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Review

A review of Spaulding's classification system for effective cleaning, disinfection and sterilization of reusable medical devices: Viewed through a modern-day lens that will inform and enable future sustainability

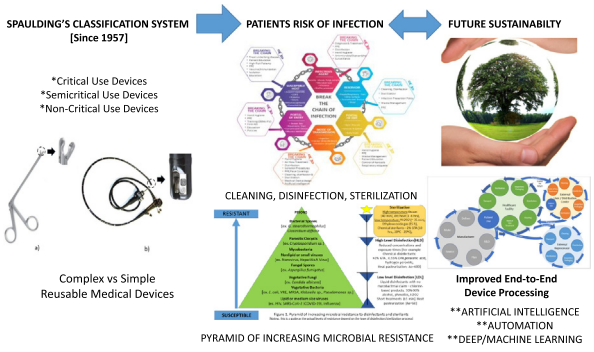
N.J. Rowan [a,b,c,*], T. Kremer [a,d], G. McDonnell [d]

[a] Centre for Sustainable Disinfection and Sterilization, Bioscience Research Institute, Technological University of the Shannon Midlands Midwest, Athlone Campus, Ireland
[b] Department of Nursing and Healthcare, Technological University of the Shannon Midwest Mideast, Athlone Campus, Ireland
[c] SFI-funded CURAM Centre for Medical Device Research, University of Galway, Ireland
[d] Microbiological Quality & Sterility Assurance, Johnson & Johnson, 1000 Route 202, South Raritan, NJ 08869, USA

HIGHLIGHTS

- Cleaning, disinfection and sterilization remain essential for mitigating patient risk from contaminated reusable medical-devices
- Spaulding's classification of 1957 remains applicable, but it needs updating for modern-day challenges and opportunities
- Pressing need for new real-time monitoring and robust cleaning of devices enabled by automation
- Future design thinking of next-generation medical devices should address ease of cleaning, processing efficacy, and sustainability
- Quintuple Helix Hub concept (academia-industry-healthcare-regulators-society) will accelerate innovation and advance device safety

GRAPHICAL ABSTRACT



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ABSTRACT

Despite advances in medicine and innovations in many underpinning fields including disease prevention and control, the Spaulding classification system, originally proposed in 1957, remains widely used for defining the disinfection and sterilization of contaminated re-usable medical devices and surgical instruments. Screening PubMed and Scopus databases using a PRISMA guiding framework generated 272 relevant publications that were used in this review. Findings revealed that there is a need to evolve how medical devices are designed, and processed by cleaning, disinfection (and/or sterilization) to mitigate patient risks, including acquiring an infection. This Spaulding Classification remains in use as it is logical, easily applied and understood by users (microbiologists, epidemiologists, manufacturers, industry) and by regulators. However, substantial changes have occurred over the past 65 years that challenge interpretation and application of this system that includes inter alia emergence of new pathogens (viruses, mycobacteria, protozoa, fungi), a greater understanding of innate and adaptive microbial tolerance to disinfection, toxicity risks, increased number of vulnerable patients and associated patient procedures, and greater complexity in design and use of medical devices. Common cited examples include endoscopes that enable non- or minimal invasive procedures but are highly sophisticated with various types of materials (polymers, electronic components etc), long narrow channels, right angle and

* Corresponding author at: Centre for Sustainable Disinfection and Sterilization, Bioscience Research Institute, Technological University of the Shannon Midlands Midwest, Athlone Campus, Ireland.
E-mail address: nrowan@ait.ie (N.J. Rowan).

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heat-sensitive components and various accessories (e.g., values) that can be contaminated with high levels of microbial bioburden and patient tissues after use. Contaminated flexible duodenoscopes have been a source of several significant infection outbreaks, where at least 9 reported cases were caused by multidrug resistant organisms [MDROs] with no obvious breach in processing detected. Despite this, there is evidence of the lack of attention to cleaning and maintenance of these devices and associated equipment. Over the last few decades there is increasing genomic evidence of innate and adaptive resistance to chemical disinfectant methods along with adaptive tolerance to environmental stresses. To reduce these risks, it has been proposed to elevate classification of higher-risk flexible endoscopes (such as duodenoscopes) from semi-critical [contact with mucous membrane and intact skin] to critical use [contact with sterile tissue and blood] that entails a transition to using low-temperature sterilization modalities instead of routinely using high-level disinfection; thus, increasing the margin of safety for endoscope processing. This timely review addresses important issues surrounding use of the Spaulding classification system to meet modern-day needs. It specifically addresses the need for automated, robust cleaning and drying methods combined with using real-time monitoring of device processing. There is a need to understand entire end-to-end processing of devices instead of adopting silo approaches that in the future will be informed by artificial intelligence and deep-learning/machine learning. For example, combinational solutions that address the formation of complex biofilms that harbour pathogenic and opportunistic microorganisms on the surfaces of processed devices. Emerging trends are addressed including future sustainability for the medical devices sector that can be enabled via a new Quintuple Helix Hub approach that combines academia, industry, healthcare, regulators, and society to unlock real world solutions.

Contents

1. Introduction

Medical devices are of critical importance to patient health, where healthcare is constantly evolving to improve the quality of care provided to patients. Pre COVID-19, there were approximately 54 million outpatient and 46 million inpatient surgical procedures conducted each year in the United States alone (Perry et al., 2012; Pendarkar et al., 2018). International studies have highlighted that addressing the COVID-19 pandemic has resulted in frequent cancellation of surgical service provision and endoscopies due to safety concerns that has placed added enormous pressure on healthcare to meet this backlog and to continue to deliver appropriate care to patients (Ebigbo et al., 2020; Belle et al., 2020). Unexpected patient complications from the use of medical devices further adds to these burdens on healthcare systems worldwide.

The most cited complications are Hospital Acquired Infections (HAIs), which are defined as infections developing after 48 h of a stay at a healthcare facility that was not present or incubating at the time of admission (McDonnell and Hansen, 2020). HAIs are estimated to affect 1.7 million patients in the US annually leading to 99,000 deaths (Bradley and Hensley, 2015; Kathryn Gold, 2013). Medical devices are a common source of HAIs and have accounted for 60 % to 80 % of all bloodstreams, urinary tract, and pneumonia-related HAIs (Kathryn Gold, 2013). Otter et al. (2016) described that transmission routes of pathogens are complicated and have been difficult to assign an assignable cause through investigation.

The medical device industry, encompassing original equipment manufacturers (OEMs) and the connected sterilization industry, is highly regulated to deliver safe and effective products for patient use. For reusable medical devices intended to be processed within a healthcare facility prior to patient use, instructions for use (IFU) and associated labelling provide the important processing requirements to ensure patient safety, including cleaning, disinfection, and/or sterilization that are typically performed by dedicated facility departments (McDonnell and OSMA Anti-Infective Working Group, 2022). Kenters et al. (2018) conducted a worldwide survey on current flexible endoscope reprocessing that identified a large variation in reprocessing practices among healthcare facilities in different countries. Most facilities (82 %) have standard procedure; however, 50 % (n = 165) of reprocessing practitioners identified the need for education and training programme with a competency assessment to prevent reprocessing lapses and to improve patient safety. To mitigate the risk of HAIs, current methods for the safe processing of medical devices still rely upon the guiding classification system of Dr. E. H. Spaulding, originally conceived and published over 50 years ago (Spaulding, 1968). The general applicability of Spaulding's classification system remains logical and practical today. Spaulding's underpinning hypothesis was that healthcare facilities should apply appropriate disinfection and sterilization methods to process medical devices and surgical instruments based on the degree to patient risk of acquiring an infection due to their use. Three categories of risk were proposed, namely critical use [where a device or item enters sterile tissue

and must be sterile], semi-critical use [where a device or item contacts mucous membranes or non-intact skin, and requires at a minimum high-level disinfection], and non-critical [where a device or item comes in contact with intact skin and requires low-to-intermediate level disinfection]. Therefore, this timely review article addresses key pressing technical challenges and embraces emerging opportunities for the sustainable development of medical devices from a reflective lens perspective.

This study drew upon publications across PubMed and Scopus databases using a PRISMA guiding framework. Of the published papers using the key words "Medical Devices" (1,679,481) and "Spaulding Classification" (180) over period 1957 to 2023. Eligibility criteria focused on studies addressing cleaning, processing and sterilization of reusable medical devices and surgical instruments that included microbiology, toxicology, infection transmission, biofilms, antimicrobial resistance and risk assessment. A total of 118 papers were excluded for the reason that reasons that they did not meet eligibility criteria that included bone stress injuries, selective depletion of uropathogenic *E. coli* from the gut, perioperative ultrasonography and echocardiography, theropod furcula, spinal cord injuries; postconcussion and consciousness symptoms and scales, periorbital dirofilariasis, traumatic brain injury, laryngectomy on women, social impact of burns, apraxia, axonal injury, cerebral edema, encephalopathy, peripheral nerve and spinal injuries, parathyroids, avian influenza, Gulf War illness, haemodialysis, schizophrenia, cardiometabolic disease risks, social anxiety, burn recovery, chronic pain, acute phase retinopathy and whole exome sequencing in cerebral palsy for the reasons that these topics did not align with eligibility criteria.

Combining "medical devices + disinfection + risk assessment" generated 301 published results on PubMed and Scopus databases over period 1980 to 2023. Of these, 232 papers were exclude for reasons that they did not align with topic that comprised criteria toilet hygiene, antiseptics and dressings, eyewear contamination, tonometer tips, obstetric infection, acupuncture needles, aseptic technique in microgravity, surgical site infections, chlorhexidine bathing, venous leg ulcers, poultry, personal and protective equipment, COVID-19 management, whole room disinfection, drinking water, corneal staining, waterborne transmission, dental exposure to pesticides, decontamination of beds, swimming pool, dental water lines, military exercise, humidifier disinfectants, oral care, cell sorting in BSL-3 facility, influenza pandemic, diagnostic assays, disposable sterile endosheaths and pulsed UV surface disinfection. Combining the keywords "biofilm", "disinfection" and "medical devices" revealed 203 matching papers on PubMed and Scopus databases over period 1995 to 2023. Also, the incorporation of "antibiotic resistance" generated 80 matching papers in these databases over the period 1972 to 2023 that were screened for eligibility criteria.

2. Spaulding classification for informing appropriateness of disinfection and sterilization of medical devices based upon relationship between use and patient risk

2.1. Current understanding principles and expectations for disinfection and sterilization of devices

This classification system is widely accepted by broad stakeholders including end-users and regulators, such as European Centre for Disease Prevention and Control (ECDC), the U.S. Food and Drug Administration (FDA), and the U.S. Centres of Disease Control and Prevention (CDC), that inform the appropriateness of disinfection and/or sterilization methods to be applied to the reprocessing of reusable medical devices and surgical instruments (McDonnell and Burke, 2011; Klacik, 2019; Rutala, 2019a, 2019b, 2019c; Rutala and Weber, 2016b; Day et al., 2021). Rutala and Weber (2016a) noted that Spaulding's system divides all medical devices into 3 discrete categories based on the severity of perceived risk to patients of acquiring an infection from their use.

1. Critical use items – where a device enters sterile tissue and must be sterile, defined as being free from viable microorganisms (McDonnell and Hansen, 2020). Items contaminated with any microorganism (including bacterial spores), or infectious agent (prion) are referred to as high risk to patients. If they are contaminated and enter sterile tissue or vascular system, they have a high potential for causing disease transmission (Rutala and Weber, 2016b). "Such items should be sterile, such as by using steam sterilization where possible. Examples include surgical instruments. Given that many items contain heat-sensitive materials, other appropriate sterilization modalities should be applied including vaporized hydrogen peroxide (VH2O2), VH2O2 gas plasma, and ethylene oxide gas (EO)" (Rutala and Weber, 2016a). The use of liquid chemical sterilants may also be considered appropriate, such as formulations based on glutaraldehyde (GTA), peracetic acid (PA), hydrogen peroxide (HP), or ortho-phthalaldehyde (OPA). Close attention should be given to the label claims of liquid chemical sterilants as these can vary regionally; they may have the ability to sterilize, depending on their application but may not always be considered practical for routine sterilization.
2. Semi-critical use items– where a device only comes in contact with intact mucus membranes or nonintact skin, it should also be subjected to sterilization, or if this is not feasible due to sensitive material composition or complex design features, then a high-level disinfection (HLD) process must be deployed at a minimum that would be expected to kill all microorganisms except for bacterial endospores (McDonnell and Burke, 2011). Examples of semi-critical items including "respiratory therapy, anaesthesia equipment, some endoscopes, laryngoscope blades and handles, esophageal manometry probes, endocavitary probes, nasopharyngoscopes, prostate biopsy probes, infrared coagulation devices, anorectal manometry catheters, cystoscopies, and diaphragm fitting rings" (Rutala and Weber, 2016b). Depending on regional claim requirements, high level disinfectants should demonstrate broad spectrum antimicrobial activity and typically the ability to eliminate at least 10^6 (or 6-logs) of mycobacterial cells on contaminated surfaces of medical devices. For the vegetative microorganisms and viruses of concern, mycobacteria are typically deemed to exhibit greater resistance to high level disinfectants; thus, mycobacterial cells are recognised as representative (or bio-indicators) for HLD process efficacy. Examples of chemical disinfectants authorized in the USA for HLD use include biocides such as glutaraldehyde, HP, OPA, hypochlorite, and PA with HP (FDA, 2022). It is important to note that the ability to inactivate microorganisms by a disinfectant/sterilant is only part of an overall safe and effective high level disinfection process, as the disinfectant residuals need to be safely removed and the device correctly maintained prior to patient use.
3. Non-critical use items – "where devices contact intact skin (but not mucous membranes), requiring low-level to intermediate-level disinfection. The skin contains intact integumentary layers, and as such, provides a natural barrier to microorganisms. There remains a risk to the skin and as a source of cross-contamination from devices, but this risk is considered low" (Rutala and Weber, 2016a). These risks can be practically reduced by the combination physical removal and disinfection (McDonnell and Burke, 2011). Examples of non-critical use items include blood pressure cuffs, bed surfaces and rails, patient furniture, bedpans, over-bed tables and so forth (Rutala and Weber, 2016b). Such product labelling support disinfection efficacy against a broad spectrum of microbial pathogens that may include methicillin-resistant *Staphylococcus aureus*, vancomycin-resistant enterococci, yeast (*Candida* sp.), mycobacteria, and viruses well within typical label claim for US EPA-registered disinfectants. Physical removal plays an important role in the removal of pathogens with higher levels of natural resistance to disinfectants such as bacterial spores (as highlighted in studies of surface contamination with clostridia; Thomas et al., 2022).

Fig. 1 illustrates the microbial resistance profile to applied disinfection and sterilization modalities. Microorganisms with higher resistance are widely used to challenge and test the effectiveness of disinfection and sterilization methods. Mycobacterial cells, as examples, are used as representative biological indicators (BIs) of microbial resistance for high level disinfection (HDL) such as in the testing of GI endoscopes, bronchoscopes,

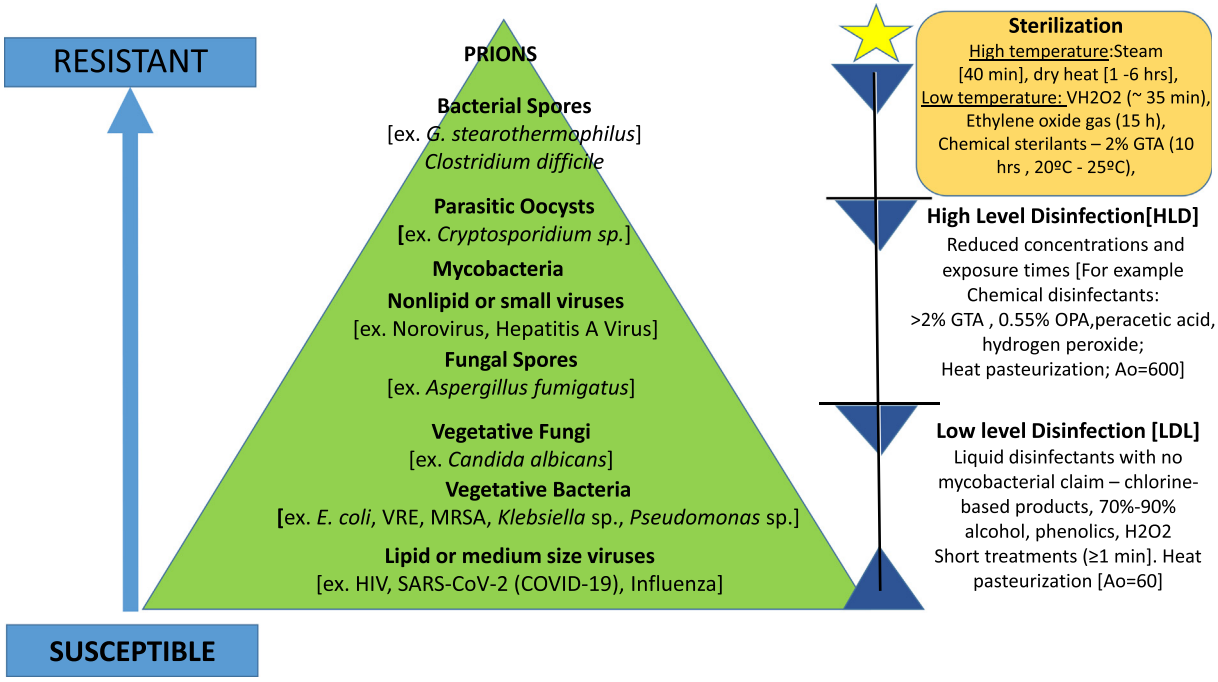

Fig. 1. Pyramid of increasing microbial resistance to disinfectants and sterilants [Noting, this is a guide as the actual levels of resistance depend on the type of disinfection/sterilization process].

and *endo*-cavity probes. Biological indicators are test systems that contain viable microorganisms with a defined resistance to a specific sterilization process (McEvoy and Rowan, 2019; McEvoy et al., 2021; McEvoy et al., 2023). *Bacillus* endospores are used as BIs to confirm sterilization efficacy with heat-tolerant critical (surgical instruments) and heat-sensitive critical and semi-critical patient care items. Although these traditional microbiological tests are useful in establishing the efficacy of such processes and applications, they are limited and there are many benefits in the use of alternative validation approaches such as parametric release or the use of higher classes of chemical indicators (McDonnell and Hansen, 2020). These can provide more robust data insights for the routine control of such processes and lend themselves to automation opportunities. Sterilization addresses the more recalcitrant pathogens that pose serious patient risks transmitted on contaminated devices. Some types of liquid chemical sterilants are frequently used to overcome complex design features associated with heat-sensitive critical and semi-critical devices. At the opposite end, a more wider array of disinfectants can be used at shorter exposure times for chemical liquid disinfection of non-critical patient care items (such as blood pressure cuffs) (Rutala, 2019a, 2019b, 2019c; McDonnell and Hansen, 2020). Some reports have found that certain strains of parasitic oocysts are particularly resistant to chemical disinfectants, but not as much to heat nor UV irradiation (Garvey et al., 2022; McDonnell, 2017). Parasitic oocysts should fall within HLD but may not always be the case; however, they are not routinely required to be tested for any disinfectant claims. It is important to note that the microbial resistance pyramid illustrated in Fig. 1 is only given as a guide as the actual levels of resistance depend on the type of disinfection/sterilization process and the different strains of microorganisms tested. Disinfectant (including HLD) claims are product specific and not just based on certain concentrations and exposure time for the active (e.g., the product formulation and exposure conditions can have a dramatic effect on antimicrobial efficacy).

2.2. Challenges and limitations for modern-day interpretation and application of Spaulding's classification system

Healthcare is constantly scrutinized regarding the effectiveness in the delivery of continuous quality improvements including practices of cleaning, disinfection, and sterilization. HAIs are reported to occur in one out of 25 patients daily on average in the US (CDC, 2014) with over 2 million patients contracting HAIs annually (Vallés and Ferrer, 2009). In the USA alone, the overall incidence of HAIs is estimated to have increased by 36 % in the last two decades (Stone, 2009). In recent times, there have been over 25 outbreaks of multidrug-resistant organisms including carbapenem-resistant Enterobacteriaceae (CRE) in hospitals internationally that have led to significant morbidity and mortality, which have linked to contaminated duodenoscopes. Moreover, contaminated gastrointestinal (GI) endoscopes and bronchoscopes are often considered as semi-critical devices, as they have contact with intact mucous membranes, but have been linked with over 130 outbreaks causing mortalities (Balan et al., 2019). Outbreaks have unfortunately not been limited to flexible endoscopes subjected to HLD but have included critical devices subjected to steam sterilization (Tosh et al., 2011; Dancer et al., 2012).

2.2.1. Failure mode analysis: critical instance case study

There are at least 18 million gastrointestinal endoscopies conduced each year in the United States (Rutala and Weber, 2016b; Rutala, 2019a, 2019b, 2019c). Each of these procedures involves use of surgical instruments or medical devices that contact a patient's sterile tissue or mucous membrane (Rutala and Weber, 2016b). However, there is a major risk of introducing infection to all patients undergoing such procedures if contaminated surgical instruments and medical devices are not appropriately processed (Rutala and Weber, 2016b). For example, a systematic search of the literature conducted during 2018 and 2019 just prior to COVID-19 pandemic, estimated the risk of contracting duodenoscope-associated infections (DAIs) in Dutch practices to be at least 180 times higher than previously published risk estimates due to underreporting of infections caused by multi-drug resistant organisms (MDROs) and sensitive bacteria (Kwakman et al., 2021; Kwakman et al., 2022). The authors advocated greater awareness by healthcare personnel involved in endoscopies, a need for improved endoscope cleaning and new solutions to address technical challenges to prevent occurrence of DAIs.

GI endoscopes can become highly contaminated during use, where the internal long narrow lumen can contain between 7 and 10 $\log_{10}$ enteric microorganisms and the microbial load of colon is ca. 9 to 12 $\log_{10}$/mL

(Rutala, 2019a, 2019b, 2019c; Alfa et al., 1999) The margin of safety associated with processing these endoscopes with semi-critical use designation is negligible and therefore are present higher risk to patients than previously considered. GI endoscopes should be subjected to cleaning and HLD that when conducted correctly can reduce microbial bioburden by ca. 2 to 6 $\log_{10}$ and 4 to 6 $\log_{10}$ respectively; thus, representing a combined maximal microbial reduction of ca. 12 $\log_{10}$ if cleaning is conducted appropriately. As flexible GI endoscopes and bronchoscopes are heat-sensitive devices, they are generally subjected to HLD using chemical disinfectants or by using low-temperature sterilization modalities. But the level of contamination of endoscopes after cleaning and disinfection could be as high as 5 $\log_{10}$/ml when not conducted efficiently. This equates to an estimated 17 $\log_{10}$ reduction of surgical instruments that are cleaned (2–6 $\log_{10}$ microbial reduction), and sterilized (at least a 12 $\log_{10}$ microbial reduction), where surgical device generally present with significantly lower levels of initial microbial contamination given their use (<2 $\log_{10}$; Cloutman-Green et al., 2015; Rutala, 2019a, 2019b, 2019c). In addition, heavily contaminated flexible endoscopes are highly complex and challenge current decontamination methods with complex features such as narrow lumens and valves resulting in approximately 100 processing steps (Ofstead et al., 2017). Overall, this pushes the margin for safety with processing endoscopes to zero. Campbell Westerway and Basseal (2022) noted, as a reusable medical device, the ultrasound transducer (also known as a probe), comes in contact with mucous membranes of vagina, anal cavity and oral cavity, and it can therefore transmit pathogenic viruses, fungi and bacteria by blood, or mucosal, genital or rectal secretions. These authors reported that only a small number of countries worldwide have implemented transducer reprocessing guidelines that adhere to recommended high level disinfection (HLD) for endocavity transducers. This is mainly due to the perception that the infection transmission risk is negligible given that endocavity transducers are covered with a single-use sheath for the procedure, intimating low-level disinfection provides sufficient protection against pathogen transmission. By highlighting the outbreaks arising from tranducer transmission, the authors recommend that HLD should be a global standard of practice. Saliou et al. (2016) reported that the rate of non-compliance of the microbiological tests performed on flexible cystoscopes is relatively high (19.5 %). Thus, there is a need to improve the processing quality of reusable devices (Ball, 2000; Foliente et al., 2001; Rohm-Rodowald and Jakimiak, 2004; Crawford, 2007; Saliou et al., 2016; Snyder et al., 2017; Link, 2018; Sherman et al., 2018; Kenters et al., 2018; Rahman et al., 2019; Pynnonen and Whelan, 2019; Wiktorczyk et al., 2020; Casini et al., 2021).

Outbreaks have been associated with “inadequate cleaning, inappropriate disinfection, and damaged endoscopes, or flaws in the design of endoscopes or automated endoscope reprocessor (AER)” (Rutala, 2019a, 2019b, 2019c). Often these devices have also been linked as causative agents in outbreaks of CRE or other MDROs in which there were no obvious breaches in endoscope reprocessing (Cabronne et al., 2010; Epstein et al., 2014; Smith et al., 2015; Marsh et al., 2015; Kola et al., 2015; Wendorf et al., 2015; Kim et al., 2016; Shenoy et al., 2019). In some instances, transmission was attributed to device design flaws that prohibited appropriate cleaning that enabled persistent contamination. Chemical disinfectants are effective against CRE and MDROs; thus, it likely that failure in HLD processing was attributed to the lack of exposure to sufficient concentration of disinfectants overtime. Rutala (2019a, 2019b, 2019c) intimated that occurrence of surviving MDROs potentially act as indicator or “red-flag” organisms for ineffective reprocessing of complex designed duodenoscopes. This is logical and very plausible given that the occurrence of specific problematic pathogens on processed medical devices, where disinfectants are normally considered to be effective (Wilson and Nayak, 2016). The latter should also be considered in the context of overall surviving cell numbers (or microbial bioburden) on semi-critical devices that presents a high infectious risk to patients. It was noted that 63 % of 249 surveyed endoscopy centres performed double HLD on duodenoscopes and linear echoendoscopes but did not reduce culture positive rates (Rutala, 2019a, 2019b, 2019c). There is also data showing that all the stages in manual endoscope reprocessing are rarely carried out (1.4 % compliance rate) including omission of essential brushing of channels and components (Ofstead et al., 2010). Endoscope decontamination was improved by using AERs, highlighting the benefits of automation and standardization of processes that also addresses shortcomings associated with mundane manual cleaning procedures.

It has been recommended over many years that as duodenoscopes commonly contact mucous membranes and sterile tissue they should be elevated from semi-critical to critical use status that would typically entail use of a low-temperature sterilization modality, replacing the use of HLD. The infection risk to patients is also potentially enhanced by the increased use of endoscopies (such as bronchoscopies) in elderly patients and those with cancers, organ transplantation, severe underlying conditions, host defence abnormalities, or immune-deficient diseases or medications (Rutala, 2019a, 2019b, 2019c). Thus, the margin of safety for processing heavily contaminated flexible endoscopes is too unforgiving to be practical as it demands near perfect compliance with OEM's IFU. Additionally, microbial tolerance to HLD due to the higher risk of the development and protection of microorganisms in biofilms within endoscope channels also presents a challenge for healthcare given that this may lead to decontamination failure of processed endoscopes (da Costa Luciano et al., 2016).

Over the decades since the initial introduction of Spaulding's classification system, there has been commensurate challenges to hurdle including increased device complexity with features that challenge the cleaning process and a better understanding of the intrinsic and acquired mechanisms of biocide tolerance seen in problematic and opportunistic pathogens including development of multidrug-resistance and cross-protection to the applied and dis-similar lethal environmental stresses. These can be further enhanced by the upregulation of microbial virulence in survivors induced by environmental-stress exposures such as drying, the presence of disinfectants (Ladicevic et al., 2022),and biofilm-mediated protection (Alfa and Howie, 2009); emergence of potential disinfectant mediated cross protection against antibiotics (Morrison et al., 2019); fixation of microbial pathogens within protective soils to contaminated surfaces due to specific regimes of cleaning and types of disinfectants (such as aldehydes) that can also potentially anchor more recalcitrant infectious agents (Kremer et al., 2021a, 2021b, 2021c), such as prions; an increasing complex and embattled healthcare environment colonized by antibiotic-resistant bacteria (Rowan and Moral, 2021; Thomas et al., 2022); and greater number of vulnerable patients with diversity of medical needs (McDonnell and Hansen, 2020).

3. Cleaning

The importance of effective cleaning of medical devices prior to disinfection and sterilization is often under-estimated. Reusable device features vary considerably in design complexity (Fig. 2) It is well known that disinfection and sterilization methods will fail if the pre-cleaning stage is not conducted appropriately, but the classification system is more focused on the antimicrobial steps to be deployed based on the device risk. To appropriately apply the Spaulding Classification system based on the patient risk level, a thorough appreciation of the complexity of device cleaning must be considered first (Kremer et al., 2019; Kremer et al., 2022). If a device is not cleaned effectively, not only can the disinfection or sterilization process step be compromised (Alfa, 2019), but residual organic matter from clinical soil may remain in concentrations that may elicit toxicological risks to patients (McDonnell and Burke, 2011; Kremer et al., 2019). Cleaning instructions should be developed and used to ensure the removal of potential residual organic matter or soil (e.g., physical removal of blood, microorganisms, protein, detergents). Moreover, this offers the potential to align with established chemical and physical analysis, along with microbiological, to determine adequate cleaning efficacy. For example, determining microbiological and cellular load reductions including real time use of rapid in vitro approaches beyond current tools that have limited efficacy, such as use of adenosine triphosphate (ATP) biomarkers (Rutala, 2019a, 2019b, 2019c). These ideas require further investigations to ensure adequate correlation.

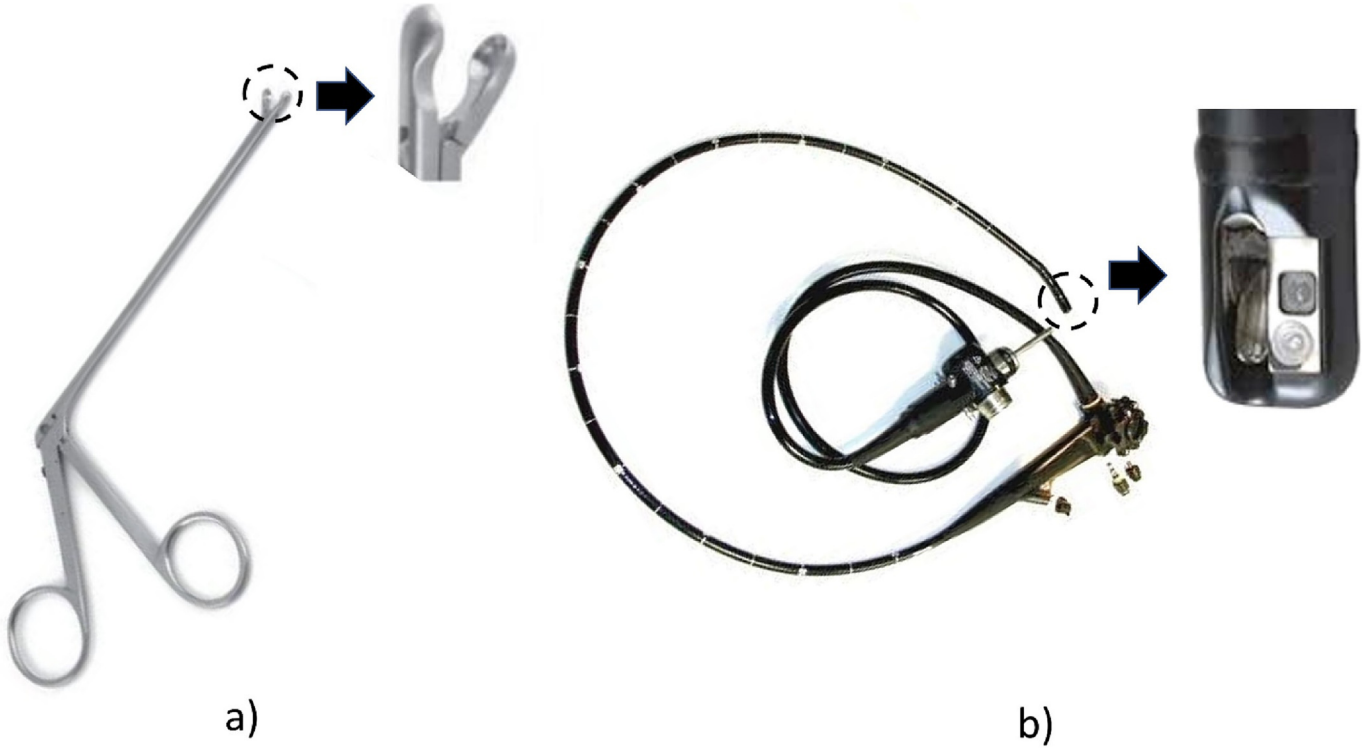

Fig. 2. Example of the variability in complex design features associated with medical devices: (a) biopsy forceps, and (b) duodenoscope.

Science in this area should adopt a holistic risk-based approach to understand the totality cleaning effectiveness from end-to-end during device lifetime (Fig. 3) where efficiently addressing the constant backlog for medical device processing based on OEM's IFU as a major challenge (Fig. 4).

Cleaning is typically a multi-step process. Treatment at point-of-use is a critical first step to prevent a more challenging cleaning process, device damage or microorganism growth during the wait time prior to cleaning (Association for the Advancement of Medical Instrumentation, 2020a,

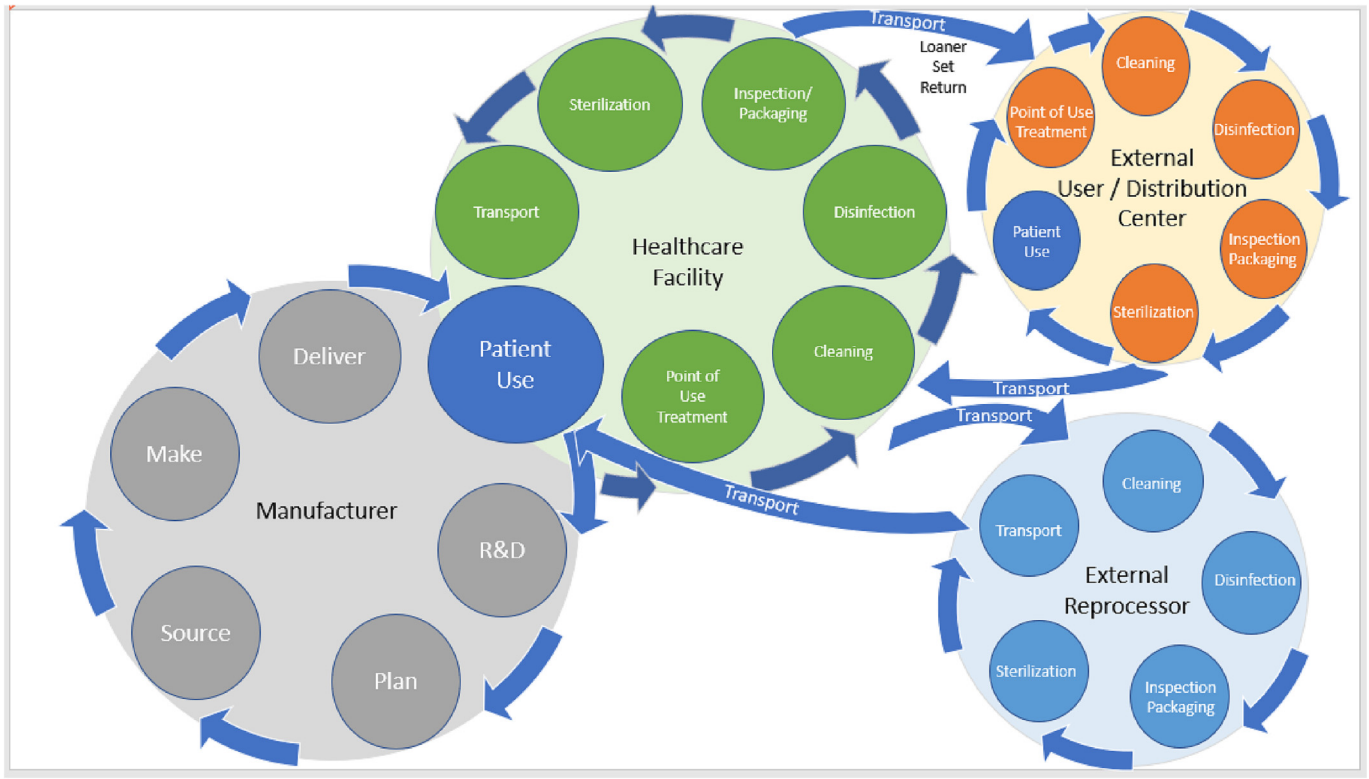

Fig. 3. End-to-end medical device processing cycle.

Fig. 4. Queue for medical device decontamination and inspection in a healthcare Sterile Services Department.

2020b). Most clinical soils, comprising of a multitude of proteins, have shown to be water soluble in a wet and semi-dry condition (Kremer, 2021a, 2021b; Kremer et al., 2022). However, if the soil is allowed to dry, protein is likely to absorb into device material and decrease the soil solubility (Lipscomb, 2007) and reduce the efficacy of cleaning chemistries (Secker, 2015). Transportation and time delays prior to device processing increase the risk of soil drying on the device and increases the challenge.

The validation of associated instructions for use (IFU) is designed to demonstrate that the method of cleaning can consistently remove analytes to a pre-determined level. However, the validation strategy employed, up to recently, was at the discretion of the medical device manufacturer (Kremer et al., 2022). Important industry standards, and commensurate guidance, were developed primarily using the validation experiences of manufacturers, academics, and regulators; however, these new regulatory expectations for device cleanliness may still remain different depending on the geographical location, local requirements, user or regulator experience, availability of cleaning chemistries and equipment, etc. An example of this difference is demonstrated with the acceptance criteria for the cleaning analyte, protein, residuals. In the United States the cleaning specification has been established as 6.4 μg/cm^2 whereas in parts of Europe the value of 50-100 μg/device is the required limit (Kremer et al., 2019). But recent standards and guidance are aligning these requirements (ISO 15883-5).

Cleaning validations have historically been performed under various different guidance and standards that can vary regionally (AAMI TIR30, 2011; ISO 15885-1, 2009b). The guidance provided in these documents was based upon best practices and publications at the time they were published, but often were based on limited independent studies that were performed within the technical competency. Recent updates to these standards (ISO 15883 series, AAMI TIR30, AAMI ST98), have encouraged further investigations to continue to strengthen the scientific foundation for cleaning efficacy. In parallel, there is a need to consider existing and new approaches to help meet the increasing complexity of devices to ensure essential cleaning validation methods generate robust data to substantiate effectiveness. The criticality of the test variables investigated has a relationship to patient safety; thus, if the validation does not appropriately challenge the device, then assurance of patient safety may be compromised. Consider, for example, two very different devices in complexity and the expectation that both have the same consideration for patient risk (Fig. 2). Biopsy forceps have some complex features, such as hinges and mated surfaces, but have one material (e.g., stainless steel) and can be effectively cleaned and terminally sterilized to a very high degree of confidence. The duodenoscope at the other end of the cleaning spectrum has extremely complex features, such as long lumens, electrical parts, restrictive access areas (e.g., encased distal tip) and O-rings that can provide an increase in cleaning challenge (Fig. 2). This highlights the need for a more updated and appropriate classification system that establishes with a relationship between device feature and patient risk from a prior cleaning perspective.

3.1. Biofilms

Biofilm is a common source of infections caused by the ability of microorganisms to adhere to and persist on medical devices (Di Domenico et al., 2022). Microbial cells embedded in the biofilm matrix can be highly tolerant to antimicrobials and, once embedded in a patient may escape or even aggravate the host immune system. The refractory nature of biofilm-related infections (BRIs) still represents a great challenge for clinicians and is a serious health threat worldwide. Despite its importance, the microbiological diagnosis of a BRI is still difficult and not routinely assessed in clinical microbiology. It is estimated that bacterial biofilms may account for 65 and 80 % of microbial and chronic infections with implanted medical devices, respectively (Jamal et al., 2017). A 2012 study suggested that biofilms can serve as a source of infections by periodically releasing planktonic bacterial cells into an environment, even remote to the location of the biofilm (Vickery et al., 2012). The use of disinfectants has already been highlighted as being important to prevent the transmission of infectious pathogens from contaminated surfaces (such as medical equipment) to patients (Rutala, 2019a, 2019b, 2019c). Fig. 5 highlights the role of disinfection in breaking the chain of infection. Thus, despite emphasis on surface disinfection, pathogenic microorganisms have been transmitted to patients through contaminated devices (Quinn et al., n.d.). Within healthcare facilities,

Fig. 5. Role of medical device cleaning, disinfection and sterilization in breaking the chain of infections.

Staphylococcus aureus and *Pseudomonas aeruginosa* are among the most problematic pathogens with *S. aureus* being the second most common pathogen that caused healthcare-associated infections (Dantes et al., 2013). Smith and Hunter (2008) reported that when clinical isolates of MRSA and *P. aeruginosa* were grown as biofilms on discs of materials found in the hospital environment (stainless steel, glass, polyethylene and Teflon) and treated with three commonly used hospital biocides containing benzalkonium chloride (1 % *w/v*), chlorhexidine gluconate (4 % w/v) and triclosan (1 % w/v), these biocides were ineffective for killing these pathogens at label concentration recommended. The diversity of bacteria developing and growing/surviving in biofilms is widely appreciated in the literature (Vickery et al., 2013; Veerachamy et al., 2014; Assefa and Amare, 2022; Dancer, 2022; Alonso et al., 2023). This has even impacted the international definition of biofilms, as a community of microorganisms, rather than the traditional definitions related to Gram negatives and water-systems.

These pathogens have been shown to grow on hard non-porous surfaces and develop an extracellular polymeric matrix that protects the cells from adverse conditions (Su et al., 2022). It has also been shown that the biofilm matrix enhances tolerance to disinfectants by encasing the underlying cells (Abdallah et al., 2015) and by limiting diffusion of disinfectants into the biofilm matrix. The bactericidal efficacy of disinfectants on biofilms is much lower compared to the efficacy of the same disinfectants against planktonic cells (Davison et al., 2010; Fagerlund et al., 2017). The tolerance of biofilms to disinfectants is dependent on the disinfectant active, formulation, temperature, and the type of surface (Abdallah et al., 2015). Moist surfaces have been shown to be more favourable for biofilm growth even though biofilms have also been reported to grow on dry surfaces (Bridier et al., 2011). The behaviour of traditional biofilms, forms under continuously hydrated conditions, differs from a 'dry surface biofilm', defined as the heterogenous accumulation of organisms and other material in a dry matrix, as it less difficult to process (Alfa, 2019). Modeling of dry surface

biofilms demonstrate that some disinfectants are not as effective if a dry surface biofilm is present and can be environmental reservoirs promoting microbial growth and transmission (Alfa, 2019). Disinfectants are primary intervention options against pathogenic microorganisms on surfaces in healthcare facilities and are used as broad-spectrum antimicrobials. Common antimicrobials used for disinfecting surfaces in healthcare facilities include quaternary ammonium compounds, phenolics, and oxidizing agents (e.g., hydrogen peroxide, and chlorine-based products) (McDonnell, 2017; Fagerlund et al., 2017). Claim structure on such disinfectants is well established, but do not generally consider the presence of biofilms (McDonnell and Hansen, 2020). Overall, there are much fewer published studies that investigate the efficacy of disinfectants on bacterial biofilms at label use concentrations and under practical use conditions.

The susceptibility of medical devices by design to recalcitrant biofilm development presents a significant risk to patients from harboured microbial cells that are protected from external stressesand particularly if contaminated surfaces are not appropriately cleaned. The occurrence of biofilms on medical devices can act as protective carrier of planktonic microorganisms leading to infection, which was originally considered by Spaulding in 1957. But our knowledge of the recalcitrance of biofilms is different today. It is well established that failure to eliminate biofilms harbouring microbial cells on contaminated surfaces (such on medical devices) due to appropriate cleaning and disinfection can cause healthcare-associated infections, which can contribute to significant morbidities and mortality (McDonnell and Hansen, 2020). Microbial pathogens in biofilms exist in reduced metabolic or physiological states including dormancy (at their extremes as spores or oocysts), further reducing their sensitivity to chemical disinfection. There is also some evidence of microbial resistance to front line chemical disinfection beyond expected adaptive tolerance that is mediated by expression of specific molecular determinations including by mutation and sharing of genes that promote resistance mechanisms to disinfectants (Table 1). Tolerance to chemical disinfectants by innate and acquired mechanisms has been reported in several problematical microorganisms including *Mycobacterium* species, *Pseudomonas aeruginosa*, *Pseudomonas fluorescens*, *Serratia marcescens*, *Staphylococcus aureus*, *Salmonella* sp., *Escherichia coli*, and *Listeria monocytogenes* (McDonnell, 2017).

Over the past two decades, there has been increased evidence of microbial adaptation to lethal environmental stresses along with subsequent cross-protection against to dis-similar stresses, such as biocides or resistance against antibiotics (McDonnell, 2017). It may be important that the survival of low number of stress-hardened microbial pathogens on devices can present a significant risk to patients. This microbial adaption to applied stress is also evident in adjacent food industry (Rowan, 1999; Yang et al., 2021). Findings suggest that house-keeping functions, such as microbial resistance to environmental stresses and virulence (pathogenesis) are regulated by the same molecular determinants in some pathogens of concern; as an example, *PrfA* expression in L. *monocytogenes* is up-regulated under conditions of environmental stress associated with acid-stress or disinfection conditions (Ladicevic et al., 2022). Microbial pathogens can also change morphologically under conditions of sub-lethal stress that maybe seen as an adaptive response mechanism to the applied stress (Rowan et al., 2000a, 2000b; Rowan et al., 2021). Such mechanisms may be important in the tolerance of mycobacteria to disinfectants, antibiotics, and the immune system (Svetlíkova et al., 2009; Shang et al., 2011). It is also probable that the infection risk to patients is complicated by the occurrence of different types of microbial pathogens that can potentially lead to co-infections in patients, which challenges subsequent disease mitigation and outcomes. Many of these BRIs are likely to be under-reported due to delayed onset in infection development and complexity in effective diagnostics, such as with fungi and mycobacteria (Garvey et al., 2022). This concern is also reflected by the WHO declaring that we are at a crisis point for addressing antifungal drug resistance and as a priority, effective solutions for mitigating against antimicrobial resistant bacteria and fungi are urgently needed (WHO, 2022). Only recently the WHO published the

Table 1
Examples of evidence-based resistance to front line disinfectants and antiseptics used in healthcare applications.

Disinfectant	Microbial resistance to applied disinfection	References
Triclosan	➢ Triclosan resistome – variations in sequencing and structure of FabMG responsible for inefficient binding of triclosan to targets resulting in higher MICs	Kim et al. (2020) Khan et al. (2018).
	➢ A primary target for triclosan is the inhibition of FabI, an enoyl-acyl carrier protein reductase (ENR) involved in bacterial type II fatty acid synthesis essential for survival.	Huang et al. (2016) Ciusa et al. (2012).
	➢ Biochemical and structural basis of triclosan resistance characterized using metagenomics and phylogenetic analysis (*Pseudomonas aeruginosa* that has formed resistance to most conventional antibiotics and forms biofilms)	Gomez et al. (2016)
	➢ Horizontal gene transfer of triclosan resistance in *S. aureus*	
Quaternary Ammonium Compounds (QACs)	➢ Detection of efflux mechanisms such as QacA/B expression *in Enterococcus faecalis*	Bischoff et al. (2012)
	➢ Polyaromatic structural core analogues to activators of QacR, a negative transcriptional regulator of efflux pump QuaA, characterized – thus informing structure-resistance relationships	Forman et al. (2016)
	➢ Detection of QAC resistance gene (*qacEΔ1*), the 1 integron gene (*intI1*), and 12 antibiotic resistance genes informing impact and mechanism of QACs on transmission of antibiotic resistance genes	Han et al. (2019a, 2019b).
	➢ Novel insight into *qac* and *norA* genotypes in *S. aureus* that relies on plasmid encoded efflux systems for biocide tolerance	Tezel and Pavlostathis (2015)
	➢ Sub-inhibitory biocide disinfectant concentrations can lead to co-resistance and cross-resistance to antimicrobial agents. Multi-biocide resistance also involves chromosomal gene encoding NorA efflux pump	Marchi et al. (2015) Pang et al. (2019)
	➢ Use of confocal microscopy to visualize biofilm formation by L. *monocytogenes* and resistance to QACs	Morrison et al. (2019) Minbiole et al. (2016). Pang et al. (2019)
Glutaraldehyde (GTA)	➢ *Mycobacterium massiliense* (recovered post surgical infection) showed high level resistance to 8 % GTA, and likely due to surface modifications reducing biocide penetration/reactivity	De Oliveira Lorena et al. (2010)
	➢ Efflux pumps as potential tolerance mechanisms in *Pseudomonas fluorescens* and *P. aeruginosa* biofilms	Vikram et al. (2015).
	➢ Resistance by unknown mechanisms to GTA found in *P. aeruginosa*, likely due to surface modifications	Kampf et al. (2013)
	➢ Reported *Mycobacterium chelonae* strains from endoscope washer disinfectors with increased resistance to GTA.	Griffiths et al. (1997a, 1997b)
Chlorhexidine (CHX)	➢ *Serratia marcescens* promiscuous INcHI2 mult-resistant plasmid to CHX and other biocides	Allen et al. (2022)
	➢ Genomic Island encoding a homolog of *Pseudomonas MexCD-OprJ* biocide efflux detected in CHX tolerant Serratia	Cieplik et al. (2019)
	➢ *Serratia* isolates possessed a Ser-83 –ile mutation in GyrA conferring fluoroqunolone resistance and increased CHX MICs	
	➢ Mechanisms conferring resistance towards CHX include multidrug efflux pumps and cell membrane changes. For instance, in staphylococci it has been shown that plasmid-borne *qac* genes encode efflux pumps	McDonnell (2017)
Hydrogen peroxide	➢ Adaptive microbial stress tolerance to H2O2, including chemical and enzymatic neutralization	Jacquel et al. (2021)
	➢ Stress induced tolerance to H2O2 in mycobacterial and *Deinococuccus radiodurans*	Li et al. (2014)
	➢ Farnesol induces H2O2 resistance in *Candida albicans* by inhibiting the Ras-cyclic AMP signaling pathway – strains lacking Ras1 or Cyr1 no longer exhibited increased protection against H2O2	Deveau et al. (2010). Wang and Schelborn (1995)

fungal priority pathogens list (WHO FPPL), which is the first global effort to systematically prioritize fungal pathogens, considering their unmet research and development needs and perceived public health importance. The WHO FPPL aims to focus and drive further research and policy interventions to strengthen the global response to fungal infections and antifungal resistance including unlocking appropriate solutions. The list is divided into three categories: critical (*Cryptococcus neoformans*, *Candida auris*, *Aspergillus fumigatus* and *Candida albicans*), high (such as *Candida glabrata*, *Mucorales*, *Fusarium* spp., *Candida tropicalis* and *Candida parapsilosis*) and medium (such as *Coccidioides* spp., *Pichia kudriavzeveii* (*Candida krusei*), and *Cryptococcus gattii*) priority based on a process focused on fungal pathogens that can cause invasive acute and subacute systemic fungal infections for which drug resistance or other treatment and management challenges exist. This list is interesting from a disinfection modality perspective as fungal spores (such as *Aspergillus* sp.) exhibit natural tolerance mechanisms to applied stresses such as UV-irradiation compared with similarly treated non-spore forming fungi (such as *Candida* sp.) (Anderson et al., 2000). This is enhanced resistance is attributed to the expression of a dark pigment in *Aspergillus* spores protecting vital genomic material that has peak absorption at 256 nm, which is natural evolutionary trait to cope with sunlight.

Mitigation strategies for BRIs will depend on the deployment of appropriate regime of verified and validated cleaning procedures before applying high-level disinfection and/or sterilization. Disinfection and sterilization processes can fail if medical device cleaning has not been conducted appropriately, including if they promote fixing of biofilms to surfaces (McDonnell, 2022). Use of life cycle assessment (LCA) tools and 360° degree thinking can help with solutions to this challenge. Innovation can also include sustainable bio-degradable materials or polymers that confer biofilm preventative properties particularly at the early stages of microbial attachment and may even be compatible with cleaning or disinfection (Masterson, 2021). The area of smart materials in medical device design is topical that includes incorporation of functional bioactives and emerging role of 4 D printing (Rtimi et al., 2019; Wang et al., 2022).

3.2. Risk of environmental transmission of cross-contaminated medical devices from a patient perspective

Published findings on the risk to patients from contaminated devices, and cross-transmission leading to outbreak situations, is potentially high (Vonberg et al., 2008; McDonnell and Burke, 2011; Percival et al., 2015). Environmental contamination, including surfaces, has been particularly highlighted over the past decade with increasing investigations with *Clostridium difficile* and extended to include other problematical microbial pathogens (Vonberg et al., 2008; Weber, 2013; Weber et al., 2013; Durovic et al., 2018). For example, Durovic et al. (2018) reported that hospital transmission accounted for 40 % of transmission pathways within the healthcare from review of 24 original articles. Durovic et al. (2018) stated "In healthcare settings, future efforts may need to focus on extending cleaning and disinfection procedures beyond the immediate surroundings of symptomatic carriers". Microbial resilience, survival and the potential for transmission to patients is now well cited in the literature (Seoane-Vazquez et al., 2007; McDonnell et al., 2020). The risks in surgery are often latent, due to the fact that antibiotic prophylaxis is a cornerstone of surgical site infection prevention; but, may often be a crutch to support poor practices in aseptic techniques in surgery (Cohen et al., 2017). This was clearly shown in the last few years with the emergence of outbreaks with carbapenem-resistant Gram negative bacteria, specifically associated with endoscope use (O'Horo et al., 2016; Adrian, 2019). Despite the previous known risk, the levels of overall reported infection outbreaks were considered relatively low; therefore, lapses in best practices evidently occur (McDonnell et al., 2020). However, this trend is now reversed, where changes in these practices are now more supported, particularly in the USA (McDonnell et al., 2020). This risk to patient is not just from an infection point of view, but also potentially toxicity and risk of complications (Seoane-Vazquez et al., 2007). It may also be argued that the overall risk to patients should not be a rationale or excuse to apply best practices in device processing.

4. Addressing microbial challenges – Quo Vadis?

Since the introduction of the Spaulding system, our understanding of microbial challenges to ensuring effective device processing has increased including various types of viruses, mycobacteria, protozoa and fungi (McDonnell and Burke, 2011). The innate resistance mechanisms of microorganisms to disinfection and sterilization methods remains an area of active research, sometimes challenging previous perspectives. In addition, as discussed above, there is evidence of the role of environmental and therapeutic stresses in conferring adaptive microbial tolerance and resistance to established and emerging pathogens (such as CRE and MDROs), that can lead to significant risks, as discussed above (Rutala, 2019a, 2019b, 2019c). There is a gap in information of the types and numbers of surviving pathogens that present a high -infection risk to patients in terms of mortality and morbidity. Healthcare innovation opportunities create a robust evolutionary environment for selecting microbial adaption to front line antimicrobial therapies, including disinfection. An example was reported by West et al. (2018) on inter-strain variability of inhibitory disinfectant concentrations and contact time for clinically relevant MDR strains of *P. aeruginosa* and 4 MRSA strains, with three disinfectant types, when tested at label and reduced contact time. The study underscored the need for a disinfectant validation method that addresses these variances. Chemaly et al. (2014) also reported on the role of the environment in harbouring and transmitting MDR bacteria leading to increased healthcare associated infections (HAIs), higher morbidity and mortality.

New molecular biological-based information, supported by next-generation sequencing highlighted the role of mobile genetic elements in the transfer of disinfectant tolerant genetic mechanisms between similar species and to different bacterial species. This advances our knowledge of the topic beyond earlier insightful reviews (McDonnell and Burke, 2011) where adaption to applied lethal stresses (such as disinfectants) was more so seen as microbial "tolerance" to these deleterious conditions. Such tolerant mechanisms may allow for these microorganisms to survive and persist under normally deleterious conditions. Investigations of outbreaks caused by contaminated duodenoscopes involving CRE and MDROs described persistence was due to lack of contact with microorganisms due to cleaning/device maintenance issues and not a lack of disinfectant effectiveness due to resistance (Rutala, 2019a, 2019b, 2019c). There is also a need to improve detection of genetic variants due to their antibiotic resistance mechanisms that would otherwise have remained undetected. The presence of residual microbial pathogens harboured in biofilm due to inadequate cleaning is of concern as there is reduced efficacy of disinfectants as the latter cannot be delivered at an appropriate concentration. There is justification for changing between the traditional use of aldehydes to oxidative-based disinfectants (such as use of hydrogen peroxide or peracetic acid) due to differences in mechanisms of action and reports of resistance development to aldehydes. A step change to switch to different classes of disinfectants may also promote loss of resistance genes carried on mobile molecular elements. This is similar to the strategic approach for rotational antibiotic use in healthcare or disinfectant rotation in environmental surface applications, as it is recognised that microorganisms will often only express genes only when required, such as in a hostile growth environment (Ciusa et al., 2012; Feng et al., 2021).

New information is required on the molecular and cellular mechanisms potentially involved in adaptive resistance and upregulation of virulence (such as seen in *Listeria monocytogenes*) due to disinfectant exposure where low numbers of microbial stressed survivors present a high infection risk to vulnerable patients. This is particularly relevant as environmental stresses associated with disinfectant use (such as reactive oxygen species [ROS]) are similarly deployed defence tactics used by our front line macrophages to prevent infection (Rowan, 1999; Rowan et al., 2001, 2009; Bradley et al., 2012). Thus, stress-mediated survival post exposure to disinfectants, as used in device processing, may theoretically provide a degree of

cross-protection against our circulating immune cells, which needs to be considered. This highlights the pivotal role of effective automated cleaning and drying, and design-thinking surrounding the creating of the next-generation devices that are less complex with generous built-in margins of safety for to ensure appropriate processing based on IFUs. This should also address simplification and reduction in the workload for healthcare workers in processing departments from a holistic device supply chain perspective, including bespoke training and developing appropriate infection control programs (such as in endoscopy units) (Day et al., 2021). This will also help to ensure the prudent, consistent, and correct use of cleaning, disinfection, and sterilization practices in healthcare facilities, as the literature has many examples of lapses of best practices leading to infection outbreaks. Ongoing and future research should also consider the inclusion of smart polymers and materials that can have antimicrobial or biofilm preventative (or disruptive) properties (Masterson, 2021), as this will reduce risk and may even facilitate compatible disinfection and sterilization processes.

5. Real time monitoring and future automation of processing

There is also a commensurate need to consider real-time monitoring approaches to develop and validate effective processing of devices that encompasses a predictive microbial contamination (or decontamination) function (Kremer et al., 2022). Current methods of assessing cleanliness of devices are typically visual and somewhat primitive, such as the use of various swab tests for analytes such as protein and adenosine triphosphate [ATP], which are unlikely to predict true microbial or soil decontamination (Olfasdottir et al., 2017). Visrodia et al. (2017) reported that ATP correlates poorly with microbiological culture findings, and particularly noted that endoscopes reported as clean by ATP use still had detectable microbial bioburden present (such as up to 1 million bacteria). Other, more sensitive, cleaning validation tools including the extraction and detection of protein, total organic carbon, carbohydrate, haemoglobin, bilirubin, and detecting specific bacterial enzymes.

Advanced studies on cell survival following antimicrobial processes also are of interest. As an example, Farrell et al. (2013) highlighted the potential of addressing a single composite study to address the relationship between use of pulsed UV light irradiation and the simultaneous occurrence of molecular and cellular damage in clinical strains of *Candida albicans*. This is particularly relevant as showed that the occurrence of late apoptotic and necrotic cell phonotypes as detected in real-time using specific markers, coincided with irreversible cell death that can potentially supplement or replace lengthy terminal culture-based methods where there was good agreement between enumeration methods. This constituted the first study to investigate mechanisms of cell destruction caused by pulsed UV using sequential and simultaneous microbial protein leakage assay, lipid hydroperoxidation in cell membrane, specific patterns of reactive oxygen species (ROS) generation, and nuclear damage to treated microbial cells using Comet assay along with detection of specific apoptotic and necrotic stages. Opportunities also exist for this topic in the combined area of photonics and image analysis to assess bioburden on surfaces after device treatment, where such data could also be automated including the provision for artificial intelligence and machine learning for intuitive processing. This reflects increasing smart specialization, such as in additive manufacturing, that embraces the future role of digital transformation including use of robotics that is aligned with the new Industry 5.0 human centric concept (Rowan et al., 2022; Rowan, 2022). For example, Allescher et al. (2022) has recently reported on the potential use of robotics managing the processing of endoscopes. Commensurate development of rapid microbiological methods will also inform real-time determinations of process efficacy for microbial inactivation. However, innovation in this field may be seen as strategically sustaining (or incremental), as opposed to disruptive, to ensure seamless integration of technologies with existing assets from a risk management and corporate operation perspective.

Considerations also need to be given to toxicology given chemical use (e.g., for cleaning and disinfection) and introduction of new biomaterials to support next-generation devices (Kremer et al., 2019). For example, chemical sterilization requires consideration of low non- toxic residues on treated surfaces, in parallel with the benefits of being an antimicrobial process and compatible with a broad range of materials used in medical devices. Some gaseous sterilants, such as VH2O2, have different material compatibility profiles compared with ethylene oxide (EO) (such as packaging materials containing cellulose cannot be practically treated by VH2O2) (McEvoy and Rowan, 2019). Opportunities for new material and biocompatibility research and innovation to advance the medical device industry include material compatibility using alternative sterilization modalities to using EO (such as VH2O2, Nitrogen peroxide, Chlorine dioxide), risk assessment leveraging material compatibility studies between two or more modalities; material compatibility studies of new and novel materials or components (e.g., electronics) in any sterilization modality or modalities; and regulatory case studies related to changing or optimising modalities, or alternative validation approaches. An example of co-application of toxicity testing was reported by Hayes et al. (2013) who developed a range of in vitro toxicity bioassays to assess the efficacy of pulsed plasma gas discharge (oxidative) treatments, where the application of high voltage pulses (16 kV, 10 pps) to gas-injected water (N_2 or O_2, flow rate 2.5 L/min) resulted in the formation of a plasma that generated free radicals, ultraviolet light, acoustic shock waves and electric fields. The antimicrobial effect killed ca. 4 $\log_{10}$ parasitic oocysts in 32 min exposure. Their studies showed the merit of broad toxicity testing including cytotoxic properties (as determined by MTT and neutral red assays), genotoxic properties (as determined by comet and Ames assays), and ecotoxic properties (as determined by Microtox™, Thamnotox™ and Daphnotox™ assays) that supplemented real-time microbial inactivation studies as determined by use of in vitro CaCo-2 tissue culture with qPCR.

6. Use of Quintuple Helix Hubs to advance reprocessing and sterilization of medical device sector

A review of PubMed and Scopus databases over period 2010 to 2023 revealed 78 publications that included the key words “Quadruple Helix”. On review of this list, 70 were not included for the reason that they were not focusing on innovation hubs, for example they included G-quadruplex, telomeric quadruple helix; C-terminal helx, molecular heterogeneity, and metal strings. Exploitation of Quadruple Helix Hub framework has been shown to promote greater engagement with stakeholders and access to specialist equipment for supporting and enabling research and innovation including with a sustainable focus (Malva et al., 2018 Rowan and Casey, 2021; Kulikauskiene, 2021; Zipfel et al. (2022); Cai and Lattu, 2022). Networking of multi-actors to solve challenges presented in the medical device sector can be supported and enabled through a Quintuple-Helix Hub that combines academia, industry, healthcare, regulators and society (Rowan and Casey, 2021). This unifies intellectual and industrial knowledge to holistically address key topics from design to commercialization, where there is a convergence of subject-matter experts with provision for engaging with regulators and society. This concept also ensures that application of digital technologies for transformation of the medtech sector, as applicable, and meets the real-world needs of the industry. This Quintuple Helix can support industry in developing new solutions ranging from compatibility research to new sterilization modalities. This interface between user and regulator can also advance other pressing areas including changes or areas of discussion with international regulatory industries, regulatory innovation approaches with processing (including sterilization) validations or post-market approvals; information and/or promotion of regulatory bodies actively pursuing collaboration to address sterilization capacity issues; use of novel approaches to knowledge management and risk assessment in regulatory submissions; impact of sustainability in the choice and clearance of sterilization modalities; and awareness of benefits of new sustainable sterilization modalities from a societal perspective.

For example, sterilization companies in partnership with universities are developing and deploying state-of-the-art biotechnology tools to unlock real-time microbial inactivation (McEvoy et al., 2021). Immersive (digital)

technologies are also partnering with medtech companies for complex virtual training on specific technical operations. For example, Mersus Technology (Immersive) has partnered with Boston Scientific in Ireland to test and apply an 'Avatar Academy Program' that uses computer gaming to recreate virtual laboratories and cleanrooms; thus, allowing medtech employees to familiarize themselves remotely with a complex work environment and processes. This approach will potentially automate training where one could theoretically run six bespoke training sessions in one day that previously would have taken a month, which can be extrapolated to address the full production chain delivered in a virtual environment (Westmeath Independent, 2020). This Quadruple Helix Hub concept also enables co-creation and design of a life cycle assessment and 360° holistic thinking perspective, thus, unlocking complexity of challenge by converging inputs that is also at the interface between users (OEMS, Healthcare, Sterilization companies, academics) and the regulators. Development and application of living labs concept through this model also addresses knowledge-based innovation systems that includes delivering real-time solutions aligned with Industry 5.0 human centric, such as human interactions with robotics (Archibald et al., 2021; Rowan and Casey, 2021; Kulikauskiene, 2021; Zipfel et al. (2022); Cai and Lattu, 2022). Such an interactive multi-actor model can also address high risk, high gain, deep technical projects that would be relevant to cleaning, disinfection and sterilization including testing and investigating new modalities and new biomaterials for next-generation devices.

There is a need to manage enormous data arising from evaluating cleaning, disinfection and sterilization validations and routine controls, in addition to introducing potentially new design changes to mitigate patient risk, where there are opportunities to manage complex database using artificial intelligence (AI), deep learning/machine learning (ML) and robotics (Gilbert et al., 2021; Aisu et al., 2022; Muehlematter et al., 2021). These sequential or simultaneous steps can be met by applying appropriate statistical analysis and modeling that embraces prediction, simulation, and automation. Such a creative approach to experimental design addresses different control variables, and a decision hierarchy informed by measurements. However, the emergence of AI/ML in medicine also creates system challenges, such as which products should be reviewed by regulators and how can we ensure the safety and effectiveness of AI/ML-based software as a medical device that may change over time as they are applied to new data (Gerke et al., 2020).

7. Sustainability

Supporting "enablers" to sustainability will inform future direction of medical devices. A review of PubMed and Scopus over period 2000 to 2023 revealed 27,804 "Sustainability" publications combined with "reprocessing" and "medical devices" gave 247 publications. Two hundred and fifteen papers were excluded for the reason that they align with specific topic these were focused on life cycle assessment for reprocessed face masks, plastic uses using COVID-9 pandemic, lithium batteries, microbial fuel cells, surgery trays, recycle permeate, photocatalytic treatment of PPE, nuclear waste management, analysis of urine, reusable biosensing element for freshwater toxicity monitoring; toilet flushing, water disinfection; quantum dot fluorescence-based formaldehyde detection; airborne decontamination; contact lens; plastic bedpans; wound care; sustainable energy harvesting techniques; green biocides; detecting organic pollutants; electrochemical membrane bioreactor; hygiene; denture material, germicidal glowsticks; ClO2-generative glovers; haemodialysis; antimicrobial electrospinning, chloroxylenol disinfection by activated sludge; microbial fuel cells; oral candidiasis; central-line associated blood stream infections; spray drying; bioprosthetic heart valves; sustained drug release; electrical potential on chlorine generation; and aerodynamic analysis of SARS-CoV-2 supercritical CO_2 treatment for FFP3s.

Future sustainability for medical device sector can be supported and enabled by the aforementioned Quintuple Helix Hub concept, which is also likely to embrace new digital innovation hubs (for example, where there are 708 new digital innovation hubs in Europe) (Rowan et al., 2022). For example, broad topics of interest that are likely to influence the future sustainability of single-use versus reusable medical devices are presented in Table 2. This highlights the diversity of key topics ranging from resource consumption and emission to global warming impact, which will be met in part through future design thinking, risk modeling and education that also embraces circularity. The recent review of MacNeill et al. (2020) highlighted that the health sector is responsible for 4.6 % of global greenhouse gas emissions of which approximately a quarter originate from the US healthcare system, and appropriately the same proportion of pollutant air emissions. Internationally, a significant proportion of healthcare GHG emissions come from the supply chain; thus, emphasizing this topic of optimal impact for current and future healthcare decarbonization interventions (Watts et al., 2018). The healthcare sector has become increasingly dependent on single-use disposable medical devices, where waste management creates a significant public health burden in terms of environmental pollutants. MacNeill et al. (2020) also noted that such single-use disposable medical devices aptly reflect an inherently unsustainable linear (or "take-make-waste") economy model in which items are produced, used once, and then sent for waste disposable. For example, this linear supply chain model can negatively impact ecology internationally by depleting natural resources along with commensurate excessive production of clinical waste, GHG and other undesirable environmental emissions. An increasing number of life cycle assessment studies comparing single use versus reusable equipment intimate that the former generally result in significantly more petrochemical use and GHG emissions (McGain et al., 2020; Eckelman et al., 2012; Sanchez et al., 2020). A "just-in-time" approach associated with linear supply chain model can reduce storage requirements and product expiration, which reduces healthcare abilities to appropriately manage reusable medical devices. Thus, future consideration should be given to adopting a circular supply chain economy approach in which medical device products are maintained at the highest-value application for as long as possible without sending to disposal. MacNeill et al., 2020 and others (Sherman et al., 2018) have also recently highlighted that reusable medical devices are typically cost-effective over many uses where lifetime costs are significantly lower than that of single-use disposables.

There is an increasing interest in defining and reviewing potential bespoke business models that would be considered potentially appropriate for supporting future sustainability in medical device industry, particularly for the circular economy (Gusso et al., 2020). Healthcare is a resource-intensive and essential ecosystem that generates considerable quantities of diverse waste that varies in non-hazardous to hazardous risk propositions including environmental impact (Minoglou et al., 2017; World Health Organization, 2016). Moultrie et al. (2015) reported that the Medical Device sector significantly contribute to waste generation, particularly when considering single-use plastic and end-of-life devices. Gusso et al. (2020) highlighted the importance of circular strategies for meeting established and emerging sustainable needs of the medical device sector, which are commensurate with the "ecodesign-thinking" concept proposed in this review for medical devices that mitigates waste; yet, satisfies essential functionality and safety requirements from an application and regulatory perspective. Greenhealth Practice (2018) noted that "medical device reprocessing and sterilization of reusable sharps are the main cost-saving initiatives for hospitals in the US". However, it is only recently that a suite of opportunities were suggested in the literature that considers different business model innovations for meeting circularity of single-use and reusable medical devices (Kane et al., 2017; Fargnoli et al., 2018; Gusso et al., 2020). Given the complexity of medical device industry, it remains challenging for healthcare providers to understand and identify a singular appropriate business opportunity that enables and maintains resource cycles. This is complicated by the lack of appropriate published circular case studies that embraces relevant stakeholders (Lewandowski, 2016).

In the medical device industry, the business model structure is a useful conceptual framework to consider real-world circularity applications that must also address risk and safety regulations (Gusso et al., 2020). These authors propose using the main tenets of a business model to consider such strategic opportunities; namely, the value proposition, value creation and

Table 2
Popular topics informing the indicative relevance and future sustainability of single versus reusable medical devices.

Topic(s)	Description of activities	Indicative relevance	Reference
Resource consumption & emissions	➢ Avoiding use of virgin materials and remanufacturing can influence environmental impacts of resource consumption, emissions. ➢ Use of Life Cycle Assessment to inform a pathway to greener processes for medical device and adjacent sectors	Reducing abiotic resource use Contributes new knowledge to the Global Warming impact (GWI) Smart use of LCA tools to inform efficiencies in device design and treatments	Peters (2016) Zhang et al. (2020) Baboudijan (2022)
Circularity assessment environmental Impact assessment LCA assessments	➢ Sustainable studies describe 16 different environmental impact categories highlighting superior use of reprocessed devices over single use in 13 categories (electrophysiology catheter). Also informed by LCA. ➢ Categories include ozone depletion; climate change; photochemical ozone formation; Eutrophication (marine and freshwater), Ionising radiation – human health, land use, non-cancer human effects, resource use, energy carriers, respiratory inorganics [Disease incidences], waste scarcity, Cancer human effects	Healthcare could cut emissions by half for some devices if opting for regulated, reprocessed items. Suite of environmental and technical categories to evaluate relevance of medical devices materials and reusability across technological readiness level from discovery (TRL 1) to commercial deployment (TRL 9).	Schuelke-Leech (2021)
Global warming impact	➢ Comparison between use of medical remanufacturing route and virgin production disposal route (single use) addressing water, sterilization gas, disinfectents, waste treatment, packaging, transport, plastic production/reprocessing, electricity/fuel	New information and approach to pivot device remanufacturing that can inform global warming	Schuelke-Leech, 2021
Economic modeling	➢ Development of appropriate economic modeling for reuse of medical devices and sustainability	Usefulness of using dedicated models to interpret and simulate to inform economics and risk assessment	MacNeill et al. (2020)
Future terminal sterilization of contaminated medical device waste management	➢ Development technologies for decontamination and reuse of contaminated N95s under EUA with provision for future sustainable waste management ➢ Also describes results for a range of modalities and approaches including simple, affordable options suitable for developing countries for PPE reuse under EUA	Future use of a safe and effective technology to reprocess PPE under EUA so as to safety ensure effective waste management	Alt et al. (2022).
Safety Biocompatability	➢ Consider potentially new disinfection and sterilization modalities and future biomaterial composition from a toxicological end-point perspective	Need to consider development of additional biocompatibility tests under ISO standards to inform sustainability.	Hayes et al. (2013)
Recycling challenges	➢ Recycling of complex medical device products needs extensive material flow analysis to make it economically and ecologically reasonable	The more complex a device, the more process steps, energy, and resources are needed for recycling Complex devices may have specific requirements for collection and disposal after use from an infection-prevention perspective and may contain complex materials not suited to municipal waste management & recycling infrastructure (including Green technology)	Gopinath et al., 2020 D'Adamo and Rosa (2016) Eze et al. (2020) Lee et al. (2017)
Profitability, employment opportunities	1. Remanufacturing in medtech sector has high profitability that embraces remanufactured items over virgin products	Potential for increased profitability through remanufacturing over reliance on using virgin products.	D'Adamo and Rosa (2016)
CE concept using R-strategies	➢ Design smarter [Refuse, Rethink, Reduce] ➢ Extend lifetime [Reuse, Repair, Refurbish, Remanufacture, Repurpose] ➢ Circularly end-point activities: Recycle and Recover	R strategies broadly considered relevant for extended and circular use in devices that can be informed by smarter designs.	Potting et al., (2017)
Reuse of PVC	➢ Recycle of Polyvinyl Chloride (PVC) several times (widely used plastic in devices) without loss of critical properties	Opportunities to reuse materials from a resource efficiency perspective	I'Ons (2021)
Design thinking	➢ Design medical devices smarter for circularity that includes appropriateness for reprocessing and sterilization ➢ Design from day one with disassembly and cleaning in mind, including reducing number of device components	Design thinking in medical devices is critical to unlocking efficiencies in usage and automation; thus enabling future sustainability	I'Ons (2021)
Rapid diagnostics Automation	➢ Efficacy for real-time determination of device cleanliness, reprocessing and terminal sterilization potentially reducing disinfectant and sterilant use.	Opportunities to use rapid diagnostics to improve turn-around of reprocessing and potentially amount of sterliant use	McEvoy et al., 2021
Improve energy efficiency	➢ Additive manufacturing can reduce material waste by as much as 90 % compared to conventional manufacturing and can speed up device prototyping and testing	Improving energy efficiency and opting for clean energy source could reduce overall costs	I'Ons (2021)
Logistical and design challenge	➢ Consider device materials in sustainable design	For example, disposable surgical drapes contain polypropylene and polyethylene, each can be recycled, but used together they cannot be recycled	La Plante (2022)
Reduce carbon footprint	➢ Recycled materials can be used without loss of technical properties or need for addition of virgin materials	For example, recycled polyethylene terephthalate (PET) has 79 % lower GHG emissions that virgin PET	La Plante (2022)
Multi-actor collaborations	➢ Work with Medical Device component and OEM manufacturers to advance circular medical device production, and to move away from traditional "take-make-waste" linear systems.	Smart approaches for stakeholders to holistically address issues to inform more efficient means of material use/reuse	La Plante (2022) Rowan and Laffey (2020)
Role of Supply Chain and Transport	➢ Steps are to reduce energy, water and chemical use	For example, reduce transport of waste from used medical devices by recycling in same region to reduce carbon footprint	La Plante (2022)
Microbial inactivation Modeling	➢ Mathematical modeling of inactivation to inform modality efficiencies ➢ Sustainable solutions (e.g, biofilms) for reprocessing	For example, longitudinal modeling to confirm key factors influencing or governing sustainability for device industry and nexus to policy and standards.	Feurhuber et al. (2022) Alfa (2009) Rowan and Moral (2021) Rowan et al. (2015)
Risk Modeling Machine learning Robotics	➢ Use of machine learning to address risks given complexity of database sets spanning processes	Risk characterization for end to end device production	Njage et al. (2019) Zhang et al. (2017) Allescher et al. (2022).

(continued on next page)

Table 2 (*continued*)

Topic(s)	Description of activities	Indicative relevance	Reference
Research translation, Training, Education, Advocacy	➢ Environmental sustainability research in anaesthesia and critical care for circularity ➢ Moving beyond clinical care, energy (renewables vs fossil fuel) and energy efficiency are important influencers in healthcare's ecological footprint.	The critical role of education and training in device manufacture and reuse from an ecological (healthcare) footprint that spans end-to-end cycle.	McGain et al. (2020).

delivery, and value capture. Gusso et al. (2020) also intimated that these business models must also align with 'criticality' according to risk level to the patient with type of contact, which supports and corroborates this review. This criticality analysis dimension considers Spaulding's classification system for devices along with a linked economic orientated endeavour (Kane et al., 2017). This circular framework for medical devices will also facilitate 'green servitization' that considers how device OEMs can also create a supply chain circularity through reprocessing (Benedettini, 2022). Such innovative business models are timely given stakeholder publications focused on defining healthcare guidelines for disinfection and sterilization of instruments in centralized SSD that recognises a pressing need to address single-use medical devices from an environmental footprint and waste management perspective (Ling et al., 2018). Such opportunities also highlight the importance of understanding the pivotal role of OEMs in effective device cleaning and processing. In addition, the challenges of servicing, maintaining and applying reprocessing and sterilization modalities for a plethora of different devices in healthcare facilities are considerable. Moreover, there is a commensurate need to consider training of healthcare staff given increasing complexity of medical equipment and increasing level of sophistication associated with OEM's instructions for use (Ling et al., 2018). Gusso et al. (2020) proposed nine potential circular business models (CBMs) for meeting established and emerging needs of medical devices that considers technical cycles (repair and maintenance, reuse and redistribution, refurbishment and remanufacturing, and recycling), value (high, medium, low), and criticality (critical, semi-critical and non-critical). These CBMs comprise (a) full-care equipment as a service, such as Medigo-Rent, (b) In-house lifecycle, such as STERIS Service contracts, (c) Support for hospital-based reprocessing, such as Medivators-Renatron, (d) mobile solutions, such as Shared Medical Solutions, (e) platform for devices circulation, such as Pioneer Medical Devices, (f) Refurbished system, such as Philips–Smart Path, (g) Full-provision of reprocessed devices, such as Sterimed, a J&J company, (h) End-of-Life Equipment collection, such as Advanced Technology Recycling, and (i) Continued collection of disposable, such as BD ecoFinity Life Cycle Solution (Gusso et al., 2020). Wilson and Nayak (2016) considered pros and cons of reusable medical devices versus single-use items and noted that the former may offer improved clinical performance and are likely to be less expensive; however, reusable devices present a risk of cross-infection, their performance may deteriorate with repeated use, there is environmental costs of decontamination, and healthcare workers are potentially exposed to chemicals and biohazards during decontamination.

However, there is commensurate need to consider the main underpinning tenets of what constitutes increasing sustaining or disruptive business practices in medical device sector in order to comprehensively appreciate and adopt appropriate CBMs for future circularity (Schuelke-Leech, 2018; Rowan, 2019; Schuelke-Leech, 2021). In addition, it is likely that these established and emerging CBMs will be actualized by addressing risk mitigation, corporate governance and digital transformation including Industry 5.0 (Rowan and Galanakis, 2020). Domegan (2021) also noted that in such complex settings, the call to action is large-scale behaviour change. This can be met in part by social marketing that "examines the interface of human and natural systems and their interconnected dynamic forces as a powerful means of influencing behaviours for the accorded transformation and betterment of individuals, communities, society and the planet." In addition, there is a commensurate need to define and include additional sustainable measurement tools beyond LCA for circularity.

8. Summary

Modern medicine and adjacent STEM disciplines are substantially more sophisticated and reflect creativity in meeting complex patient needs in an embattled healthcare environment struggling to also cope with surge in antimicrobial resistance to frontline therapeutic interventions. Our understanding and appreciation of microbial opportunistic pathogens (such as viruses, mycobacteria, protozoa, fungi), and infectious agents (prions), has challenged current definitions and expectations of high, intermediate, and low-level disinfection. The margins of safety appear to be set very tight for cleaning and processing many medical devices with complex features, when performed correctly. Given the increased need to meet a near perfect compliance with manufacturer's IFUs in these cases, combined with over-stretched processing departments that need to implement all processes appropriately, the basis of the Spaulding Classification is challenged. Thus, an understanding of the applicability and limitations of different types of disinfection and sterilization methods is essential to ensure safe, effective and appropriate processing of modern-day devices that will address patient risk of mitigating infection (as per Spaulding's classification).

This paper reviewed challenges and limitations of cleaning, disinfection, and sterilization methods for medical device in the context of modern-day practice using Spaulding's Classification as a guiding framework. Given this challenge in terms of evaluating multiple permutations of data governing processing steps including potentially new features, the need for an updated approach is apparent to accommodate the use of tools including new real-time monitoring and diagnostic interventions to supplement contemporary culture-based methods (such as introduction of robotics, automation, machine learning, and new statistical modeling) for evidence-based decision-making. However, a systems based approach will be required to ensure future AI and deep learning/machine-based trustworthiness occurs for the appropriate regulation of software and its applicability for medical devices. Future proofing the medical device industry will also avail of life cycle assessment (LCA) tools and 360° degree holistic thinking to inform next-generation medical devices that embrace future sustainability. The commensurate role of smart bioactive and biodegradable materials for coating medical devices (including biofilm disruptive properties) combined with sustainable processing methods will contribute towards future solutions. The multi-actor use of a new Quintuple Helix Hubs (combining academia-industry-healthcare-regulators-society) coupled with digital transformation (such as Industry 5.0 – human centric concept) (Rowan et al., 2022) will also contribute to the co-creation of next-generation medical device and management models. Addressing efficacy of new design features from an appropriate end-to-end processing perspective that spans technological, policy and societal readiness levels will meet the pressing needs of medtech sector, and holistically inform future sustainability.

CRediT authorship contribution statement

Neil Rowan (NR), Terra Kremer (TK), Gerard McDonnell (GMcD).

Conceptualization (NR, TK, GMcD), Data Curation (NR, TK, GMcD); Formal Analysis (NR, TK, GMcD); Funding Acquisition (NR, TK); Methodology (NR, TK, GMcD); Writing/Original Draft (NR, TK, GMcD); Writing – Review & Editing (NR, TK, GMcD).

Data availability

Data will be made available on request.

Declaration of competing interest

The authors declare no conflict of interest.

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