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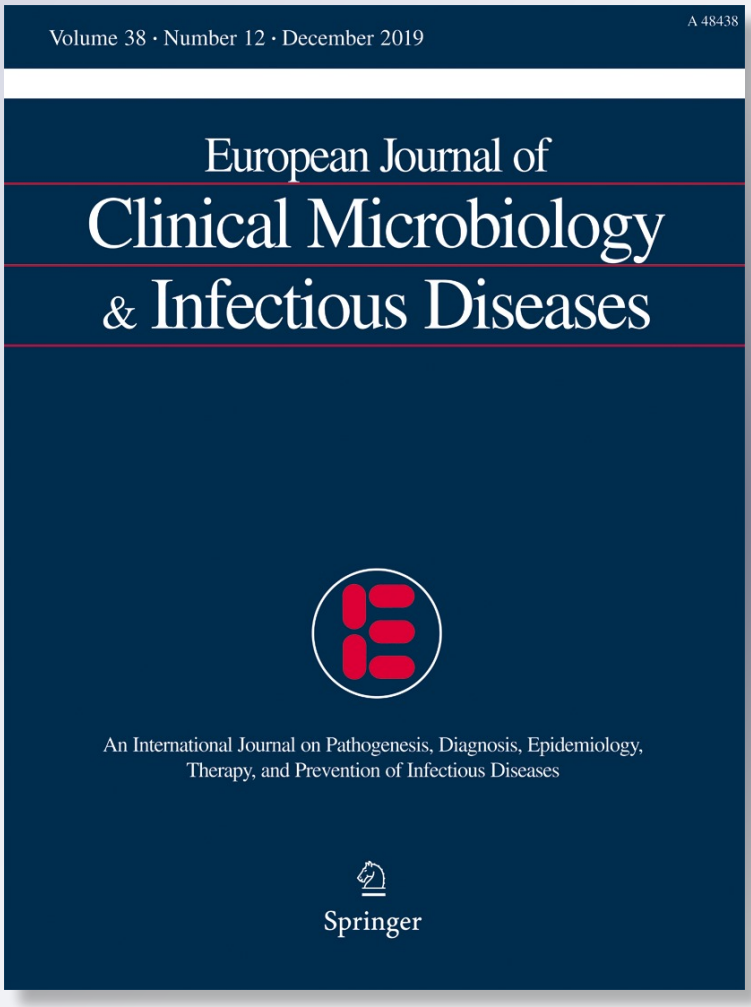

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REVIEW

Duodenoscope-associated infections: a review

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Abstract

Flexible digestive endoscopes are used for the management of various conditions with hundreds of thousands of therapeutic procedures performed worldwide each year. Duodenoscopes are indispensable tools for the delivery of minimally invasive vital care of numerous pancreaticobiliary disorders. Despite the fact that nosocomial infections after endoscopic retrograde cholangiopancreatography (ERCP) have always been among the most frequently cited postprocedural complications, recent emergence of duodenoscope-transmitted multiple drug-resistant bacterial infections has led to intense research and debate yet with no clearly delineated solution. Duodenoscope-transmitted nosocomial infections have become one of the most visible topics in the recent literature. Hundreds of high-impact articles have therefore been published in the last decade. This review article discusses how such infections were seen in the past and what is the current situation in both research and practice and thus tries to solve some of the unanswered questions for the future. With the persistence of nosocomial infections despite strict adherence to both manufacturer-issued reprocessing protocols and international guidelines and regulations, an urgent and proper microbiologically driven common action is needed for controlling such nosocomial worldwide threat.

Keywords Duodenoscope · Nosocomial infections · Biofilm · Reprocessing · Endoscopic retrograde cholangiopancreatography

Introduction

Millions of gastrointestinal (GI) endoscopy procedures are performed each year worldwide, as endoscopy is an integrated and vital part of the GI daily practice. Gastroenterologists and surgeons use flexible endoscopes for providing minimally invasive diagnostic, therapeutic, and palliative care, and the overall low rates of associated adverse events have offered such procedures optimal risk-benefit ratios [1]. Among such procedures, endoscopic retrograde cholangiopancreatography (ERCP) has been the most important procedure used in delivering care for patients with pancreaticobiliary diseases. Microbiological safety and infection control have always been important issues regarding quality assurance in GI endoscopy. Historically, endoscope-associated bacterial infections have been reported mainly due to potential lapses in reprocessing protocols although no clear breach of such protocols has clearly been documented [2]. However, in the light of some very recent research, endoscopy-related infections and nosocomial infections may not be such rare events, and thus, special measures should be taken to minimize persistent contamination and transmission of infections through GI scopes [3].

Endoscopes containing an elevator mechanism, among which the duodenoscopes being the most frequently used, have frequently been implicated in the transmission of nosocomial infections. As numerous medical research and also lay press articles conclude, such elevator mechanisms make reprocessing of duodenoscopes difficult or even inadequate [4]. Therefore, multiple reports of infectious adverse events with multidrug-resistant organisms (MDRO) suggest that duodenoscope-associated nosocomial infections have clearly been underestimated in the past and may require special control measures. A detailed schematic representation of the most frequent biofilm- and MDRO-harboring areas on duodenoscopes in descending order according to their frequency can be found in Fig. 1.

Numerous safety alerts have been issued and several new reprocessing standards have been adopted, including a joint European Society of Gastrointestinal Endoscopy

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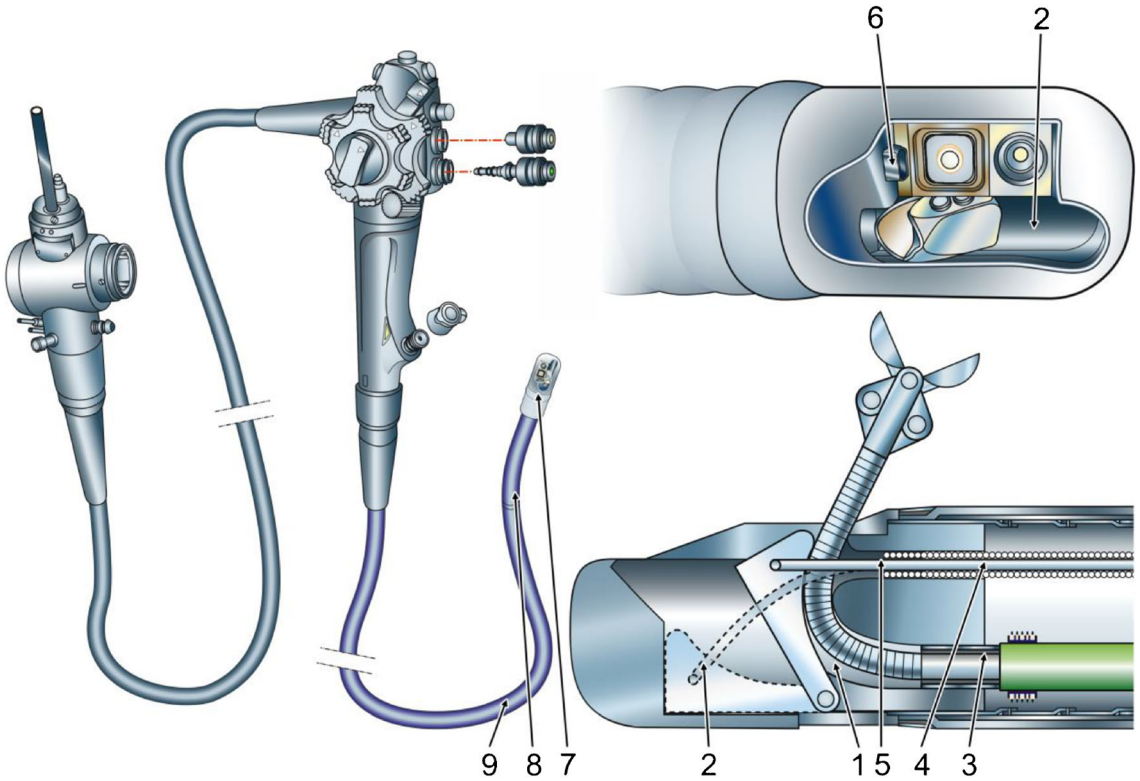

Fig. 1 Schematic representation of the most frequent biofilm- and MDRO-harboring areas on duodenoscopes in ascending order according to their frequency: (1) channel port side of elevator; (2) recess under the elevator; (3) biopsy channel; (4) elevator channel; (5) O-ring sealing of the elevator channel; (6) air-water channel; (7) distal cap; (8) distal tip of the scope; (9) coating polymer of the flexible scope

(ESGE) and European Society of Gastroenterology Nurses and Associates (ESGENA) revision for the medical devices reprocessing protocols [5] and a new American Society for Gastrointestinal Endoscopy guideline for infection control during GI endoscopy [6]. According to these new guidelines and recommendations, special measures should be taken for reprocessing of duodenoscopes mainly because of their complex design and high risk for persistent contamination [5]. These safety issues together with a vigilant approach of the Centers for Disease Control and Prevention (CDC) and the industry, the latter recalling duodenoscopes for technical revision and replacement of suspected parts [7], have raised an intense media attention on the possible MDRO transmission by ERCP procedures. Consequently, general population concerns may have altered the patient trust in ERCP [8], challenging endoscopists on their responsibilities over liability prevention measures [9]. Nosocomial infections have consequently become a new hot topic in need for prompt intervention in the ERCP-related medical practice [10].

There are numerous routes of infection related to the endoscope use, and as acknowledged by current literature, it may be impossible to eliminate all potential ways of microbiological contamination and subsequent nosocomial infection [11]. As ERCP will remain a yet irreplaceable platform for the treatment of a myriad of pancreaticobiliary diseases, the epidemiological consequences could be increasingly severe. Consequently, such epidemiological reality concerning the duodenoscope-related nosocomial infections overlaps with a clear decrease in the use of ERCP during the last 20 years secondary to the substitution of diagnostic ERCP procedures, paralleled by an increase in the total number of therapeutic procedures [12], a process that raised the overall invasive character of the procedure. Furthermore, it seems that infections occur more frequently in patients with highly invasive maneuvers like retrograde cholangioscopy or biliary stenting, performed in jaundiced patients, with malignant hilar tumors or primary sclerosing cholangitis, especially when an endoscopic and percutaneous approach is performed [13]. The presence of such risk factors may trigger an ERCP infection–related mortality of up to 5% of patients [14].

This article reviews the history of duodenoscope-related infections, the current challenges that it triggers, and the possible innovations for the future. Given the versatile character of the procedure in time, we aimed a chronologic approach to the ERCP-related infections in order to describe the proofs of the past, to highlight the present problems, and to evaluate the possible future solutions.

The past

Historically, duodenoscope-transmitted infections have been considered consequences of inadequate reprocessing or of non-compliance to the manufacturer-issued cleaning protocols. In 1987, Allen et al. reported that duodenoscopes were associated with several *Pseudomonas aeruginosa* infections transmitted between patients, resulting in sepsis and death [15]. Infections were detected especially in the first patient of the day, thus incriminating the overnight storage after reprocessing [9, 15]. Therefore, this problem was considered resolved after adoption of channel drying by alcohol flushing or forced air perfusion after disinfection [9]. Hence, it can be acknowledged that although not a novel topic, duodenoscope-associated infections have been kept in the shadows until the complex design issue began to be incriminated for such adverse events.

During the last decade of the twentieth century, multiple successive standards and protocols of high-level disinfection (HLD) have been adopted and duodenoscopes have been classified according to the Spaulding classification as semi-critical devices which need HLD. Both the use of ERCP and the HLD reprocessing standards have improved over the years, and for a long period of time, endoscopists were either lucky to avoid transmitting infections or, more likely, ignorant that it was occurring [16].

It was only after 2000 that more and more outbreaks of duodenoscope-associated infections began to be reported in the literature, one of the most important being that of Epstein et al. who reported in 2014 findings from a large carbapenem-resistant *Enterobacteriaceae* (CRE) outbreak at a US hospital clearly linked to nosocomial duodenoscope exposure [17]. *Salmonella* spp. and *Pseudomonas* spp. have been most commonly associated with endoscopy-transmitted infections throughout the medical literature [2]. Moreover, during the last 5 years, numerous outbreaks of duodenoscope-related infections have been published in both medical journals and in the press generating an increased concern among both patients and endoscopists.

The present

There are at least 32 MDRO outbreaks involving almost 400 patients and over 20 deaths between January 2000 and December 2017 [18]. Such situation, although intensely debated in the USA, is spread all over the world with outbreaks reported also in high volume centers from the Netherlands, France, or Germany [19]. Interestingly, such outbreaks have not been identified in smaller hospitals [18]. Thus, it became clear for healthcare administration representatives that previous recommended protocols for reprocessing and HLD of duodenoscopes may have been inadequate mainly due to the design features of duodenoscopes [7, 20]. Given the frequency of the procedures, such allegations have culminated with ranking failure to effectively reprocess flexible endoscopes among the top 10 health technology hazards for 2018 [21]. In this manner, the risk of endoscopy-associated bacterial transmission has been given a major impact worldwide.

Despite such worrisome situation, the US Food and Drug Administration (FDA) has been alerted about a potential association between multidrug-resistant bacteria and duodenoscopes and opted not to prohibit continued use of duodenoscopes. The FDA has otherwise issued safety communications, alerting healthcare providers and the public of the relevant and mandatory protocols on duodenoscopes' cleaning and reprocessing [22]—a decision based on the important role of ERCP in clinical practice with over 650,000 procedures being performed annually in the USA, thus involving a low overall incidence of infections [23].

Such statement is confirmed also by database analysis of endoscope-related medical device reports from 1977 to 2015 that includes 433 cases of endoscope-related infections, among which 146 reports were linked to duodenoscopes including 13 deaths, most of the reports being submitted between 2010 and 2015 during which time approximately 3 million ERCP procedures have been performed as reflected by Tokar et al. [23]. These data show that ERCP has been a constant reality in the clinical practice worldwide, and therefore, limitation of its downsides should first rely on strict and appropriate use of duodenoscopes according to manufacturer indications and more importantly on the compliance with ERCP indications.

In order to assess reproducible and evidence-based up-to-date epidemiology of duodenoscope-associated MDRO infection clusters reported over the last decade, we performed a systematic search of MEDLINE and EMBASE databases for published outbreaks between 2008 and 2018. We used combinations of keywords including "cluster," "duodenoscope-associated infection," "ERCP," "cholangitis," "*Enterobacteriaceae*," and "multidrug resistant organism." Abstracts were assessed for cluster reports. Full-text versions of selected papers were secondarily analyzed. As shown in Table 1, we identified 24 reported clusters including 490 infected patients and 32 reported deaths worldwide. The trends regarding the total number of infected cases per year versus the total number of clusters reported per year over the last 10 years can be observed in Fig. 2. Consistent data before 2008 is scarce.

Risk factors for ERCP-associated infections and the preventive measures

During ERCP procedures and periprocedural handling of scopes, both external and internal surfaces of duodenoscopes

Table 1 Reported clusters for MDRO duodenoscope-associated infections over the last decade

Outbreak location	Year	Patients per outbreak	Reported deaths	Responsible microorganism(s)	Reference
Chicago, IL, USA	2008	3	NS	*Pseudomonas aeruginosa* *Stenotrophomonas maltophilia*	Reiner (2008) [24]
Groningen, Netherlands	2008	3	0	*Pseudomonas aeruginosa*	Kovaleva et al. (2009) [25]
FL, USA	2008–2009	10	NS	Carbapenemase-producing *Klebsiella pneumoniae*	Alrabaa et al. (2013) [26]
NS, USA	2008–2009	9	NS	Carbapenemase-producing *Klebsiella pneumoniae*	Sanderson et al. (2010) [27]
Paris, France	2009	13	4	KPC-2-producing *Klebsiella pneumoniae*	Carbonne et al. (2010) [28]
NS, Italy	2009–2010	2	1	Carbapenem-resistant *Acinetobacter baumannii*	Cristina et al. (2011)d [29]
Clermont-Ferrand, France	2009–2010	16	NS	ESBL-producing *Klebsiella pneumoniae*	Aumeran et al. (2010) [30]
Hospital de Bicetre, France	2010	7	0	ESBL-producing *Escherichia coli*	Naas et al. (2010) [31]
NS, Spain	2011	12	NS	OXA-48 and CTX-M-15-producing *Klebsiella pneumoniae*	Espasa-Soley et al. (2012) [32]
UPMC Presbyterian Hospital, Pittsburg, USA	2011–2013	70	NS	*Klebsiella pneumoniae* sequence type 258	Marsh et al. 2015 [33]
PA, USA	2012	13	NS	Carbapenem-resistant *Klebsiella pneumoniae*	McCool et al. (2014) [34]
Erasmus MC, University Medical Center	2012	30	NS	VIM-2-producing *Pseudomonas aeruginosa*	Verfaille et al. (2015) [4]
NS, USA	2012–2013	32	11	Carbapenem-resistant *Escherichia coli*	Wendorf et al. (2015) [35]
Charité University Medicine, Berlin, Germany	2012–2013	12	NS	OXA-48-producing *Klebsiella pneumoniae*	Kola et al. (2015) [36]
WI, USA	2013	3	1	NDM-producing carbapenem-resistant *Escherichia coli*	Smith et al. (2015) [37]
NS, IL, USA	2013	39	2	New Delhi MBL producing carbapenem-resistant *Escherichia coli*	Epstein et al. (2014) [17]
NS, China	2012–2015	125	7	*Enterococcus faecium*, *Escherichia coli*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, *Enterococcus cloacae*	Du et al. (2017) [38]
CT, USA	2014	12	NS	ESBL-producing *Enterobacteriaceae*	Ross (2017) [39]
MA, USA	2014	28	NS	Ceftriaxone-resistant *Escherichia coli*	Coffey et al. (2017) [40]
NS, USA	2014–2015	24	6	Carbapenem-resistant *Klebsiella pneumoniae*	Humphries et al. (2017) [41]
NS, USA	2014–2015	15	NS	Carbapenemase-resistant *Enterobacteriaceae*	Kim et al. (2015) [42]
Hangzhou, China	2015	3	NS	*Pseudomonas aeruginosa*	Qiu et al. (2015) [43]
Nantes University Hospital, France	2015	5	NS	OXA-48-producing *Klebsiella pneumoniae*	Bourigault et al. (2018) [44]
Glasgow, UK	2017	4	NS	*Salmonella enteritidis*	Robertson et al. (2017) [45]

NS not specified, *CR* carbapenem-resistant, *KPC K. pneumoniae* carbapenemase, *OXA* oxacillinase, *MBL* metallo-beta-lactamase, *ESBL* extended spectrum beta-lactamase

are exposed to potential endogenous (gut bacteria) and environmental contaminants. Persistent contamination of duodenoscopes is the result of bacterial factors, among which, biofilm production is the most important [46, 47]. Biofilms are a matrix of extracellular proteins produced by bacteria to protect themselves against antibiotics and disinfectants [18], thus being able to survive on contaminated scopes for months or even years, especially in most environments [48–51]. There are numerous original studies and research programs published to date that describe pathogenical features of biofilms and how such biofilms are sources for duodenoscope-related transmission of nosocomial infections [52–54].

To decrease the amount of biofilms in endoscopes, enhanced reprocessing algorithms with chemical sterilizing

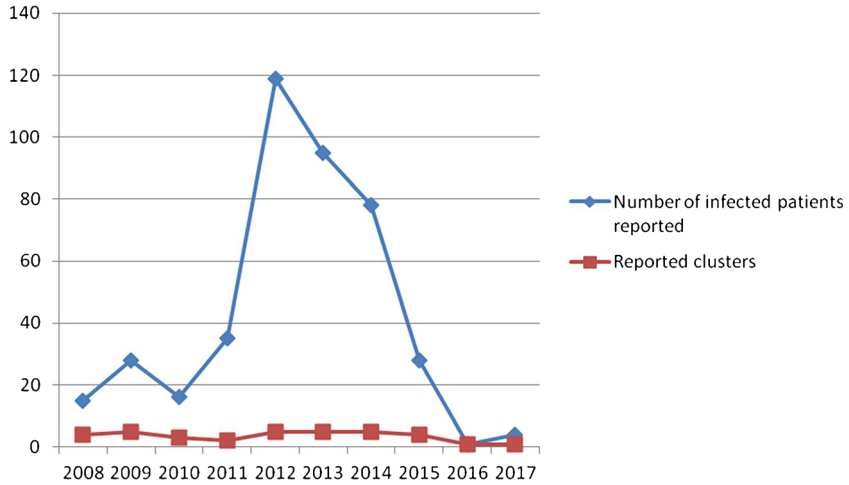

Fig. 2 Total number of infected cases per year versus the total number of clusters per year over the last 10 years

agents like peracetic acid [55], active drying of endoscopes after disinfection [9, 56, 57], and the use of automated endoscope reprocessing machines [58] and controlled storage cabinets [59] are unfortunately the only feasible methods used in the present [11]. However, studies on reprocessing, drying, and storage procedures for endoscopes reported microbial growth on endoscopes independently on postprocedural and interprocedural handling protocols implying even microbiologically controlled environments [2, 60].

On the other hand, contributive to this process are also several endoscope factors, the most important being the elevator mechanism at the distal tip which linked to a hinge and a wire channel to allow control of the elevator. The elevator mechanism facilitates access to the ampulla to manipulate guidewires and accessories. Such complex duodenoscope design features create hard-to-reach areas for optimal physical cleaning and disinfecting. More specifically, the recesses behind the elevator and the elevator channels are difficultly accessed during both precleaning and HDL and thus contribute to biofilm formation and subsequent device contamination [4, 61, 62]. However, aggressive reprocessing protocols including gas ethylene oxide sterilization themselves may damage duodenoscopes through chemical-based processes that alter both inner and outer surfaces of scopes [63]. Thus, the presence of scratches, shreds, or stains of both outer surfaces and inner endoscope channels [64, 65] secondary to either aggressive reprocessing or routine use may themselves allow harboring of biofilm and debris even after proper reprocessing [8] and independently on the scope model and manufacturer involved leading to an approximate 22% rate of contamination of duodenoscopes [66] with an almost 2% rate of MDRO harboring after HLD [8, 23].

Incidence of such risk factors triggers a handful of questions related to the proper evaluation and subsequent reduction of duodenoscope bioburden. A very recent study characterizing such bioloads shows that *Pseudomonas aeruginosa* alongside with *Staphylococcus* spp., *Enterococcus* spp., *Escherichia coli*, *Enterobacter* spp., and *Clostridium* spp. can be detected in up to almost 40% of the elevator channel swabs leading to a rate of over 20% of positive bile cultures after ERCP, involving extremely high antibiotic resistance rates [67].

The future

The main question for the future is that how can the risk of contamination and the overall ERCP infection rates be reduced? Manufacturers of both duodenoscopes and automated endoscope reprocessors provide instructions for use, describing the steps for reprocessing, such protocols reflecting the gold standard for practice. Furthermore, duodenoscope reprocessing protocols need to be characterized by at least a 6-$\log_{10}$ reduction in *Mycobacterium* spp., a surrogate marker—this standard being consistent with HLD targets. The aim is elimination of risk for scope-to-person transmission of infectious agents by semi-critical devices according to the Spaulding classification [68]. However, as recent reported outbreaks of CRE occurred despite strict adherence to standard reprocessing protocols in around 1.9% of cases [8], the FDA has issued a safety communication in 2015 on the first hand recommending revision of current reprocessing protocols and on the other hand emphasizing the need for one or more supplemental reprocessing measures to the standard one, including repeat HLD, microbiological culture, ethylene oxide gas sterilization, and liquid chemical sterilization [22].

A relatively feasible alternative to standard HLD is gas sterilization using ethylene oxide (EtO), but the fact that it involves use of carcinogens alongside with the high costs and the long reprocessing time spans made such method almost scarcely used worldwide [19]. Moreover, there are numerous concerns about the potential damage to duodenoscopes brought by EtO [63]. Interestingly, in one study on duodenoscope cultures following EtO, Naryzhny

et al. found that up to 1.2% of duodenoscopes remained contaminated with high-risk organisms despite EtO use, a rate which is similar to contamination rates seen with single HLD, suggesting that EtO may not be superior to single HLD for disinfecting duodenoscopes [63]. A cost-effectiveness analysis brought by Almario et al. estimated that the cost of each ERCP is increased by 1043 US dollars when EtO was used, meaning that more than half-billion dollars to healthcare expenditure for more than 600,000 ERCPs performed in the USA annually [69, 70]. Such reasons led experts not to recommend routine use of EtO for duodenoscope reprocessing [70].

According to the advisory panel convened by the FDA due to the poor level of safety offered by single HLD protocols, another alternative proposed was that of adding another HLD reprocessing cycle [22] including that the scopes would each time be precleaned, tested for leaks, manually cleaned, HLD, and dried with filtered forced air after each use before storage [18]. Through such a process, experts at the Gastroenterology and Urology Devices Panel of the Medical Devices Advisory Committee meeting convened by US FDA in 2015 urged FDA to mandate that all duodenoscopes be sterilized by 2018 [23, 71], a mission yet unaccomplished. Despite the HLD protocol used, it should be underlined that adherence to manufacturer-issued endoscope reprocessing steps is mandatory. Routine postprocedure manual cleaning of the endoscope, flushing the channels, and brushing the elevator lever immediately after use and before the surfaces have become dried are effective, as biofilm can only develop in a moist environment [19]. Furthermore, routine flushing of the channels with alcohol as a desiccant followed by forced air drying and dry storage is also important supplementary steps [60].

Nevertheless, independently on the reprocessing method used, it seems more and more obvious that duodenoscope disinfection monitoring should be a standard procedure after each reprocessing cycle [18]. In this respect, baseline and surveillance duodenoscope culture samples should always be obtained even on a "culture and quarantine" protocol wherein a duodenoscope is not reused until after negative 48 to 72-h surveillance cultures [2]. Such protocols were implemented by some institutions. However, it would require higher costs led by the need for purchasing many additional duodenoscopes. This downside could be solved by the use of ATP real-time detection kits that offer on-site information when bacterial ATP is detected on the tested surfaces [72]. ATP samples are obtained through various methods such as brushing, flushing, or swabbing. Downsides of ATP detection include poor correlation rates with microbial cultures and thus lack of adequacy as an overall reprocessing indicator [73]. Given such limitations, future research for rapid and point-of-care indicators as an alternative to culturing is needed [18].

Beyond new notifications for alternative reprocessing methods as non-thermal sterilliants, innovative ways to prevent both alterations and accessibility in the technological design of endoscopes, or enhanced protocols for surveillance of reprocessing, the need for disposable endoscope parts or even for disposable endoscopes seems now a futuristic but potentially necessary endpoint. Duodenoscopes with a detachable distal end have now been developed by many manufacturers, but it is not clear whether these will reduce the number of infection transmission [16, 18].

Despite advances in manufacturing technology, constant inspection of on-the-market duodenoscopes should become a usual practice in all centers. Optical analysis and the use of inner channel inspection devices as borescopes allow early detection of both damages brought to duodenoscopes and biofilm formation [74] and may therefore help in isolation and technical revision of vulnerable scopes. Not the least, additional device treatment with fluorescent stains binding to organic material may help trigger fluorescent properties to biological debris making it more likely detectable through routine optical inspection before use [18].

The sole potentially optimal method for bioburden and contamination risk exclusion for ERCP care would be introducing single-use duodenoscopes and devices in general practice. Although seen by many as yet unfeasible, the outcomes and costs proven so far for single-use flexible ureteroscopes showed no significant success rates, stone-free rates, operation time, radiation exposures, and overall complication rates with relatively equal per-procedure costs when compared with reusable ureteroscopes [75]. As single-use standard endoscopes have been introduced recently on the marker, such future perspective may not be unrealistic also for duodenoscopes.

Conclusions

The use of duodenoscopes for ERCP procedures has represented a major advance in gastrointestinal endoscopy, and adverse events including infections would not alter its critical importance. Recognizing the important therapeutic role of ERCP in clinical practice with hundreds of thousands of procedures performed in the USA and millions of procedures performed worldwide each year, prohibition of ERCP continues to seem impossible. Such reality raises the burden and the reasonability of healthcare providers and endoscopists in what prevention of infectious and nosocomial adverse events are concerned. Therefore, endoscope reprocessing must remain a consistent priority in order for contamination of duodenoscopes to remain a "never event." Hence, despite millions of gastrointestinal endoscopies done annually, associated infections remain rare. This means either that the risk of infection is low or that the true incidence is underreported.

Until such problems can be resolved in both hospital and research settings, we should continue to provide lifesaving ERCP procedures while constantly and strictly adhering to

both current endoscope reprocessing guidelines and manufacturer instructions. Not the least, offering the best comprehensive information to patients about the risks for procedure-related infections should be regarded as a legal duty of each practitioner while obtaining the informed consent.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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