Selection of Low-Temperature Sterilization for the Prevention of Multidrug-Resistant Bacterial Infections During Flexible Endoscopy

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Introduction

Patient exposure to a duodenoscope emerged in 2012 as a recognized risk factor for transmissions of carbapenem-resistant *Enterobacteriaceae* (CRE) and related multidrug-resistant organisms (MDROs).[1-4] In several well-documented instances, outbreaks of these bacteria occurred despite apparent confirmation that the duodenoscope was being cleaned and high-level disinfected correctly.[1-5] In earlier years, the cause of infections linked to a contaminated duodenoscopes had been invariably attributed to an identifiable reprocessing breach (or defective equipment)—for example, to faulty cleaning, inadequate high-level disinfection, or improper drying of the duodenoscope prior to storage.[6,7] Featuring a complex physical design, duodenoscopes are used to perform endoscopic retrograde cholangiopancreatography as many as 500,000 times annually in the U.S.[5]

On the heels of these outbreaks linked to duodenoscopes, reports confirmed that other types of flexible endoscopes, including bronchoscopes and flexible intubation endoscopes, could also infect patients with multidrug-resistant bacteria.[8,9] Primary risk factors for these less physically complex endoscopes to transmit multidrug-resistant bacteria include damage to and both insufficient maintenance and faulty repair of the endoscope (in addition to inadequate cleaning or disinfection).[8] No matter the type of flexible endoscope, however, an accurate estimate of the true infection risk has been difficult to calculate in part due to a lack of post-endoscopic surveillance designed to monitor patients for infections. NDM-producing *E. coli* and VIM-producing *Pseudomonas aeruginosa* are respective examples of CRE and a related MDRO.[3,4]

Device Classifications: Critical, Semi-Critical, Non-Critical

Flexible endoscopes including less complex intubation endoscopes, which are used to examine a patient's larynx, trachea and vocal cords, contact intact mucous membranes or non-intact skin, and therefore are classified as *semi-critical*. These devices pose a lower risk of infection than more invasive surgical devices classified as *critical*, such as biopsy forceps, surgical scalpels and orthopedic implants.[7,10] Even though they do not ordinarily penetrate sterile tissues, the FDA recommends sterilizing *semi-critical* devices to provide a greater margin of safety and prevent transmission of diseases, including those caused by CRE and related MDROs, as well as by colistin-resistant bacteria whose infections can be even more difficult to treat.[10-12] When sterilization of a *semi-critical* device is not practical or feasible, however, the FDA recommends high-level disinfection.[10] For completeness, *non-critical* devices contact intact skin (but not mucous membranes) posing a low infection risk.[7] Examples include bedpans, stethoscopes and crutches. The Centers for Disease Control and Prevention (CDC) recommends cleaning alone, or cleaning followed by low- or intermediate-level disinfection of *non-critical* devices, depending on the nature and extent of contamination.[7,10]

High-level disinfection is generally achieved by completely immersing cleaned flexible endoscopes in an FDA-cleared liquid chemical germicide.[7,10] In addition to the immersion temperature, the disinfectant's concentration and exposure time directly impact the process's effectiveness. Sterilization of surgical instruments, on the other hand, may be accomplished using heat, usually pressurized steam.[7] If heat damages the instrument, a low-temperature sporicidal technology may be used instead. The success of low-temperature sterilization depends on several factors, however, particularly the effectiveness of cleaning and that the device's design and physical dimensions comply with the technology's labeling claims. For example, the labeling of low-temperature sterilization processes generally requires that the length and diameter of the flexible endoscope's internal channels not be longer or narrower, respectively, than predetermined dimensions established during sterilization validation testing.

Objectives

This article provides guidance for healthcare facilities that have decided to replace high-level disinfection with low-temperature sterilization of flexible endoscopes. Prevention of transmissions of CRE and related MDROs via these endoscopes, which is the focus of this article, has taken on heightened public awareness and regulatory focus, primarily because the patient mortality rate associated with these diseases can be as high as 50%.[1] Recognizing this risk, the FDA recommended in 2015 that U.S. facilities consider implementing at least one of the following four "supplemental measures" to improve the safety of duodenoscopes: ethylene oxide (EO) gas sterilization, use of a liquid chemical sterilant processing system, microbiological culturing and "repeat" high-level disinfection.[12] A facility's decision to use a low-temperature technology to sterilize duodenoscopes would comply with the FDA's recommendation.

Results: Labeling Claims of Low-Temperature Sterilization Processes

Several low-temperature technologies cleared for the sterilization of flexible endoscopes are listed in Table 1. The chemicals these processes use, either alone or as a mixture, are: EO gas, hydrogen peroxide as a vapor or plasma, liquid peracetic acid and ozone. No matter the chemical, low-temperature sterilization requires that the soiled instrument first be thoroughly cleaned. Moreover, due to impedance, the flow of these chemicals through a flexible endoscope's long, narrow internal channels can be restricted, interfering with sterilization. While a duodenoscope's physical design poses challenges to any low-temperature sterilization (or disinfection) procedure,[1-5,7,10,11] a "channel-less" probe without any complex crevices or difficult-to-clean recessed areas generally presents the least challenge.

In general, low-temperature sterilization processes are cleared for sterilizing only certain types of flexible endoscopes based, in large part, on the endoscope's physical dimensions. In addition to the constraints that an endoscope's long and narrow channel(s) can impose, the number of endoscopes that a low-temperature technology can process, at once, is limited. As this number increases, sterilization generally becomes more difficult to achieve. Displayed in Table 1, most of the low-temperature sterilization processes cleared by the FDA are labeled to process bronchoscopes, choledochoscopes and ureteroscopes, but not necessarily duodenoscopes. A few of these processes are cleared to sterilize at least two endoscopes at the same time.

Table 1: Low-Temperature Sterilization Technologies Cleared by the FDA for Processing Flexible Endoscopes

Device name	Manufacturer/ Distributor	Low-temperature sterilizing agent	Clearance year, 510(k) clearance #	FDA product code	Example of the dimensions of a single-lumened flexible endoscope the process is cleared to sterilize: (ID: inner diameter; L: the lumen's length)	Cleared to sterilize a flexible endoscope with at least two lumens?*	Cleared to sterilize more than one flexible endoscope at a time?*	Examples of flexible endoscopes the process is cleared to sterilize:	Is the device cleared to sterilize duodeno-scopes?
V-PRO maX 2	STERIS	vaporized hydrogen peroxide	2018; K172754	MLR	≥ 1 mm ID and ≤ 1050 mm in L	Yes	Yes	B, Cy, H, ENT, Ur[a]	No
EOGas 4 Sterilizer	Andersen Products	ethylene oxide gas (100%)	2015; K150646	FLF	≥ 1.2 mm ID and ≤ 700 mm in L	Yes	Yes	B, Ch, Cy, G, Ur	No
3M Steri-Vac Sterilize/Aerator (GS Series)	3M	ethylene oxide gas (100%)	2015; K142034	FLF	No restrictions on the ID or L of the channel	Yes	Yes	Co, Du, Ul[b,c]	Yes[d]
STERIS System 1E	STERIS	liquid peracetic acid	2018; K180342	MED	No restrictions on the ID or L of the channel	Yes	No	B, Co, Cy, Du, Ur	Yes[e]
STERIS System 1E Endo	STERIS	liquid peracetic acid	2018; K173256	MED	No restrictions on the ID or L of the channel	Yes	No	B, Co, Cy, Du, Ur	Yes[e]
STERRAD NX	ASP	hydrogen peroxide vapor/ gas plasma	2017; K162007	MLR	≥ 1 mm ID and ≤ 850 mm in L	No	No	B, Ch, Cy, H, Ur[f]	No
STERIZONE VP4 Sterilizer	$TS0_3$	vaporized hydrogen peroxide and ozone	2018; K172191	PJJ	≥ 1 mm ID and ≤ 850 mm in L	Yes	Yes	B, Co, Du, G, Ur	Yes[g]

Companies:

3M	St. Paul, MN
Andersen Products, Inc.	Haw River, NC
STERIS Corp.	Mentor, OH
ASP (Advanced Sterilization Products, Inc.)	Irvine, CA
TS03, Inc.	Quebec, Canada

Types of endoscopes:

B	bronchoscopes	ENT	flexible ENT endoscopes
Ch	choledochoscopes	H	hysteroscope
Co	colonoscope	Gas	gastroscope
Cy	cystoscope (flexible)	Ur	ureteroscope (flexible)
Du	duodenoscope	Ul	ultrasound endoscope

* Certain restrictions may apply.

[a–g] Please see page 14.

Recommendations: Selection Considerations

A healthcare facility's decision to replace high-level disinfection with low-temperature sterilization of flexible endoscopes requires careful planning. Explained in detail in Table 2, which is provided to facilitate this process, it is suggested that the facility consider classifying its inventory of flexible endoscopes into one of three groups, based primarily on published data and the facility's assessment of the device's infection risk. Indeed, not all flexible endoscopes pose the same risk of transmitting CRE and related MDROs. Those endoscopes placed into the first group (e.g., duodenoscopes) would pose the highest risk of infection, arguing to be sterilized now to improve safety. Flexible endoscopes that the facility places into the second or third group would pose a lower relative infection risk and, while ideal, sterilization's implementation might be deferred until practical and feasible.

Ideally, the types of flexible endoscopes classified into each of these three groups would be standardized and based on identical risk assessments. However, because a facility's resources and capabilities required to perform sterilization may vary, the endoscopes placed into these three groups could be facility-dependent. Currently, infection-control guidelines recommend high-level disinfection (at a minimum) of flexible endoscopes including duodenoscopes,[6,7,10] but none (to date) requires sterilization. Once the facility has classified each of its endoscopes into one of these three groups, it is recommended that the facility confirm congruity between one or more marketed low temperature sterilization processes under consideration and the endoscope types to be sterilized. For example, if a facility has decided that sterilization of duodenoscopes is necessary, it would confirm that the selected low-temperature sterilization process is labeled for this application or for which there is a plethora of safety and validation data supporting the process's implementation. **Table 2** explains these considerations.

Table 2: A Multi-Step Process for the Low-Temperature Sterilization of Flexible Endoscopes

1 Assess the facility's sterilization resources, management capabilities and staff training, and determine whether low-temperature sterilization of flexible endoscopes is possible and practical.

- If sterilization is deemed infeasible (for one of several reasons), then it is recommended that the facility consider applying and implementing, as circumstances warrant, at least one of the FDA's other supplemental measures published in 2015, in addition to standard cleaning and high-level disinfection[12]—for example, perform microbiological sampling or repeat high-level disinfection to improve safety.
  - The FDA's four supplemental measures are adjunctive steps intended to be combined with, not to replace, reprocessing of the duodenoscopes according to its manufacturer's instructions, which includes meticulous manual cleaning.[12]
  - Moreover, the FDA published these four measures to mitigate the risk of duodenoscopes transmitting diseases. This article suggests that the application of these measures to other types of flexible endoscopes, when feasible and deemed warranted, be considered to improve their safety.[13]
- If the facility deems low-temperature sterilization of flexible endoscopes practical and warranted, proceed to STEP 2.

Table 2: A Multi-Step Process for the Low-Temperature Sterilization of Flexible Endoscopes *(continued)*

❷ Consider **classifying** all of the facility's flexible endoscopes into one of three groups, based primarily on the device's published risk of transmitting CRE or a related MDRO, including colistin-resistant bacteria. For example, endoscopes could be grouped according to the following scheme (or a comparable one):

Group #1
Flexible endoscopes for which the facility has decided sterilization (in lieu of high-level disinfection) is feasible and necessary at this time to improve safety.

- In general, reports will have linked the endoscopes in this group to outbreaks of CRE and related MDROs and, according to the facility's risk assessment, these endoscopes could remain persistently contaminated even if cleaned and high-level disinfected in accordance with the manufacturer's instructions for use ("IFUs).
- The endoscopes in this group would generally be complex in physical design, posing challenges to effective cleaning.
- The classifying of endoscopes in this group may be subject to change as more safety data become available.
- Duodenoscopes are an example of an endoscope that the facility would likely include in this group.[1-5] The facility might also reasonably classify bronchoscopes and possibly linear array echo-endoscopes in this group.[9,13]
  - Chapman et al. (2017) recommended that measures published to reduce the risk of duodenoscopes transmitting multidrug-resistant bacteria be similarly applied to (curvilinear array) echo-endoscopes, which may also remain contaminated with "high-concern organisms" following standard reprocessing and high-level disinfection procedures.[13]

Table 2: A Multi-Step Process for the Low-Temperature Sterilization of Flexible Endoscopes *(continued)*

Group #2

Flexible endoscopes for which the facility desires sterilization to improve safety compared to high-level disinfection, but whose immediate implementation the facility has deemed is currently impractical.

- The flexible endoscopes in this group can pose a risk of transmitting CRE and related MDROs if contaminated at the time of use but are generally simpler in design and easier to clean, and the likelihood of infection is reported to be less than that of the endoscopes in *Group #1*.
  - The infection risk associated with the types of flexible endoscopes in this group could increase significantly, however, if management cannot assure that the endoscope has been serviced, maintained and repaired in accordance with the manufacturer's IFUs.
  - Notably, Parr et al. (2016) concluded that gastroscopes and other types of flexible endoscopes less complex in design than duodenoscopes "may fail high level disinfection and cause infections."[14]
- Cystoscopes, ureteroscopes, choledochoscopes, flexible intubation endoscopes and ureteroscopes are examples of flexible endoscopes a facility might reasonably classify into this group, or into *Group #1*. The facility might also classify colonoscopes in this group.[15]
- The facility would ideally phase-in the sterilization of endoscopes in this group over time consistent with the facility's assessment of risk and available resources and capabilities.
- The classifying of endoscopes in this group may be subject to change as more safety data become available.
- High-level disinfection of the endoscopes in this group would continue to be practiced until sterilization became practical and was implemented.
- Until the facility adopts sterilization of the endoscopes in this group, it is recommended that the facility consider applying and implementing at least one of the FDA's other supplemental measures published in 2015, in addition to standard cleaning and high-level disinfection[12]—for example, performing microbiological sampling or repeating high-level disinfection to improve safety.

Table 2: A Multi-Step Process for the Low-Temperature Sterilization of Flexible Endoscopes *(continued)*

Group #3
Flexible endoscopes for which the facility has concluded, based on clinical evidence and a risk assessment, sterilization may not be currently necessary to substantively improve safety.

- The flexible endoscopes in this group, according to the facility's risk assessment, would pose a low or negligible risk of transmitting CRE and related MDRO infection provided the endoscope is cleaned, high-level disinfected, stored, serviced, maintained and repaired in strict accordance with the manufacturer's IFUs.
- The endoscopes in this group would be the exception, and the facility would document the rationale for not classifying the endoscopes in this group into either *Group #1* or *Group #2*.
- The classifying of endoscopes in this group may be subject to change as more safety data become available.
- Hysteroscopes, ultrasound probes and transesophageal echocardiography probes are examples of flexible endoscopes the facility might reasonably classify into this group.
- **Note**: No matter the group in which the endoscope has been classified, its sterilization may be necessary in some circumstances—for example, to terminate an identified outbreak, or if surveillance cultures suggest the endoscope is persistently contaminated with CRE, related multidrug-resistant bacteria, or another pathogenic organism.

❸ **Identify** the low-temperature technologies that are currently available and cleared by the FDA for sterilizing one or more types of flexible endoscopes. Table 1 lists several of these processes.

- Review the labeling of each of these low-temperature sterilization processes and confirm which is suitable to sterilize (e.g., based on the length and diameter of the endoscope's internal channels; see: Table 1) the flexible endoscopes the facility has classified into *Group #1* (and has decided sterilization is necessary at this time to improve safety).
  - Repeat the previous step for those flexible endoscopes the facility has classified into *Group #2* (which the facility desires to sterilize, but whose immediate implementation it has deemed is currently not practical).

Table 2: A Multi-Step Process for the Low-Temperature Sterilization of Flexible Endoscopes *(continued)*

4 **Select** an appropriate low-temperature technology.

- Ideally, the selected low-temperature sterilization process would satisfy the following criteria:
  - The process is labeled to sterilize one or more of the flexible endoscopes the facility has classified into *Group #1*, or there is a plethora of safety and validation data supporting the process's implementation for sterilizing the endoscopes in this group.
  - The process's labeling claims are relatively broad and ideally also include one or more of the flexible endoscopes the facility has classified into *Group #2*.
  - The facility has determined the process is cost-effective, and that it has the resources and capabilities to train staff in the process's safe and effective use.
  - The endoscopes' manufacturers have confirmed that the process is compatible with the endoscope's materials and will not void the device's warranty.
    - A process's sterilization effectiveness does not assure its compatibility with the endoscope's materials. (An extreme example is a steam autoclave, which would sterilize the endoscope, but also would damage it.)
- If no sterilization process is found to be suitable for any of the facility's endoscopes in *Group #1* (and/or *Group #2*), then continuing to clean and high-level disinfect the endoscope in accordance with the manufacturer's IFUs is recommended.
  - It is further recommended that the facility consider applying and implementing at least one of the FDA's other supplemental measures published in 2015, in addition to standard cleaning and high-level disinfection[12]—for example, performing microbiological sampling or repeating high-level disinfection to improve safety.

Discussion

This article helps to guide a healthcare facility's decision to replace high-level disinfection with low-temperature sterilization for one or more types of flexible endoscopes. Based on the number of reports since 2012 linking duodenoscopes to outbreaks of CRE and related MDROs, particular focus is placed on increasing the safety of this device.[2-5,12] One of the technologies listed in Table 1 has been cleared by the FDA for processing duodenoscopes, and the FDA lists this technology, which uses liquid peracetic acid, as one of the four supplemental measures to consider to reduce the risk of duodenoscopes transmitting infections.[12]

Ethylene oxide gas sterilization is also a technology listed in Table 1 that the FDA recommends facilities consider as a supplemental measure to improve the safety of duodenoscopes. While the FDA has not yet cleared a device, per se, that uses EO gas specifically to sterilize duodenoscopes, some of the duodenoscope manufacturers have validated this technology as effective and compatible.*

Further, several studies found that the replacement of high-level disinfection with EO gas sterilization terminated outbreaks of CRE and related MDROs.[4,16,17] EO gas sterilization requires the endoscope be aerated for several hours before reuse, however.

When sterilization of a duodenoscope or other type of flexible endoscope either is deemed infeasible or currently impractical, facilities are encouraged to consider either disinfecting the endoscope twice or culturing the endoscope microbiologically to confirm its safety.[12,18] This latter preventive measure, like EO gas sterilization, however, would likely require the facility to purchase more endoscopes to meet patient demand and account for endoscope "downtime." Nevertheless, no biocidal agent used to reprocess reusable medical instrumentation is without certain limitations, whether a gas, vapor, plasma or a liquid. Identifying and comparing the advantages and disadvantages of each of the technologies listed in Table 2 is recommended.

*Olympus America. Reprocessing manual for the TJF-Q180V duodenoscope. Reference: RC2409 02.

Conclusion

A healthcare facility's decision to replace high-level disinfection with low-temperature sterilization of flexible endoscopes requires careful planning to ensure the necessary resources, capabilities and training are available. It is recommended that facilities perform an evidence-based risk assessment to evaluate and decide which flexible endoscopes may require low-temperature sterilization now to prevent the transmission of CRE and related MDROs and improve safety. This article provides guidance to help with this decision, understanding that not all flexible endoscopes are associated with the same risk of transmitting multidrug-resistant bacteria. When sterilization is not feasible, facilities should consider implementing at least one of the FDA's other supplemental measures to improve the safety of duodenoscopes and, as warranted and deemed appropriate, applying these measures, too, to other "high-risk" endoscopes.

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a. https://www.steris.com/onbDocs/V440/0/1375474.pdf

b. http://multimedia.3m.com/mws/media/1057877O/3m-steri-vac-ethylene-oxide-sterilization-systems.pdf

c. "*Always refer to the instrument manufacturer's Instructions for Use (IFU) for validated sterilization modalities and cycles." (Refer to 3M's previous reference, link.)

d. Yes, according to the manufacturer's literature. See: http://multimedia.3m.com/mws/media/1057877O/3m-steri-vac-ethylene-oxide-sterilization-systems.pdf

e. https://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/ReprocessingofReusableMedicalDevices/ucm483896.htm

f. https://www.emea.aspjj.com/sites/aspjj.com.emea/files/pdf/STERRAD_NX_System_Wall_Chart_1.pdf

g. https://www.tso3.com/new-clearance

Questions may be directed to the author, Lawrence F. Muscarella, Ph.D., at: Larry@LFM-HCS.com

Citation:
Muscarella LF. Selection of Low-Temperature Sterilization for the Prevention of Multidrug-Resistant Bacterial Infections During Flexible Endoscopy. Ambu: Columbia, MD. 2019.