Endoscope-Associated Infections (EAI): An Update and Future Directions

I. INTRODUCTION

The number of endoscopic and minimally-invasive procedures performed has exponentially increased in recent years, as the realm of endoscopy has expanded.1 Annually, around 20 million endoscopic procedures are performed in the United States, of which at least 600,000 are endoscopic retrograde cholangiopancreatographies (ERCPs).2-3 The parallel upsurge in multi-drug resistant organisms (MDRO) has augmented the worldwide attention to the study of and efforts to mitigate nosocomial infections. Endoscope-associated infections (EAIs), especially those associated with the endoscope conventionally used for ERCP (i.e. the duodenoscope), has been a growing concern in the healthcare system in recent years and has garnered significant attention in the mainstream news. When compared to a standard flexible endoscope, the duodenoscope has a more complicated structure that makes it more susceptible to infection; this is especially
The paradigm for cleaning endoscopes (including duodenoscopes), as recommended by the United States Food and Drug Administration (FDA) and Centers for Disease Control and Prevention (CDC), encompasses comprehensive and extensive cleaning followed by high-level disinfection (HLD). Heat-labile endoscopes are not able to undergo the same sterilization method for surgical instruments, thus making HLD important. In 2013, the CDC alerted the FDA to a potential association between MDRO and duodenoscopes. The initial obvious suspicion was placed on reduced effort in cleaning, missed steps and/or other lapses involved in duodenoscope cleaning and HLD. However, upon further investigation, it became clear that these cases of infection were occurring despite user adherence to multiple expert societies suggested guidelines and manufacturer’s instruction for use (IFU), which had been previously considered to be adequate. Unfortunately, after the increases in the frequency of infection in healthcare centers despite adhering to the guidelines/IFU, the FDA and CDC began to re-evaluate the infection risk with duodenoscopes.

There have not been well-established, specific guidelines for endoscopic disinfection strategies to better ensure safety from EAI. Furthermore, the complexity of duodenoscope design makes it difficult to achieve efficient and effective disinfection and reprocessing. In this review, we focus on EAI (particularly duodenoscope) and the challenges related to it, and additionally discuss the current standards of reprocessing as well as the changes proposed for reprocessing technique and their effect on future of EAI.

II. ENDOCOSPIC REPROCESSING PROCESS

Pre-cleaning is a crucial first step to prevent drying of pathogens attached, and is performed immediately after the procedure, at patient bedside, usually by the endoscopy technician/staff. Pre-cleaning starts with wiping the insertion section of endoscope (with clean water or detergent solution), followed by aspiration of water through the channel for 30 seconds, while raising and lowering the elevator, followed by aspiration of air for 10 seconds. After this, the AW channel-cleaning adapter is attached to the air/water cylinder and flushed with water and air, before detaching accessories from the endoscope, and subjecting the scope to a leak test. Certain automated endoscope reprocessors (AERs) have automated cleaning before HLD, and although it allows for standardization and reduces error, this method has not been vindicated with adequate peer-reviewed evidence.

Once the endoscope/duodenoscope is transferred to endoscopy suites’ designated scope reprocessing area, the five stages of endoscope reprocessing begin, as described in manufacturers’ IFUs, which include manual cleaning, HLD, rinsing, drying, and storage. The steps of manual cleaning of duodenoscope include (i) cleaning the external surface of scope using medical grade, low-foaming, neutral pH detergent, (ii) brush clean the elevator and recess along with guidewire-locking groove, (iii) brush clean the suction channel, (iv) brush clean the instrument channel from suction cylinder to distal end of insertion section (scope tip) and reverse, (v) brush clean the suction cylinder.
to endoscope connector, and reverse, (vi) brush clean the suction cylinder, (vii) brush clean the instrument channel port, (viii) aspirate detergent solution through the instrument channel and suction channel, (ix) flush forceps elevator recess with detergent solution, (x) flush the air/water channel with detergent solution, (xi) immerse the endoscope and accessories in detergent solution, (xii) remove detergent solution from all channels, (xiii) dry external surfaces of the scope. Disinfectants for HLD (glutaraldehyde, orth-phthalaldehyde, peracetic acid) must have a broad range of activity against microbes at a specific concentration.\(^5\) Glutaraldehyde is a less expensive choice; however with reported incidence of bacterial resistance.\(^5\)

After deep cleaning, the next step is HLD, which can be performed manually or through AER.\(^5\) The steps of manual HLD include (i) immersing scope in high-level disinfectant after attaching channel plug and injection tube, (ii) flushing all channels and forceps elevator recess with disinfectant solution using luer-lock/regular syringe; (iii) leave endoscope and accessories immersed in disinfectant solution for recommended contact time, temperature and concentration. Rinsing includes extensive rinsing of the scope and accessories, as well as using suction pump to aspirate air through the instrument channel, followed by alcohol flush (medical grade 70% ethyl or 70% isopropyl alcohol) and then filtered with air-drying. Alternately, units may use automated endoscope reprocessor (AER), if available. If drying is inadequate, the duodenoscope is at higher risk of increased bacterial growth and biofilm formation.\(^5,6\) The duodenoscope should be stored for a period that ranges from hours to 21 days (exact time is not defined), but more importantly, it should be stored in a manner that shields it from contamination, moisture, and damage.\(^5\)

Duodenoscopes are generally more susceptible

---

**Table 1a. Reported ERCP Associated Infection Outbreaks Since 2002 in the United States**

<table>
<thead>
<tr>
<th>Year</th>
<th>Location</th>
<th># of Patients</th>
<th>Organism</th>
<th>Cause</th>
<th>Manufacturer</th>
</tr>
</thead>
<tbody>
<tr>
<td>2002(^9)</td>
<td>Illinois</td>
<td>5</td>
<td>MDR Pseudomonas aeruginosa</td>
<td>N/A</td>
<td>Not reported</td>
</tr>
<tr>
<td>2012(^33)</td>
<td>Pennsylvania</td>
<td>135</td>
<td>Carbapenem resistant Klebsiella</td>
<td>N/A</td>
<td>Olympus</td>
</tr>
<tr>
<td>2012-13(^11,24)</td>
<td>Washington</td>
<td>32</td>
<td>AmpC-producing E. Coli</td>
<td>N/A</td>
<td>Olympus</td>
</tr>
<tr>
<td>2013(^34)</td>
<td>Illinois</td>
<td>39</td>
<td>NDM-producing carbapenem-resistant E. Coli (CRE)</td>
<td>N/A</td>
<td>Pentax</td>
</tr>
<tr>
<td>2013(^35)</td>
<td>Wisconsin</td>
<td>3</td>
<td>NDM producing E. Coli</td>
<td>N/A</td>
<td>Olympus</td>
</tr>
<tr>
<td>2014(^31)</td>
<td>Florida</td>
<td>9</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Olympus</td>
</tr>
<tr>
<td>2014(^96)</td>
<td>California</td>
<td>7</td>
<td>CRE</td>
<td>Not reported</td>
<td>Olympus</td>
</tr>
<tr>
<td>2014(^37)</td>
<td>Connecticut</td>
<td>12</td>
<td>ESBL-producing Enterobacteriaceae</td>
<td>N/A</td>
<td>Olympus</td>
</tr>
<tr>
<td>2014(^38)</td>
<td>Massachusetts</td>
<td>28</td>
<td>Ceftriaxone resistant E. Coli</td>
<td>N/A</td>
<td>Not reported</td>
</tr>
<tr>
<td>2015(^31)</td>
<td>North Carolina</td>
<td>18</td>
<td>Carbapenem resistant enterococci</td>
<td>N/A</td>
<td>Olympus</td>
</tr>
<tr>
<td>2015(^31)</td>
<td>Pennsylvania</td>
<td>3</td>
<td>Carbapenem resident Klebsiella pneumoniae</td>
<td>Improper drying; improper storage of duodenoscope</td>
<td>Fujifilm</td>
</tr>
<tr>
<td>2015(^31)</td>
<td>Colorado</td>
<td>9</td>
<td>MDRO/ESBL E. Coli</td>
<td>N/A</td>
<td>Not reported</td>
</tr>
<tr>
<td>2015(^31)</td>
<td>Massachusetts</td>
<td>3</td>
<td>MDRO/ceftriaxone resistant E. Coli</td>
<td>N/A</td>
<td>Pentax</td>
</tr>
<tr>
<td>2017(^39)</td>
<td>Massachusetts</td>
<td>2</td>
<td>Mcr-1 positive Klebsiella pneumoniae</td>
<td>Poor duodenoscope reprocessing “Distal cap defect” reported</td>
<td>Not reported</td>
</tr>
</tbody>
</table>
to bacterial contamination because of their long channels and sophisticated design (as discussed below in detail), but effective cleaning has the potential to exponentially remove microbes and debris (almost as high as 99.99%). Healthcare workers who are directly involved in duodenoscope reprocessing should have dedicated device disinfection training, scheduled competency testing, and routine quality measure inspections to ensure adherence with all current protocols and manufacturer IFUs. In 2009, the CDC began an infection control audit during the inspection of 68 ambulatory surgical centers, and they had found that 28% of the surveyed centers lacked a uniform protocol for duodenoscope reprocessing.

**III. DUODENOSCOPE-ASSOCIATED INFECTION**

**a. General Information**

Most EAI s are detected through the outbreak investigations, with at least 35 outbreaks reported between 2012 until 2015. The estimated incidence of duodenoscope contamination ranges in literature from 0.3–30%. Attack rate for duodenoscope-associated infections, defined as number of infected or colonized cases over the number of exposed cases, has been estimated between 12-41%. In a recent international endoscopic processing survey, one-fifth of the 165 responding institutions from 39 countries testified at least one EAI outbreak, despite presence of standard operating procedure for endoscope cleaning 82% facilities. Main contributors to EAI outbreaks have been thought to be breaches in reprocessing standards, use of unapproved disinfectants, poor endoscope maintenance, lack of microbiologic surveillance and contaminated automated endoscope reprocessors (AERs). Additional risk factors that specifically predispose duodenoscopes to infection include, but not limited to inadequate disinfection due to their sophisticated design/elevator mechanism and acquired damage with frequent instrumentation. Moreover, there are a few patient-centric risk factors which may also contribute to duodenoscope-associated infections, including bile duct obstruction/infection and immunocompromised host status.

Intricate designs of duodenoscopes require augmented attention during reprocessing process. Duodenoscopes have a moveable unique lever/elevator mechanism at the tip, which allows the endoscopist to orient guidewire/instruments into the visual field; however, this exclusive design is poorly accessible with the standard cleaning brushes and makes the disinfecting process challenging. Duodenoscopes also have an elevator wire channel and a long, braided wire connecting the “elevator mechanism” to the control. These channels can be unsealed and are susceptible to bacterial colonization, and recently, been implicated in some outbreaks. The water and air channels of duodenoscopes, both with small diameter than standard endoscopes, are may also harbringer infection in case of inferior cleaning. The design of linear array echoendoscopes (used for therapeutic EUS), also is very similar to duodenoscope, with distal elevator mechanism, and is prone to similar challenges with cleaning and reprocessing (Figure 1).

Biofilms are polysaccharide matrices that allow bacterial colonies to attach to surfaces, are a specific pathogen-associated risk factor. Biofilms protect bacterial colonies from drying and inhibit disinfectants and antibiotics. To eradicate biofilms, mechanical and ultrasonic cleaning is an effective method comparing to chemical cleaning. The current disinfection and reprocessing protocol has not been found to eradicate biofilms efficiently, which further complicates the issue of efficient reprocessing of duodenoscopes, and has been attributed to recent reported outbreaks.

**b. Outbreaks**

In late 2013, Virginia Mason in Seattle, and Advocate Lutheran in Chicago, independently linked an outbreak of antibiotic-resistant infections to use of duodenoscopes, which first brought to attention this growing problem. This led to further investigation by Senator Patty Murray (Ranking member of the Senate Health, Education, Labor and Pensions Committee) who concluded that these incidents were not isolated, but recognized that between 2012-2015 at least 25 different incidents of antibiotic-resistant infections had sickened at least 250 patients worldwide, and implicated duodenoscopes made by all three major manufacturers (Olympus, Fujifilm and Pentax).
In 2018, Rauwers et al. reported that 26 out of 73 Dutch ERCP centers (39%) had at least one contaminated duodenoscope, which was thought to be patient-ready, despite compliance with reprocessing guideline and recommendations.\textsuperscript{32}

Table-1 is a comprehensive list of reported outbreaks, number of affected patients, the cause (if determined) and the company of duodenoscope, both within the United States and outside.\textsuperscript{11,17,19,20,23,24,33-47}

**Table 1b. Reported ERCP Associated Infection Outbreaks Since 2002 in the United States**

<table>
<thead>
<tr>
<th>Year</th>
<th>Location</th>
<th># of Patients</th>
<th>Organism</th>
<th>Cause</th>
<th>Manufacturer</th>
</tr>
</thead>
<tbody>
<tr>
<td>2005\textsuperscript{40}</td>
<td>Marseille, France</td>
<td>1</td>
<td>Methylobacterium mesophilicum</td>
<td>N/A</td>
<td>Not reported</td>
</tr>
<tr>
<td>2005\textsuperscript{41}</td>
<td>Lucknow, India</td>
<td>3</td>
<td>Pseudomonas aeruginosa</td>
<td>Insufficient cleaning</td>
<td>Not reported</td>
</tr>
<tr>
<td>2005\textsuperscript{40}</td>
<td>Groningen, Netherlands</td>
<td>3</td>
<td>MDR Pseudomonas</td>
<td>N/A</td>
<td>Not reported</td>
</tr>
<tr>
<td>2008-09\textsuperscript{17}</td>
<td>Clemont-Ferrand, France</td>
<td>16</td>
<td>ESBL Klebsiella</td>
<td>Poor cleaning, insufficient drying before storage</td>
<td>Not reported</td>
</tr>
<tr>
<td>2009\textsuperscript{42}</td>
<td>Paris, France</td>
<td>13</td>
<td>KPC Klebsiella</td>
<td>Insufficient drying</td>
<td>Not reported</td>
</tr>
<tr>
<td>2010\textsuperscript{43-44}</td>
<td>Paris, France</td>
<td>13</td>
<td>Carbapenem resistant Klebsiella</td>
<td>Delay in the pre-cleaning after usage, insufficient drying</td>
<td>Not reported</td>
</tr>
<tr>
<td>2012\textsuperscript{23}</td>
<td>Rotterdam, Netherlands</td>
<td>30</td>
<td>VIM2-producing pseudomonas</td>
<td>Duodenoscope obstructing proper cleaning of the elevator channel</td>
<td>Olympus</td>
</tr>
<tr>
<td>2012-13\textsuperscript{45}</td>
<td>Berlin, Germany</td>
<td>12</td>
<td>Carbapenem-resistant Klebsiella</td>
<td>N/A</td>
<td>Olympus</td>
</tr>
<tr>
<td>2015\textsuperscript{46}</td>
<td>Hangzhou, China</td>
<td>3</td>
<td>MDR pseudomonas</td>
<td>Failed cleaning and disinfection</td>
<td>Olympus</td>
</tr>
<tr>
<td>2017\textsuperscript{47}</td>
<td>Glasgow, United Kingdom</td>
<td>4</td>
<td>Salmonella enteritidis</td>
<td>Poor adherence to disinfection protocols</td>
<td>Olympus</td>
</tr>
</tbody>
</table>

In 2018, Rauwers et al. reported that 26 out of 73 Dutch ERCP centers (39%) had at least one contaminated duodenoscope, which was thought to be patient-ready, despite compliance with reprocessing guideline and recommendations.\textsuperscript{32}

Table-1 is a comprehensive list of reported outbreaks, number of affected patients, the cause (if determined) and the company of duodenoscope, both within the United States and outside.\textsuperscript{11,17,19,20,23,24,33-47}

**c. Spaulding Classification**

This classification, proposed in 1974, splits medical instruments into three different categories, based on the risk of infection.\textsuperscript{48} Non-critical instruments come in contact with intact skin, thus low infection risk, and hence require simple disinfection with water and possibly detergent (stethoscopes, sphygomanometers, etc.). Semi-critical instruments come in contact with mucous membranes and carry moderate infection risk\textsuperscript{2,3,49-50} and hence require high-level disinfection (HLD) (all flexible endoscopes fall in this category). Critical instruments enter the sterile tissues, body cavities (peritoneum) and vasculature, and carry high risk for infection, and hence need detailed sterilization.

It is debatable if Spaulding classification is dependable in the current era, when endoscopy has shifted from a diagnostic to an interventional/therapeutic procedure, with continued efforts to push the frontiers in pancreato-biliary system as well as the third space. Duodenoscopes are typically classified as semi-critical instruments, but technically enters sterile portion of GI tract (biliary system), and hence carries high risk of infection. FDA currently recommends intensive cleaning and HLD for optimal disinfection, but one could argue these require sterilization and would not be wrong. The counter-arguments presented
include sterilization being more time and resource consuming, and HLD is not clinically inferior to sterilization in preventing infections. However, in the light of recent infection outbreaks, this field needs further investigation.

d. Microbiology of DuodenoScope-associated Infections:

i. Endogenous Infections:
Endogenous infections involve intra-procedural breach of mucosal barrier and subsequent infection with gut’s flora and are most common of all infections associated with GI procedures. It is well understood that therapeutic upper endoscopic procedures (viz. variceal ligation, esophageal dilation, or sclerotherapy) have significantly higher rates of infection, than general endoscopic procedures (EGD with biopsy/snare, colonoscopy with biopsy/snare). ERCP also has significantly high infection related complications such as ascending cholangitis, cholecystitis, abscess, and bacteremia/sepsis. As endogenous infections involve the gut’s flora, the underlying pathogens might differ depends on the examined area anatomical location, i.e. upper or lower GI tract or biliary system. Most common pathogens in upper endoscopic procedures related infection are coagulase-negative Staphylococcus, Streptococcus; while Enterobacteriaceae, enterococci, and Streptococci are the most common pathogens in lower GI procedures. The commonest organisms implicated in ERCP include E. Coli, Klebsiella and Enterobacter.

ii. Exogenous Infections:
Exogenous infections are generally from contamination (including EAI) and should be preventable with adequate disinfection strategies. As discussed above, insufficient pre-cleaning, manual/automated cleaning, and drying are well-described potential missteps that lead to direct transmission of microbial pathogens. Since the advent of HLD, the exogenous most commonly implicated pathogen has changed from Salmonella to Pseudomonas. The reason for this is the high tendency of Pseudomonas aeruginosa to produce biofilms in moist environments (for example, wet endoscopic channels); which are difficult to eradicate even with HLD. Other common microorganisms implicated in exogenous infections are Mycobacteria, Helicobacter pylori, and Clostridium difficile.

e. Multi-drug Resistant Organism (MRDO) Infections:
In addition, the recent outbreaks (as in Table-1) have been due to multi-drug resistant organisms (MRDO), like multidrug resistant Enterobacteriaceae infections, including Extended Spectrum Beta- Lactamases/Carbapenem-resistant Enterobacteriaceae (ESBL/CRE), despite strict adherence of accepted standards of reprocessing and manufacturers’ IFUs. This is not only a significant healthcare concern, but also garnered significant media attention, requiring urgent attention by institutions. The mortality and morbidity from multi-drug resistant infection led to increased collaboration between device manufacturers, hospitals/health care centers, and encouraged regulatory agencies to revisit duodenoscope reprocessing guidelines, mandate standards of reprocessing to be followed/reported by healthcare institutions and establish supplementary recommendations (as discussed below).

IV. EFFORTS TO DECREASE THE RISK OF INFECTION
Since the outbreaks, in order to decrease infection rate, the CDC and FDA have recommended increased reprocessing quality, with stringent adherence to detailed reprocessing protocols. DuodenoScope reprocessing requires high compliance, along with knowledgeable and well-trained healthcare workers, and lapses in attention or bypassing steps in the processing must be curtailed. Rutala and Weber reviewed most common attributors to increased risk of infection, which were incomplete cleaning or HLD, endoscopes internal damage, and flaws in automated endoscopic reprocessors/ endoscopes. The authors also discussed unrecognized infections, which are attributed to inadequate surveillance due to long delay from colonization until infection. To overcome such issues, FDA emphasizes on implementing a quality control protocol at healthcare facilities, which encompasses a comprehensive list of written
The automated endoscope reprocessor (AER) is FDA approved as an alternative for endoscope disinfection, capable to remove proteins and other bioburden efficiently. However, AERs are susceptible to contamination and damage, which has been implicated in previous outbreaks also.\textsuperscript{2,61-64} Moreover, most AERs do not have adequately high flushing pressure to adequately disinfect the elevator channel, hence manual reprocessing with 2-5 ml syringe is more reliable than AER. For these reasons, currently, the FDA advises using AER only as a supplementary step to the current recommended manufacturer’s IFU, rather than a standalone reprocessing strategy.

In 2015, the FDA released four recommendations to supplement reprocessing protocols in order to reduce contamination rates. These new supplements include consideration of repeat HLD, sterilization with ethylene oxide (EtO), liquid chemical sterilant, and culturing for surveillance.\textsuperscript{9-11,14, 65-68} Although some of these studies demonstrated a reduction of contamination, but not a zero contamination rate, even with double HLD. The flip sides of these steps include increased cost and resources, and increased scope downtime (thus need for purchase of more scopes) and additionally exposure of toxic EtO to reprocessing personnel.

a. Repeat HLD:
HLD is believed to eradicate $10^5$ bacteria in single processing, whereas endoscopes are usually contaminated with $10^{10}$ bacteria.\textsuperscript{69} Theoretically, it would be expected that two consecutive HLD cycles would effectively remove 99% of bacterial contamination, and this may have been the basis of FDA suggestion of two consecutive HLD cycles a supplement to existing reprocessing protocols. Many healthcare facilities readily adopted this strategy, for the ease of implementation, minimal extra cost or financial burden, and acceptable increase in length of reprocessing time/scope downtime. However, there is little substantial evidence to support the efficacy of 2 consecutive HLD cycles, and in areas without outbreaks, there is little efficacy and utility for multiple HLD cycles.\textsuperscript{2,11,66,70} More importantly, multiple cycles of HLD did not eradicate the bacteria that led to multiple outbreaks of duodenoscope-associated infectious outbreaks.\textsuperscript{69} Notably, one specific prospective randomized study showed no significant differences in contamination rates between single HLD group, double HLD group, and single HLD followed by EtO sterilization group.\textsuperscript{13} Considering the complex design and elevator mechanism of a duodenoscope, a universal and improved reprocessing method is paramount to reduce infection contamination.

b. Sterilization:
Sterilization of endoscopes can be performed using gaseous (ethylene oxine, EtO) or liquid (per-acetic acid) sterilants. Gas sterilization with ethylene oxide (EtO) for reprocessing is performed at low temperatures, however, due to its potential flammability and possible carcinogenic risk to reprocessing personnel, EtO use has been limited in most facilities. Another major limitation of EtO sterilization is the long aeration time, which increases scope downtime, and may become a major financial burden for endoscopy units. Moreover, as discussed above, EtO sterilization after single HLD has not shown to be any better than single HLD alone.\textsuperscript{13} In addition to Eto, other agents including hydrogen peroxide and plasma-activated water have been tried, and are under investigation.\textsuperscript{71,72} On the other hand, liquid sterilant flushing of the endoscope is thought to potentially re-introducing microbes and hence not favored. For these reasons, sterilization of endoscopes is not a widely accepted practice.

c. Microbiologic testing:
European and Australian societies for gastrointestinal endoscopy have favored use of routine culturing as a quality measure of duodenoscope reprocessing,\textsuperscript{73-74} and inspired FDA in conjunction with CDC and American Society of Microbiology (ASM) to release standardized protocols for duodenoscope culturing.\textsuperscript{75} However, this approach is not widely adopted across the United States due to several reasons, including the high cost associated with culturing process, unclear intervals at which culturing should be performed, and lack of adequate evidence of test performance.
and characteristics. Furthermore, a negative culture result of duodenoscope does not eliminate the possibility of infection, as there are cases in which duodenoscopes outbreak occurred despite negative cultures.

V. Future Directions in the Prevention of Duodenoscope-associated Infections

a) Augmented manufacturer accountability:
In the light of these duodenoscope-associated infection outbreaks, the FDA claimed post-market surveillance studies on the manufacturer IFU by all three major manufacturers, Fujifilm, Olympus, and Pentax, which they all initially failed to provide. In 2018, the interim results demonstrated contamination rates of up to 3% for high concern organisms, which was higher than expected. Further sampling and culturing studies by these companies showed presence of high risk organisms including E. Coli and P. aeruginosa. The FDA then ordered these companies to conduct post-market surveillance studies to evaluate if the staff could understand and follow manufacturer’s IFU in real-world healthcare settings (called human factors studies), which showed users often had difficulty understanding and following IFU, and hence unable to successfully complete reprocessing. These data ultimately encouraged FDA to recommend measures supplemental to existing reprocessing protocols, and also led to development of several endoscopy unit quality checks, as discussed below.

FDA also has recently raised concerns regarding the practice of semi-automatic renewal of market authorization of new endoscope models, without additional analysis, if the new modified design of new endoscope was sufficiently similar to the previously approved designs. As an example, prior to these outbreaks, Olympus introduced TJF-Q180V with sealed elevator channel, as opposed to the previous model with exposed elevator wire channel, but after the outbreaks linked to this model, FDA suspected a possible safety compromise due to changed design, leading to worldwide recall of this model of duodenoscope.

These instances encourage manufacturers to assume greater accountability in this overall mission of minimizing EAI transmission.

b) Augmented endoscopy unit accountability:
Since these MRDO outbreaks associated with duodenoscope use, FDA and CDC have put in place many regulations, all aimed at preventing risk of infection transmission and minimizing the patient risk. These measures include identification of risk factors responsible for infection transmission, maintaining adequate communication to mitigate such occurrences, making process of reprocessing efficient and creating quality control measures, which can serve as check points.

FDA and CDC recommend recognizing patient specific and endoscope specific risk factors, which can lead to infection transmission. In case of duodenoscope, as previously discussed in this manuscript, they pertain to its complex design and distal tip elevator mechanism. In addition, a duodenoscope may have internal channel damage, which may be independent of age of the scope but dependent on use frequency and user characteristics, which may render it more difficult to clean, and currently there are no guidelines regarding endoscope durability/longevity and optimal inspection frequency, and these needs to be focus of future research. Some endoscopy centers, hence, maintain an endoscope specific log file to keep a track of number of procedures done, repair

Table 2. FDA recommendations for Hospitals and Endoscopy Facilities

1. Consider using duodenoscopes with disposable components, if available (this design may lower but not eliminate risks of infection).
2. Ensure staff meticulously follows reprocessing instructions.
3. Institute quality control program including sampling and microbial culturing, and other monitoring methods.
4. Consider reprocessing with supplemental measures such as sterilization or use of liquid chemical sterilant processing system.
5. Monitor reprocessing procedures.
6. Develop schedules for routine inspection and periodic maintenance in accordance with manufacturer's IFU.

Table 2. FDA recommendations for Hospitals and Endoscopy Facilities
history, report regarding their borescope channel examinations, and infection/culture results.

FDA and CDC also recommend all endoscopy centers to maintain transparent communication between endoscopists, reprocessing personnel and medical devise and infection control experts as a core strategy to minimize EAIs. Appropriate reporting of any adverse events, in regards to infection control, which would include any infection outbreaks, device failures and reprocessing lapses, is paramount to minimize patient risk. If an outbreak is detected, then a detailed investigation of root-cause analysis by experts, along with dismantling of alleged duodenoscope is advised. In addition, endoscopy centers are encouraged to maintain protocols regarding endoscopy/reprocessing staff education and examination on a periodic basis, as measures of quality control.

Refer to Table-2 for a comprehensive list of FDA recommendations for hospitals and endoscopy units.

c) ATP bioluminescence as an alternative to microbiologic surveillance and use of borescope:

Adenosine triphosphate (ATP) is present in microorganisms and human cells, and its detection in endoscope allows as a surrogate of bacteriologic/biologic residue. A few recent studies from Stanford interventional group led by Subhas Banerjee have explored the use of ATP bioluminescence as a surrogate of microbiologic culturing. In study by Sethi et al., ATP bioluminescence was measured after pre-cleaning, manual cleaning, and HLD on rinsates from suction-biopsy channels of all endoscopes and elevator channels of duodenoscopes/linear echoendoscopes. The authors noted that ideal ATP bioluminescence benchmark of <200 relative light units (RLUs) after manual cleaning was achieved from suction-biopsy channel rinsates of all endoscopes, but 9 of 10 duodenoscope elevator channel rinsates failed to meet this benchmark. Re-education reduced RLUs in duodenoscope elevator channel rinsates after pre-cleaning (23,218.0 vs 1340.5 RLUs, P < .01) and HLD (177.0 vs. 12.0 RLUs, P < .01). Also authors noted that after 2 cycles of manual cleaning/HLD, duodenoscope elevator channel RLUs achieved levels similar to sterile water, with corresponding negative cultures. This led authors to propose re-education of endoscopy staff and 2 cycles of cleaning and HLD to minimize the risk of transmission of infections by duodenoscopes.

Barakat and Girotra then utilized ultrathin flexible inspection endoscope to inspect working channels of 68 endoscopes in their unit, and correlated to ATP bioluminescence values from working channel rinsates. They noted superficial scratches (98.5%) and scratches with adherent peel (76.5%) and few small drops of fluid in 42.6% endoscopes after reprocessing and drying. The authors noted that presence of residual fluid predicted higher ATP bioluminescence values, and hence proposed periodic visual surveillance of duodenoscope, using borescope, for working channel damage (standard wear and tear/debris/water), and taking remedial actions on duodenoscope with extensive damage to achieve additional benefits in overall infection reduction strategy. Barakat et al. further demonstrated fewer water droplets and delayed ATP bioluminescence values within endoscope working channels after automated drying compared with manual drying, thus favoring automated drying to decrease risk of infection transmission. The group also showed that use of medium/high concentrations of simethicone was associated with increased retention of fluid droplets and higher ATP bioluminescent values in endoscope working channels, compared to when water or lower concentrations of simethicone was used. The group hence proposed using lowest possible concentration of simethicone, if needed at all, and Facilities may consider 2 automated
endoscope reprocessor cycles for reprocessing of endoscopes when simethicone has been used.

d) Advances in duodenoscope design:
Lessons learnt from these outbreaks, which were clearly attributable to the complex design of the distal tip of duodenoscope, especially the elevator mechanism, and particular difficulty in cleaning these, and persistence of infection despite reprocessing, served as fulcrum for research and development towards endoscope redesign, and will open new frontiers in endoscopic research. What started with introduction of single use parts of duodenoscope (disposable protection caps and air/water channel plugs)\textsuperscript{86} led to models with disposable or sterilizable forceps elevators.\textsuperscript{87} Till date, the FDA has cleared 5 duodenoscopes with disposable components that facilitate reprocessing, including Boston Scientific EXALT Model D single-use (fully disposable duodenoscope), Fujifilm ED-580XT (disposable endcap duodenoscope), Olympus Evis Exera III TJF-Q190V (disposable endcap duodenoscope), Pentax ED34-i10T (disposable endcap duodenoscope) and Pentax ED34-i10T2 (disposable elevator duodenoscope).\textsuperscript{79} Disposable designs may reduce between-patient duodenoscope contamination by half as compared to reusable, or fixed endcaps, and are hence being advocated by the FDA. Other devices are also in development, including ScopeSeal (GI Scientific LLC, Arlington, VA), which is a single-use device cleared by FDA for Olympus TJF-Q180V, which provides a sealed barrier for the distal end of duodenoscope, while maintaining the superior optical capability and other performance attributes of reusable duodenoscopes.\textsuperscript{88}

More recently, reusable single use duodenoscope has been introduced by Boston Scientific Corporation (Figure-2), which has garnered significant clinical attention and positive press.\textsuperscript{89} A clinical evaluation of single-use duodenoscope was recently conducted at 6 academic medical centers and included ERCPs with a wide range of complexity (ASGE complexity grade 1 = 7, grade 2 = 26, grade 3 = 26 and grade 4 = 1).\textsuperscript{90} The results suggests that 96.7\% (58/60) ERCPs were successfully completed using single-use duodenoscope and another 3.3\% (2/60) completed after crossover to reusable duodenoscopes, with median overall endoscopist satisfaction of 9/10. Although this study supports performance characteristics of this single-use disposable duodenoscope, its wide adoption will depend on its cost effectiveness, which must take into account not only the face value of the procedure cost and disposable equipment cost, but also balance it against several factors associated with reusable duodenoscopes, including maintenance cost and reprocessing cost after each use. In addition, there are several hidden costs which need to be taken into consideration, including cost of managing colonized/infected patients, associated litigation costs, and costs of remedial actions (discarding the infected duodenoscope away, downtime costs and cost of new duodenoscope, etc.). This is an area that needs detailed studies, but is extremely promising.

VI. CONCLUSIONS
In summary, the upsurge in EAIs, in particularly multi-drug resistant infections, noted in the last decade, despite adherence to reprocessing protocols, has not only directed worldwide attention to this issue but also led the FDA and CDC to regularize several aspects at the ends of endoscope manufacturers and the endoscopy units. This also commanded potent research focused at improving reprocessing protocols including increased automation to decrease human errors in reprocessing and introduction of checkpoints and surrogates to detect potential bacteriologic/biologic residue in the duodenoscopes. This research is now taking a direction towards advancements in design of duodenoscopes, including use of disposable distal attachments to facilitate cleaning, and even introduction of fully disposable duodenoscopes. These exciting advances instill a strong hope amongst the endoscopy community that we will be able to put the issue of EAIs behind us and thereby minimize patient risk while provide high level endoscopic services.

References
4. Kovaleva J, Peters FT, van der Mei HC, Degener JE. Transmission of
Endoscope-Associated Infections (EAI): An Update and Future Directions

Endoscope-Associated Infections (EAI): An Update and Future Directions


77. Olympus Medical System Corp. TJF-Q190V duodenscope. Available from: https://www.olympus-europa.com/medical/en/medi/content/Content-MSD/Documents/Brochures/B16428371_TJF-Q190V_A4_Flyer_EN_ABC02-2_FINAL_42690.pdf


