagnostic methods are recently used in outbreak investigations. For example, Humphries et al. utilized whole genome sequencing and single nucleotide polymorphism analysis to investigate Carbapenem-resistant bacterial infections associated with duodenoscopy [39]. RT-PCR techniques have also been used to monitor colonoscopy reprocessing efficiency [127]. However, such molecular diagnostic methods are technically challenging and need to be validated before being routinely employed in clinical practice.

Disposable Endoscopes

A recent meta-analysis has shown that duodenoscopes could act as a vector for transmitting microbes, with a reprocessed scope contamination rate of 15.25% [8]. Several reports of patient-to-patient transmission of MDRO have been linked to endoscopes without any breaches in the reprocessing protocol [127]. The disposable single-use endoscopes have been proposed as a potential alternative as the complex design of endoscopes is a likely culprit of persistent contamination and transmission. Because of this reason, disposable gastroscopes, disposable endoscope sheaths, and more recently, disposable duodenoscopes for ERCP were designed [59, 128–131]. The first disposable GI endoscope that underwent clinical trial was a sheathed flexible sigmoidoscope which reported reduced instrument turnaround time with a potential for improved safety for staff and patients [132]. The disposable endoscopes have comparable visualization and diagnostic ability to conventional endoscopes. However, some studies showed shorter maneuver and overall operating time favoring conventional endoscopes [129]. A portable ultrathin version of disposable endoscope has also been proposed to improve non-sedated esophagoscopy in the outpatient setting [128]. Similarly, disposable colonoscopes have also entered the market [133], claiming potentially decreased EAI. However, RCTs comparing infection rates of disposable and conventional endoscopes are lacking. Considering that most common EAIs result from endogenous sources, such claims of possible improved post-endoscopy infection rates merit well-controlled randomized studies.

In August 2019, the FDA recommended that healthcare facilities and manufacturers "begin transitioning to duodenoscopes with disposable components to reduce risks of patient infection." FDA has approved duodenoscopes with disposable end-caps from Fujifilm™ Corporation (model ED-580XT) and Pentax™ Medical (model ED34-i10T2 with disposable elevator cap DEC™). ASGE also took a stand in favor of this decision and endorsed the use of disposable endoscopes [68]. However, disposable endoscopes have been a topic of debate considering the increased healthcare cost that will be imposed. Although Garbin et al. developed and validated a low-cost disposable endoscope with a cost of $35 [129], the actual cost likely levied will be significantly higher. The break-even costs for disposable duodenoscope were estimated by Bang et al. to be ≥ $1300 for low-volume centers (≤ 50 ERCPs/year) and ≥ $800 for high-volume centers (≥ 150 ERCPs/year), depending on infection rates. They have also calculated that substituting with disposable endoscopes at a rate of $612/procedure will incur a cost 10 times higher than current reprocessed endoscopes [134]. For conventional endoscopes, on the other hand, besides the initial high cost of acquisition, reprocessing has been estimated to incur an additional expenditure of $114 to $280 per use [135]. A recent study analyzed the cost of purchase, maintenance, reprocessing, repair, labor, and infections requiring hospitalization for colonoscopy using the microcosting approach. The cost per colonoscopy procedure was estimated to range from $188.64 in high-volume centers to $501.16 for low-volume centers. Based on these figures, the authors argued that low volume centers will achieve higher cost savings with disposable colonoscopes [133].

Another potential problem that may surface with disposable endoscopes is the impact on the environment. Carbon dioxide-equivalent emissions calculated using a simplified life-cycle assessment methodology for single-use

bronchoscope (Ambu® aScope™ 4) varied according to the choice of materials for cleaning procedures and personal protective equipment; however, it was comparable to that from a reusable, flexible bronchoscope [136]. A recent study estimated the volume of non-recyclable waste generated if disposable GI endoscopes are adopted universally in the USA compared to that of reprocessed endoscopes. They estimated that reprocessed endoscopes currently produce approximately 532,918 m^3 of waste annually across the USA. Using disposable duodenoscopes and colonoscopes would generate an additional waste of 100,682 m^3 annually [137]. Further studies for quantitative assessment of the true environmental impact of disposable endoscopes are needed.

Knowledge Gap

Although tremendous advancements have been made in GI endoscopy, EAIs persist as a lingering problem. With the evolution of MDRO, the challenges have attained new dimensions. Reporting EAI incidence from developing countries is insufficient; thus, the data are skewed for western Europe and North America. The true incidence of EAI, the microbiological profile of such infections, and its impact on healthcare expenditure in developing countries need to be studied.

Conclusion

The composite infection rate following GI endoscopic procedures was calculated to be 0.2% in our systematic review. However, this low rate could be because of the underrecognition and underreporting of the data, especially from developing countries. Nonetheless, EAI is a common complication following endoscopic procedures. Data have led to the revision of original concepts around routine periprocedural antibiotic prophylaxis. The pathogen profile related to such infections has evolved with time, with MDRO commonly reported in recent years. Strict adherence to disinfection methods and the use of adequate surveillance can help reduce the burden of EAI. Bioburden assays and ATP bioluminescence-based assays are some recent innovations in this field. The use of disposable endoscopes is a topic of debate, with controversies around their financial viability and environmental impact weighing against potential reduction in EAI rates. Further evidence is needed to incorporate their use in daily routine gastroenterology practice. Since there are insufficient data on EAI from developing countries, research and surveillance programs should be encouraged to understand a true global picture of the problem.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s10620-022-07441-8.

Author's contribution Conception and design: AP, HG, Literature search: AD, AP, HG, First draft: AD, Critical revision and editing: All authors, Final approval: All authors.

Funding None.

Declarations

Conflict of interest Hemant Goyal serves as consultant for Aimloxy LLC. All other authors declared no potential conflict of interest relevant to this article.

Ethical approval This manuscript, as submitted or its essence in another version is not under consideration for publication elsewhere and will not be published elsewhere while under review by *Digestive Diseases & Sciences.* All authors have made substantive contributions to the study, and all authors endorse the data and conclusions.

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