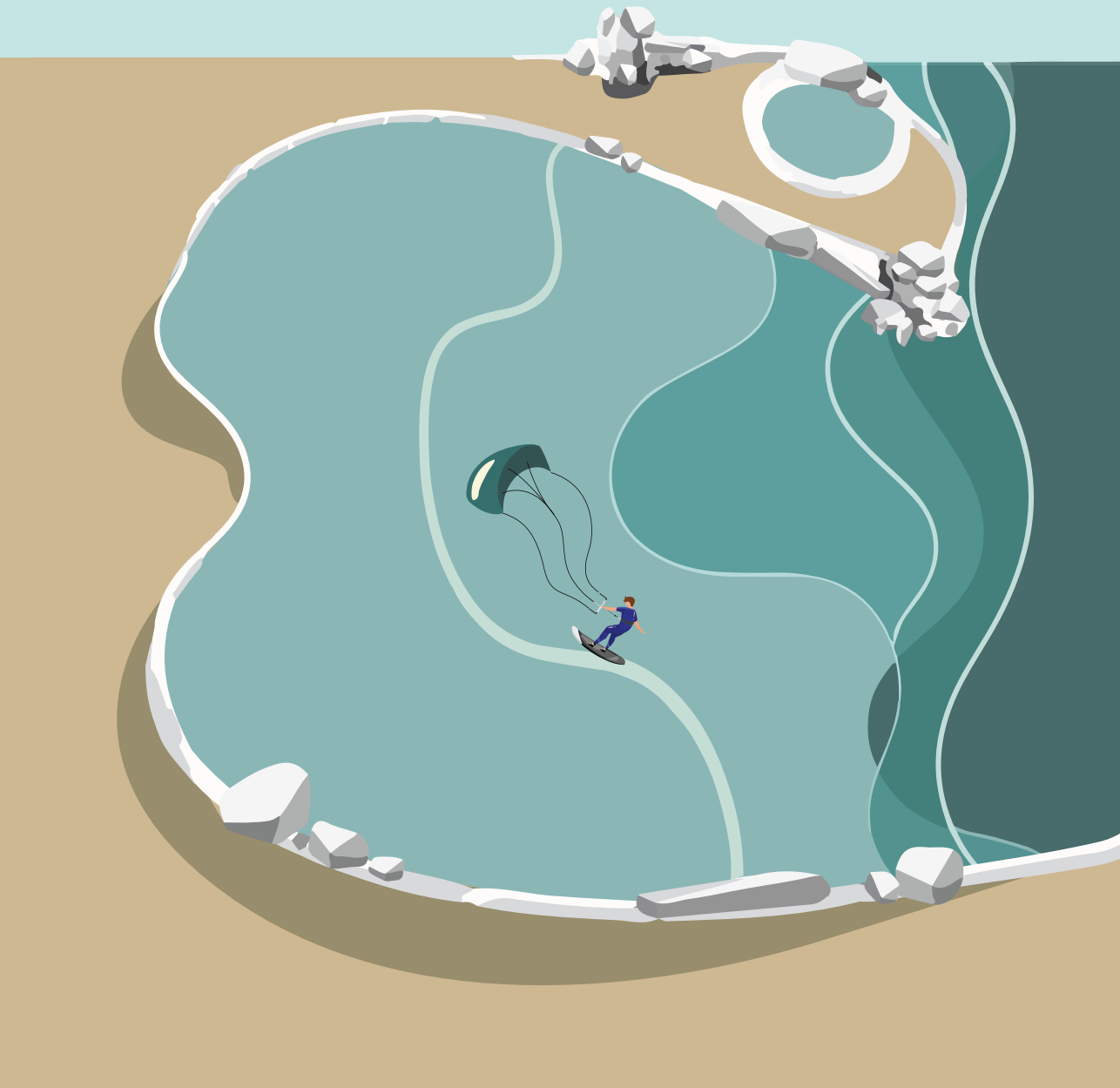
BACTERIAL CONTAMINATION OF COMPLEX GASTROINTESTINAL ENDOSCOPES

Arjan W. Rauwers



Bacterial Contamination of Complex Flexible Gastrointestinal Endoscopes

Bacteriële contaminatie van complexe flexibele gastro-intestinale endoscopen

Arjan Wouter Rauwers

Colophon

Bacterial contamination of complex gastrointestinal endoscopes

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CHAPTER
1

Introduction and outline of the thesis

Endoscopes are reusable flexible instruments which are used for millions of diagnostic and therapeutic gastrointestinal procedures worldwide each year.[1-3] This includes complex design endoscopes such as duodenoscopes used for endoscopic retrograde cholangiopancreatography (ERCP) procedures in patients with pancreaticobiliary diseases. An infection by endogenous microorganisms (i.e. bacteria originating from the patient's own flora) because of translocation during the procedure, is a risk inherent to ERCP.[4] Infections by transmission of bacteria through contaminated endoscopes, i.e. exogenous sources of infection, should be prevented by post-procedure reprocessing of endoscopes. Compared to regular gastrointestinal endoscopic procedures such as gastroscopy and colonoscopy, the post-ERCP infection rate of 1%-4% is higher.[5-8] This rate consists of infections by endogenous bacteria and from exogenous sources from contaminated duodenoscopes, but the relative contribution of either one is unclear. Since the new millennium, a rising number of duodenoscope-associated outbreaks have been reported,[9-11] including a large outbreak in the Erasmus MC Medical Center in 2012.[12] Our research group started an investigation whether this outbreak was the result of local incidents, or an indicator of a structural problem. From the analysis of this outbreak we learned that the risk of exogenous infections is higher than suspected previously and that the cause is multivariable. This started the formation of a multidisciplinary research group to investigate the impact, cause and solutions for this problem. In this thesis we give insight into the multifactorial cause of infectious outbreaks due to contaminated complex endoscopes, assess the nationwide Dutch prevalence of complex endoscope contamination and the associated risk factors, and present the results of a large-scale interventional study studying whether the use of a post-manual cleaning test is able to reduce contamination rates of patient-ready endoscopes.

Gastrointestinal endoscopy

Endoscopy is an essential part of gastrointestinal medicine. The development of the endoscope started already before 1900, with pioneers performing the first gastroscopy in 1868.[13] Issues with rigidity and illumination had to be solved, until in 1957 the first fully flexible endoscope using fibreoptics was designed.[13, 14] Since 1968, flexible endoscopes are available on a large scale, at first for diagnostic investigations and later for therapeutic procedures.[14] Gastroscopy is used in the upper (esophagus, stomach, duodenum) and colonoscopy in the lower gastrotintestinal tract (sigmoid, colon, distal ileum). The introduction of ERCP in 1968 enabled a minimal invasive way to treat biliary, pancreatic and hepatic pathology such as bile stones and benign and malignant strictures. Due to technologial advancements in diagnostic imaging, ERCP has developed into a almost exclusive therapeutic procedure. In the Netherlands and US nowadays yearly 17.000 and 700.000 ERCP procedures are performed, respectively.[15-17] Another important milestone was development of endoscopic ultrasound (EUS) in the

early 1980s.[13, 14] The addition of ultrasonography provided endoscopy an extra imaging dimension and novel interventional possibities such as EUS-guided fine needle biopsy.

Complex endoscopes used for ERCP and EUS

Endoscopes are delicate devices with long, narrow channels which are used to guide devices, flush water and/or the suction of debris (Figure 1). During the procedure endoscopes are in close and direct contact with bodily fluids. Depending on their complexity determined by the number and type of channels, these endoscopes are categorized as low, middle and high contamination risk (Table 1).[18] Low-risk endoscopes such as cystoscopes or laryngoscopes have a front-facing tip with a light source and camera, but no channels are included in the light connector cable. Regular gastrointestinal endoscopes such as gastro- and colonoscopes are categorized as medium-risk as their design includes a biopsy and air/water channel. The air/water channels are incorporated in the light connector cable (Figure 2).

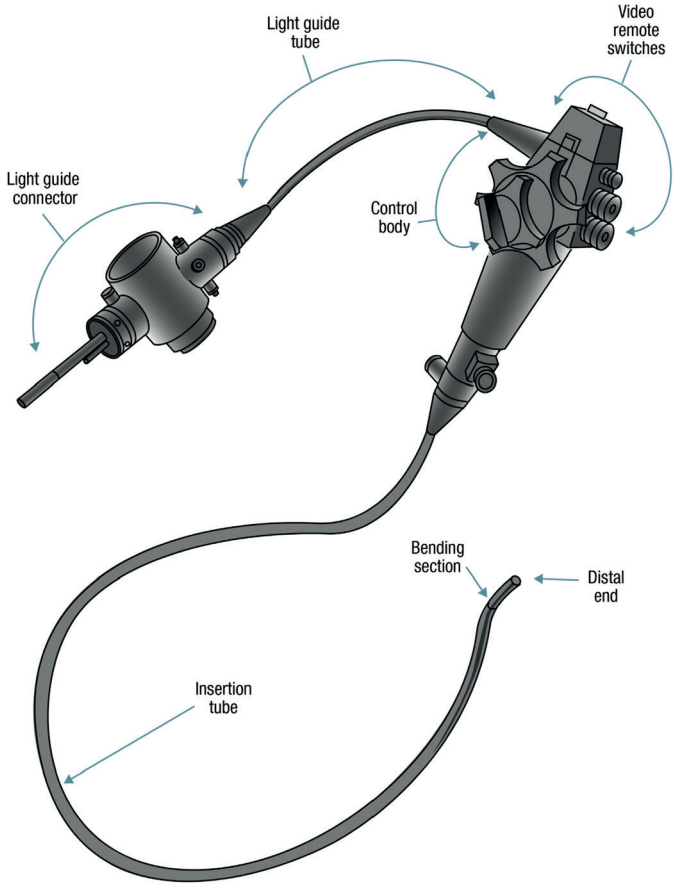

Figure 1. Schematic image of an endoscope.

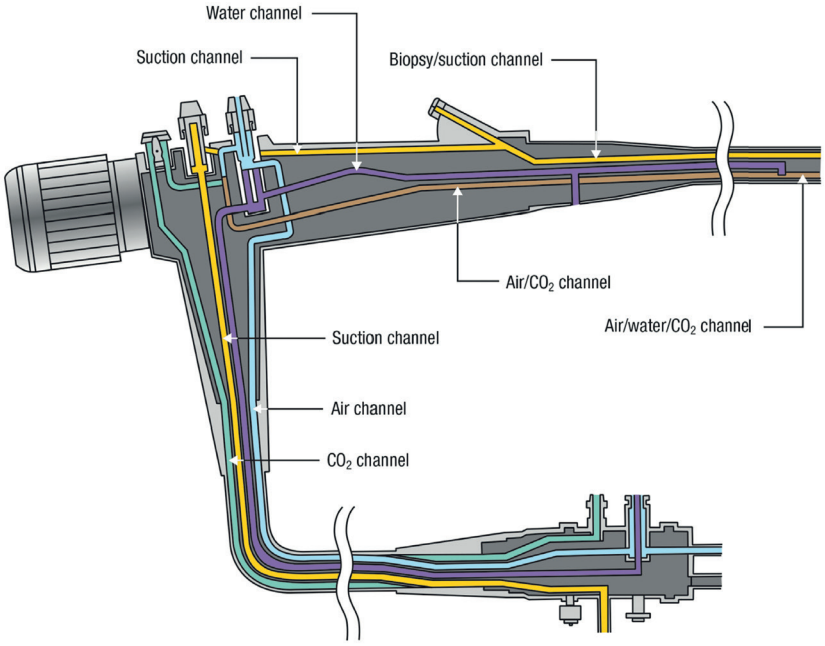

Figure 2. Schematic image of the internal channels of an endoscope.

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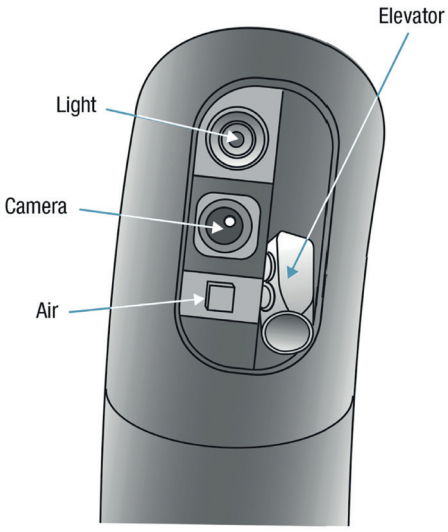

Figure 3. Schematic image of a duodenoscope tip

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Duodenoscopes which are used for ERCP procedures are classified as high risk because of their complex design. As duodenoscopes are used in the treatment of pancreaticobiliary pathology for which the papilla of Vater needs to be cannulated, they have a side-viewing tip instead of the front facing tip. In addition, the tip contains an elevator mechanism which is used to fixate and adjust accessories such as guidewires, biopsy forceps or stone retrieval baskets (figure 3). The elevator is adjusted by a guidewire which runs through an extra elevator channel. For EUS procedures two types of echoendoscopes can be used, which both have an extra balloon channel for inflation of a balloon around the tip. While the radial echoendoscope has a regular front facing tip, the linear echoendoscope has a design similar to the duodenoscope with the ultrasound probe attached to a side-viewing tip. Because of the complex design (side-viewing tip, elevator mechanism and extra channels) duodenoscopes and linear echoendoscopes are more difficult to clean compared to regular endoscopes.[12, 19] Furthermore, additional differences exist between endoscopes depending on model, type and manufacturer including sealed channels and fixed instead of reusable or single use caps.

Table 1. Dutch risk classification of endoscopes

Family	Risk	Characteristics		Examples
1	Low	No biopsy channel Maximum of 2 channels No channels in the light connector cable		(Rhino)Laryngoscope Bronchoscope Cystoscope
2	Medium	Air/water channel 1 or 2 biopsy channels Waterjet channel		Gastroscope Colonoscope Bronchoscope
3	High	Air/water channel 1 or 2 biopsy channels Waterjet channel	Forceps elevator Elevator channel	Duodenoscope
			Forceps elevator Elevator channel Balloon channel	Linear echoendoscope Linear echobronchoscope
			Balloon channel	Radial echoendoscope Radial echobronchoscope Double balloon enteroscope

Dutch risk classification of endoscopes based on NEN-EN-ISO-norms, classifying endoscopes according the number and type of channels.[18]

Reprocessing

As re-usable endoscopes become heavily contaminated with blood, bodily fluids and a high microbial load during an endoscopic procedure, they need to be decontaminated which is carried out by means of reprocessing the endoscope. In the Netherlands reprocessing is performed according the Instructions For Use (IFU) provided by the endoscope manufacturer and the Dutch reprocessing handbook of the SFERD (Advisory Board Cleaning and Disinfection Flexible Endoscopes).[20] Reprocessing is a multistep

(>100 steps) process consisting of a bedside flush, manual cleaning, and high-level disinfection (HLD) in an Automated Endoscope Reprocessor (AER).[21] If not used for a next procedure within 4 hours, the endoscope is dried in a storage cabinet.[22] Meticulous manual cleaning is essential as it removes blood, protein, soil and other organic debris from the endoscope. If organic material is still present, adequate disinfection or sterilization is not possible, and it can contribute to biofilm formation. HLD is performed on a low temperature with the chemical disinfectants glutaraldehyde or peracetic acid (PAA). Inadequate removal of biofilms by cleaning, can cause failure of disinfection as biofilms become potentially less susceptibel to disinfectants.[23, 24] Steam sterilization as is used with surgical instruments is not an option as endoscopes are heat-liable. Low-temperature sterilization options such ethylene oxide (EtO) gas, hydrogen peroxide are not widespread. In case of EtO this is due to hazard risks for staff, patients and environment, potential damaging effect to endoscopes, high (investment) costs and/or the up to 12 hour long process duration.[25] Hydrogen peroxide has poor penetration into long and narrow lumens and there is limited evidence on the microbicidal efficacy.[25] Low temperature plasma-activated gas (PAG) is a promising new method but is not yet proven and/or commercially available for endoscopes.[26]

Disinfection or sterilization

Since decades, the choice to disinfect or to sterilize a medical device is based on the Spaulding Classification which defines three classes of risk of transmission of microorganisms. While disinfection reduces the microbiological load up to 3-log, sterilization reduces a much higher load of up to 6-log (meaning 1 of 1 million microorganisms survive), giving a larger margin of safety.[27] Only instruments that come in contact with sterile tissue or the vascular system, are categorized as 'critical' and require sterilization.[27] Flexible endoscopes are categorized as 'semi-critical' instruments requiring HLD, implying that they contact mucous membranes or non-intact skin.[27] HLD completely eliminates all viruses and microorganisms (fungi, mycobacteria, vegetative bacteria), excluding small numbers in bacterial spores.[28]

In the European Union and the US, because of the categorization as semi-critical medical instruments, endoscopes with modified designs are allowed market access if their effectiveness and safety are equal to an earlier approved design. If this is the case, which may be assessed by the manufacturer itself, clinical studies are not required.[29, 30] Potentially, small sequential changes may lead over time to a substantial difference to the original design. If the manufacturer considers that the design changes may influence their effectiveness and safety, it asks for a 'premarket notification' or 510(k) in which case the FDA assess the new design. Over time, flexible endoscopes are used more and more with a therapeutic intent rather then purely as a diagnostic tool. These therapeutic interventions are of a longer duration and have a more invasive character during which

mucosal barriers are often breached. Secretions come in close contact with both the endoscope and for example exposed bloodvessels and hence the bloodstream. The same goes for ERCP. Through cannulation of the papilla of Vater, sterile spaces such as the biliary tract or the pancreatic ductal system are targeted to carry out interventional procedures. Examples include performing a papillotomy to widen the entrance to the common bile duct to remove bile duct stones or biliary stent placement to resolve obstructive jaundice in case of a malignant biliary stricure. Accessories (e.g., guidewires, sphincterotomes, biopsy forceps) are packaged sterile but are easily contaminated while passing through a contaminated endoscope channel or by handling via a contaminated forceps. As the indications and complexity of the procedures as well as the design of the endoscopes have evolved, the original classification assigned to the endoscope may need to be revised.

Margin of safety

Reprocessing has a very small margin of safety which leaves no room for error.[19, 25, 31-33] During procedures gastrointestinal endoscopes are contaminated with a microbiological load of 7-10 log_{10}.[19, 31-33] Manual cleaning reduces 3-6 log10, and in combination with the 4-6 log10 reduction by HLD, reprocessing reduces at maximum between 7 and 12 log10.[19, 25, 31-33] The margin of 0-2 log_{10} leaves no room for error. However, due to the multitude of steps and manual components, reprocessing is error-prone.[34-36] Examples of critical reprocessing lapses include failure of precleaning, inadequate manual cleaning or incorrect storage.[37] Causes for this are multifactorial including the complex cleaning process, lack of training and high-pressure working environments.[37] Reprocessing can also be inadequate despite strict adherence to the IFU. Endoscopes can be damaged as they are subject to heavy wear and tear.[38-40] These parts are vulnerable to biofilm formation and may contribute to persistent contamination.[41-43] Also, the complex design of duodenoscopes and linear echoendoscopes may hinder effective cleaning.[1, 12, 19, 44] Inadequate reprocessing can lead to biofilm formation. A biofilm consists of a extracellular matrix containing microorganisms which is attached to surfaces, e.g. channels or sealing rings. Once present it is very difficult to remove, which can result in a remaining ineffective reprocessing.

Endoscope-associated infections

From protocol, process control to end control

Since the introduction of endoscopy, endoscopes have caused nosocomial infections which led to continuous evolvment of reprocessing techniques.[45, 46] Initially endoscopes were cleaned with water, detergent and/or alcohol; but no strict protocols were in place.[14, 45] National gastroenterology societies started to develop guidelines for reprocessing protocols. Centers began to add disinfectants to the reprocessing process which was later on incorperated by national guidelines from 1980s onwards.[45, 47]

Reprocessing was also improved with the introduction of fully immersible endoscopes in 1985,[14] and the introduction of high-level disinfection (HLD) in 1990. AERs were developed to standardize reprocessing steps further eliminating human error and minimizing contact of disinfect assistants with chemical materials,[25, 48] with the first European guideline on the subject in 2007.[49] Eventually also the drying process of endoscopes was standardized.[50] In the US between 1974 and 2004, 30 outbreaks of endoscopy-associated infections were reported.[51] These outbreaks were in almost all cases caused by improper reprocessing or malfunctioning equipment, requiring better quality control.[5] However, the actual number of transmission of microorganisms was unknown due to a lack of or inadequate surveillance.[5] While some advocated regular surveillance cultures,[52-55] in some countries including the US process control instead of outcome control was used for quality assurance.[56, 57] Frequent microbiobiological monitoring of endoscopes was considered expensive, time-consuming and unnecessary if the manufacturer's instructions for use were followed.[56] Process control implies that if reprocessing is performed exactly according the manufacturer's instructions and all equipment is regularly updated and checked, the chance of any infection would be eliminated. Also in the Netherlands process control was adopted;[58] surveillance cultures were only required annually or after repairs. Guidelines on microbiological monitoring were issued by the infection prevention working group (WIP),[59] which was dissolved in 2016 because of insufficient funding.[60] To deal with the growing body of regulations, guidelines and legislation, multiple professional bodies involved in endoscope reprocessing in the Netherlands formed the Advisory Board Cleaning and Disinfection Flexible Endoscopes (SFERD) in 2006.[20] In 2010, an assessment by the Dutch Health inspectorate showed that the Netherlands was on track with the implementation of process control, but in several hospitals there was room for improvement.[61] After the detection of the worldwide surge of duodenoscope-associated outbreaks in 2015, a new Dutch guideline for microbiological surveillance for gastrointestinal endoscopes was introduced, based on half-yearly prevalence cultures.[18]

Red flag: contamination of a new-design duodenoscope

After the outbreak in the Erasmus MC in 2012, independent experts of the Technical University of Delft investigated the dismantled Olympus TJF-Q180V duodenoscope and showed it to be the culprit of the outbreak. Adequate cleaning was hampered by its design, as multiple locations could not be reached using prescribed brushes.[62, 63] Also the O-ring that sealed the elevator channel could potentially leak moisture. In 2012, this duodenoscope type was newly introduced into the market with a modified design with a fixed distal cap (instead of a removable) and a sealed elevator channel (instead of an open channel). Olympus had introduced the endoscope to the market as the manufacturer considered the modified design to be equal to the older earlier approved TJF-160 duodenoscope design. The US Food and Drug Administration (FDA)

indicated that the latest modification affected patient safety. After this, Olympus revised the design and recalled all TJF-Q180V worldwide in 2016. In the meantime, outbreaks were identified with duodenoscopes of al three major manufacturers, i.e. Fujifilm, Pentax and Olympus.[9] Importantly, multiple outbreaks occurred while manufacturer's instructions were followed to the letter,[9, 41, 64] suggesting a structural problem. In 2015, the FDA warned that the complex design of the duodenoscope might impede adequate cleaning and disinfection,[9] stressing the need for further research.

Present: a new surge of duodenoscope-assocated outbreaks

Since the new millenium a rising number of duodenoscope-associated outbreaks have been reported worldwide,[9, 11, 65] mostly of multidrug-resistant microorganisms (MDRO). Outbreaks are traced by bacterial typing. Detection of outbreaks is easier when MDRO strains are involved; retrospective tracing is often possible as laboratories commonly store resistant strains and MDRO bear distinct features which enable retrospective tracing. Adverse events resulting from the use of medical devices such as endoscopes are registered by the European Database on Medical Devices and in the US by the FDA. Both end-users and manufacturers are required to report any potential device related issue. However, detection of this surge of outbreaks was not a result of the monitoring system. Between 2013 and 2015 a large number of major outbreaks were publlished, including the outbreak in the Erasmus MC in 2012,[12, 41, 42, 64, 66, 67] which led to raised awareness on infection via contaminated duodenoscopes. In 2015, an infection control summit by the American Society of Gastroenterologists (ASGE) stressed that size of the problem of endoscope contamination and its reasons should be identified, and communication between users and manufacturers must be improved.[37] In 2016, an US Senate committee published their report explaining how ineffective monitoring of medical devices led to preventable duodenoscope-associated infections and deaths.[9] The report concluded that the outbreaks were not isolated incidents but part of a larger problem. The published outbreaks occurred between 2008 and 2013,[12, 41, 42, 64, 66, 67] but manufacturers never reported to the Food & Drug Administration (FDA) or alerted hospitals until the reports became public in 2015.[9] Furthermore, the report stated that two manufacturers did not acquire the required FDA clearance before introducing new "closed-channel" duodenoscopes, and reprocessing of duodenoscopes of all three manufacturers were not adequately tested in real-life setting.

The majority of this new surge of outbreaks were related to duodenoscopes, and a few publications report outbreaks related to bronchoscopes,[68-70] gastroscopes,[71, 72] and colonoscopes.[73] One review identified 32 duodenoscope-associated outbreaks involving almost 400 patients between 2000 and 2017,[11] and another review identified 24 clusters with 490 infected patients and 32 deaths between 2008 and 2018.[10] In the Netherlands three duodenoscope-associated outbreaks were reported by three tertiary academic centers.[12, 43, 74] However, the at present reported number of duodenoscope-associated

outbreaks is considered to be a underestimation.[9-11, 75] Detection and retrospective tracing of the reported outbreaks was only possible because of the distinct features of the MDRO. Hospitals, especially smaller centers, may not always detect outbreaks, therefore transmission of suspectible microorganisms can remain unnoticed, and even if detected the registration of outbreaks is imperfect.[9, 11, 76] In a global survey, one in five of the responding hospitals had experienced an endoscope-associated outbreak.[77] It is likely that the acutal number of transmissions of microorganisms via contaminated endoscopes and infected patients is higher than is now assumed based op published literature reports.[9]

Aims and ouline of this thesis of this thesis

The aim of this thesis was to gain insight into the reasons why duodenoscope-associated outbreaks occur and the extent of contamination of complex endoscopes, and to investigate possible (short-term) solutions to mitigate the risk of endoscope contamination and related patient infections.

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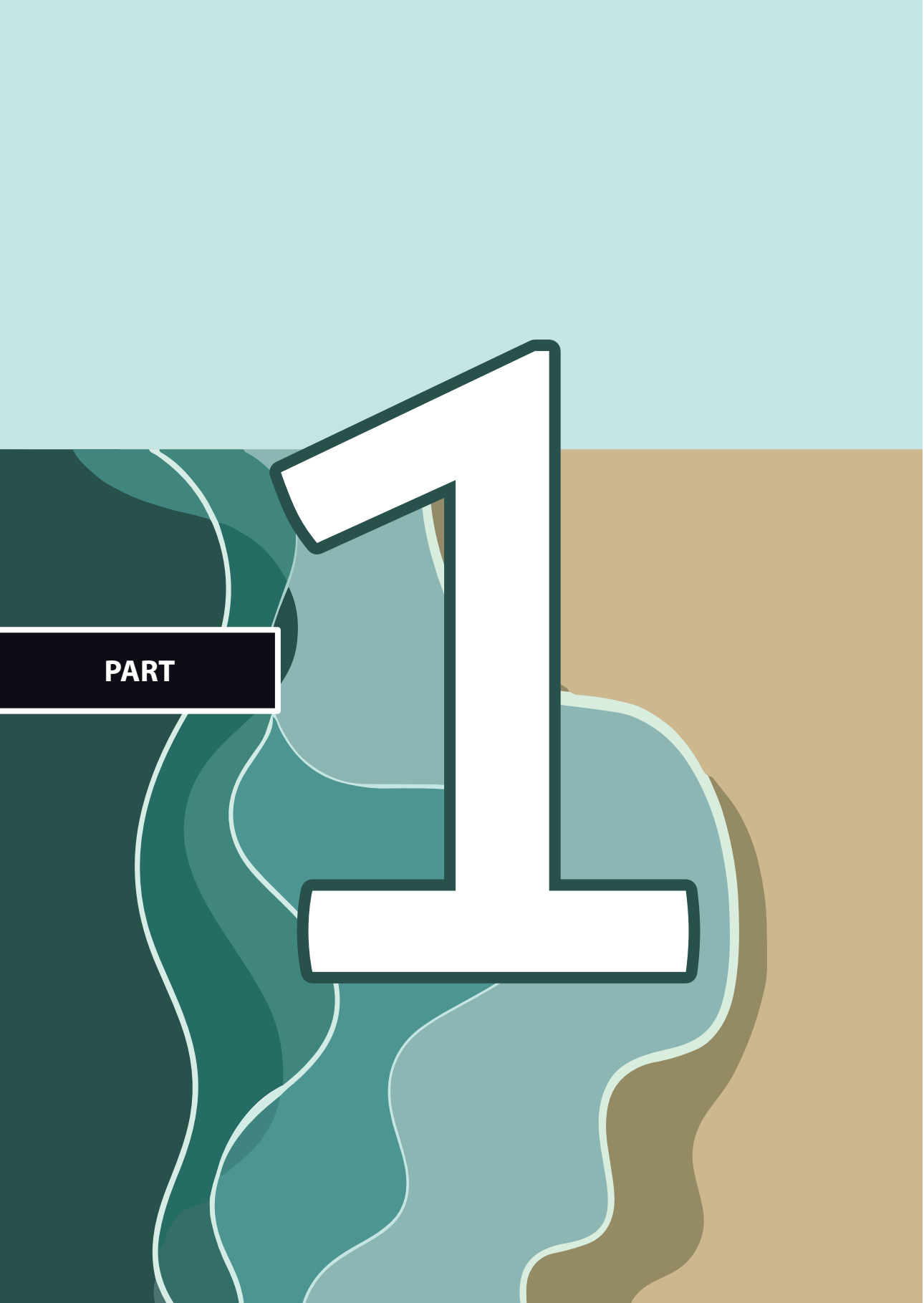
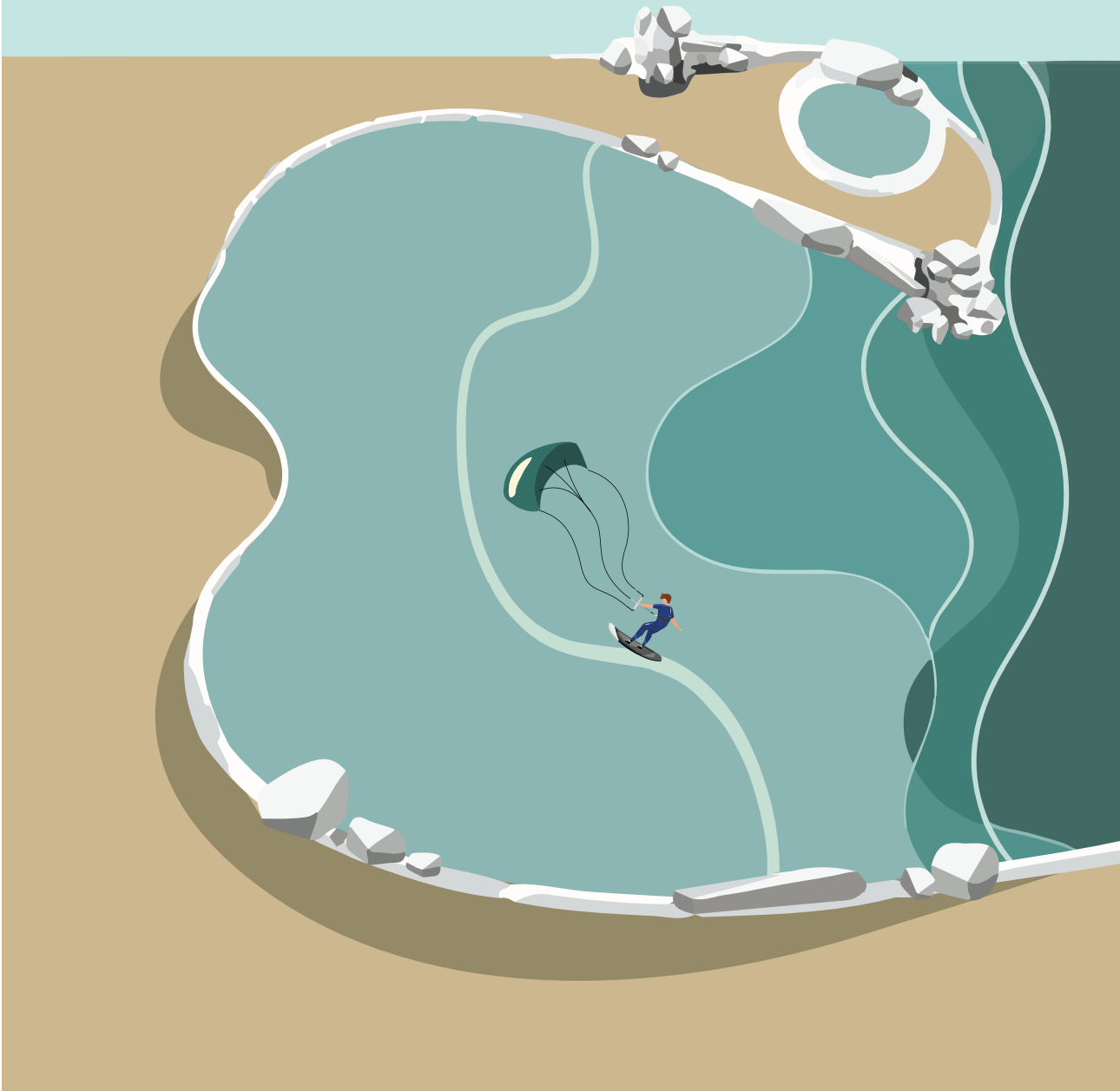

PART
1

Duodenoscope-associated outbreaks




CHAPTER
2

Outbreaks related to contaminated duodenoscopes: causes and solutions
Uitbraken door gecontamineerde duodenoscopen: Oorzaken en oplossingen

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Abstract

Duodenoscopes for Endoscopic Retrograde Cholangiopancreatography (ERCP) are used for diagnostic and, presently predominantly, for minimally invasive therapeutic procedures involving the biliary tree and the pancreatic duct. In 2012, in the Erasmus MC in the Netherlands, a large outbreak of multidrug-resistant bacteria was caused by a contaminated duodenoscope; its design was such that thorough cleaning was not possible. Worldwide, an increasing number of outbreaks involving multidrug-resistant bacteria caused by contaminated duodenoscopes have been reported on. This raises the question whether current cleaning and disinfection procedures for duodenoscopes are sufficient. In view of the recent outbreaks, it is imperative that all relevant parties (manufacturers, regulatory bodies, government agencies, gastroenterologists and medical microbiologists) actively contribute to the development of standard operating procedures that – in the interim - minimize the risk of contamination. In the long-term, novel duodenoscope designs and innovation in cleaning, disinfection and/or sterilization techniques must prevent interpatient transmission of bacteria during ERCP.

Samenvatting

Met duodenoscopen voor endoscopische retrograde cholangiopancreaticografie (ERCP) worden diagnostische, maar tegenwoordig vooral therapeutische procedures op minimaal invasieve wijze uitgevoerd in de galwegen en de alvleesklierbuis. In 2012 was er in het Erasmus MC een grote uitbraak met een resistente bacterie door een gecontamineerde duodenoscoop, die door het ontwerp niet goed gereinigd kon worden. Sindsdien zijn er wereldwijd meerdere uitbraken met resistente bacteriën gemeld waarbij de transmissie via duodenoscopen verliep. Hierdoor is de vraag gerezen of het huidige proces van reiniging en desinfectie van duodenoscopen wel toereikend is. Gezien de recente uitbraken is het van belang dat alle partijen (fabrikanten, controlerende instanties, overheid, mdl-artsen, artsen-microbiologen) actief bijdragen aan het ontwikkelen van werkprotocollen en procedures die op korte termijn het risico op nieuwe besmettingen minimaliseren. Op lange termijn zullen nieuwe ontwerpen van duodenoscopen en innovatie in reinigings- en desinfectie- of sterilisatietechnieken ervoor moeten zorgen dat overdracht van infecties wordt voorkomen.

Duodenoscopen voor endoscopische retrograde cholangiopancreaticografie (ERCP) zijn, net als gastro- en coloscopen, flexibele, herbruikbare instrumenten die worden ingezet bij de diagnostiek en behandeling van aandoeningen in het maag-darmkanaal. Tijdens deze procedures raken endoscopen gecontamineerd met darmflora. Deze flora omvat bacteriën, maar kan bij bloedige procedures ook virussen bevatten zoals het hepatitis B-virus. Als flexibele endoscopen inadequaat gereinigd en gedesinfecteerd worden, kunnen patiënten besmet raken.[1]

In 2012 was er in het Erasmus MC een grote uitbraak met een resistente bacterie door een gecontamineerde duodenoscoop. Deze uitbraak bleek niet op zichzelf te staan; wereldwijd worden nu uitbraken met resistente bacteriën in toenemende mate beschreven.[2] Een belangrijke vraag is of dit komt door inadequate reinigings- en desinfectieprocessen of doordat het complexe ontwerp van de duodenoscoop adequate reiniging en desinfectie verhindert. Daarnaast dringt zich de vraag op of dit een nieuw probleem is of dat deze uitbraken nu vaker worden vastgesteld door enerzijds een hogere prevalentie van resistente – of zelfs multiresistente – bacteriën, die herkenbaar zijn door hun exceptionele resistentiepatronen, en anderzijds een hogere alertheid.

De duodenoscoop

Met 17.000 en 668.000 ERCP-procedures per jaar in respectievelijk Nederland en de Verenigde Staten (VS) is de duodenoscoop een onmisbaar instrument binnen de hedendaagse patiëntenzorg.[3, 4] Door verbetering van niet-invasief beeldvormend onderzoek is de duodenoscoop veranderd van een diagnostisch naar een bijna exclusief therapeutisch instrument. De duodenoscoop wordt ingezet bij de verwijdering van galwegstenen en het behandelen van patiënten met een goed- of kwaadaardige vernauwing van de galwegen of alvleesklierbuis door plaatsing van een endoprothese. Vaak wordt hierbij de slijmvliesbarrière (mucosa) doorbroken, zoals bij het dilateren van de galwegen of alvleesklierbuis bij stenoses, het vergroten van de toegang ervan door het doornemen van de sfincter van Oddi (papillotomie) of het inwendig ontlasten van empyemen en abcessen.

Figuur 1. ERCP duodenoscoop

(a) ERCP-duodenoscoop met afneembare beschermkap en open liftkanaal, en
(b) ERCP-duodenoscoop met een verlijmde, niet-afneembare kap en afgesloten liftkanaal.[5]

Vergeleken met andere endoscopen heeft de duodenoscoop een complex ontwerp. Om vanuit het duodenum in de galwegen en alvleesklierbuis te kunnen werken heeft de duodenoscoop geen tip die standaard voorwaarts is gericht, maar een zijwaarts gerichte tip. Hierin zitten de lichtbron, camera, werkkanaalopening, lucht- en waterkanaalopening, en een liftmechanisme. Met het liftmechanisme kan de stand van de instrumenten aangepast worden. Om dit liftmechanisme te bedienen loopt een draad door een separaat, smal liftkanaal (figuur 1a). Door de zijwaarts gerichte tip, het liftmechanisme en het liftkanaal zijn duodenoscopen moeilijker te reinigen vergeleken met andere flexibele endoscopen.[4]

Desinfectie of sterilisatie

De keuze voor desinfectie of sterilisatie wordt bepaald door het Spaulding-schema, dat gebaseerd is op het infectierisico (tabel). Sterilisatie zorgt voor een reductie van het aantal micro-organismen met 6log, dat wil zeggen: 1 op 1 miljoen micro-organismen overleeft; desinfectie reduceert het aantal met 3log. Duodenoscopen zijn nu geclassificeerd als 'semi-kritisch', ondanks dat ze worden gebruikt op kritische locaties. Thermische sterilisatie is geen optie, omdat flexibele endoscopen niet tegen de bijbehorende hoge temperaturen kunnen.

Table. Spaulding-schema voor de bepaling van het infectierisico.

Categorie	Uitleg
Niet-kritisch	Instrumenten komen in contact met intacte huid; reiniging volstaat
Semi-kritisch	Instrumenten komen in contact met niet-intacte huid of slijmvliezen; desinfectie volstaat
Kritisch	Instrumenten komen in aanraking met steriele organen en lichaamsholten; sterilisatie is noodzakelijk

Na een procedure worden flexibele endoscopen doorgespoeld en -geblazen. Hierna vindt handmatige voorreiniging plaats en aansluitend machinale reiniging en chemische desinfectie. Als de endoscoop niet binnen 4 h wordt gebruikt, wordt deze gedroogd. Het voorreinigingsproces is van groot belang. Als hierna nog organisch materiaal aanwezig is, kan er geen adequate desinfectie of sterilisatie plaatsvinden.

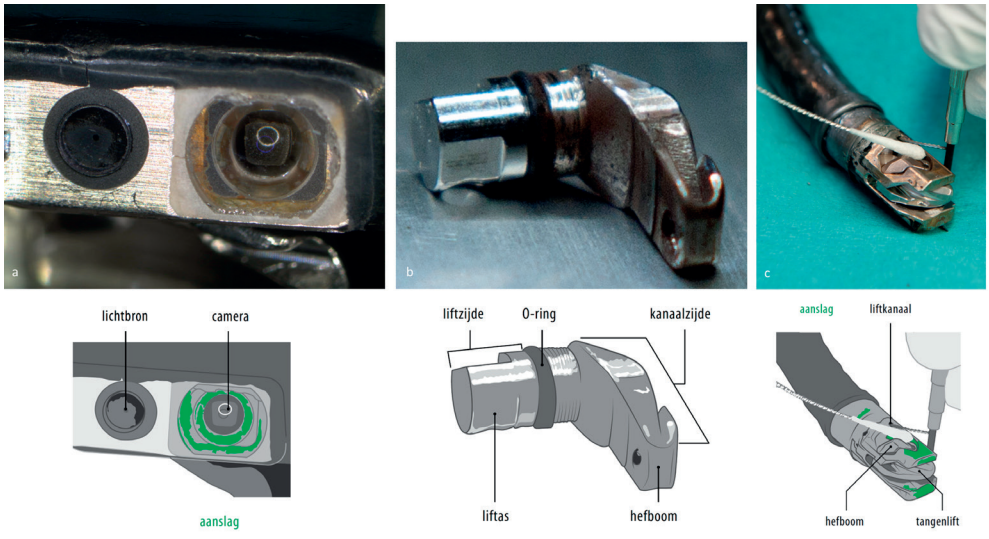
Bij inadequate desinfectie door een fout in het proces, beschadiging van de endoscoop, of een complex endoscoopontwerp kan een biofilm ontstaan. Dit is een cluster van bacterieel en humaan materiaal dat zich bindt aan materiaaloppervlakken, bijvoorbeeld in een endoscoopkanaal. Een biofilm is uitermate lastig te verwijderen en zorgt voor een blijvend ineffectief reinigings- en desinfectieproces.[1]

Transmissie van micro-organismen

De afgelopen 3 jaar zijn er wereldwijd ten minste 25 uitbraken met resistente bacteriën door gecontamineerde duodenoscopen gemeld, waarbij ten minste 250 patiënten een infectie opliepen.[2] In de VS heeft dit tot nationale onrust geleid en patiënten twijfelen of ze de noodzakelijke ERCP-behandeling nog wel willen ondergaan.6 Het is onduidelijk op welke schaal transmissie daadwerkelijk voorkomt. De uitbraken zijn herkend door het opvallende patroon van resistente bacteriën, wat bij niet-resistente bacteriën nauwelijks mogelijk is. Het is waarschijnlijk dat patiëntbesmettingen en uitbraken op grotere schaal plaatsvinden dan wij nu weten. Bij meerdere uitbraken was het reinigings- en desinfectieproces geheel verlopen conform de fabrikantinstructies.[2] Dit suggereert dat de uitbraken geen afzonderlijke incidenten zijn, maar dat ze een structureel probleem

vormen, waarbij het complexe ontwerp en de onmogelijkheid tot adequate reiniging en desinfectie een rol spelen.

De duodenoscopen van de nieuwste generatie die worden geproduceerd door 3 fabrikanten, de Fujifilm ED-530XT8, Olympus TJF-Q180V en Pentax ED34-i10T, hebben een afgesloten liftkanaal. Dit heeft als doel contaminatie op deze locatie te voorkomen, waardoor reiniging en desinfectie hiervan in principe overbodig is. Bij de uitbraak in het Erasmus MC bleek een duodenoscoop van het type Olympus TJF-Q180V de bacteriebron te zijn.[5] Bij dit type is het liftkanaal afgesloten met een 'O-ring' en is de beschermkap om de tip niet afneembaar maar verlijmd (figuur 1b). De betreffende duodenoscoop werd in samenwerking met de Technische Universiteit Delft en fabrikant Olympus destructief gedemonteerd en onderzocht (figuur 2). Een van de conclusies was dat door het nieuwe ontwerp meerdere locaties niet goed bereikt kunnen worden met standaardborstels en dat optimale handmatige voorreiniging hierdoor wordt belemmerd.[7, 8] Hierna heeft Olympus in 2013 en 2014 waarschuwingen ('field safety warnings') doen uitgaan naar Europese ziekenhuizen, waarin het belang van juiste reiniging en desinfectie werd benadrukt, met name met betrekking tot de endoscooptip.[2]



Figuur 2. Gedemonteerde TJF-Q180V duodenoscoop met onderdelen die niet bereikbaar zijn voor reiniging. (a) Detailopname van de distale tip met lichtbron en camera. Bruinige aanslag werd aangetroffen achter het afdekglas van de camera. (b) Foto van de liftas met de O-ring en (c) de positie van de liftas in de distale tip. Vervuiling werd gevonden aan de 'kanaalzijde' van de O-ring en in mindere mate aan de 'liftzijde', die in indirect contact komt met de patiënt. Daarnaast werd bruine aanslag aangetroffen op het frame van de tip.[5]

Marktautorisatie van duodenoscopen

De huidige risicoclassificatie van de duodenoscoop in zowel Europa als de VS stelt dat bij marktintroductie van een gemodificeerd ontwerp de effectiviteit en veiligheid gelijkwaardig moeten zijn aan die van het eerder goedgekeurde ontwerp. In Europa worden hulpmiddelen beoordeeld door een commerciële keuringsinstantie ('notified body'), die onder toezicht staat van nationale overheden. Als het hulpmiddel voldoet aan de Europese richtlijnen, krijgt het een CE-markering (CE staat voor 'Conformité Européenne') en Europese marktautorisatie.

In de VS controleert een overheidsinstantie, de Amerikaanse Food and Drug Administration (FDA), dit proces. Deze stelt dat fabrikanten zelf het beste kunnen inschatten of ontwerpmodificaties de veiligheid of effectiviteit kunnen beïnvloeden. Als de fabrikant van oordeel is dat er geen significante invloed is, mag het gemodificeerde ontwerp zonder tussenkomst van de FDA op de markt. Als de ontwerpmodificaties mogelijk wel invloed hebben, dient de fabrikant een 'premarket notification', ook wel bekend als 510(k), aan te vragen; dan verricht de FDA de beoordeling.

Bij de huidige risicoclassificatie zijn klinische studies niet vereist in de VS en Europa.9, 10 Door marktautorisatie van gemodificeerde ontwerpen op basis van vermeende gelijkwaardigheid aan eerdere ontwerpen kunnen kleine opeenvolgende verschillen uiteindelijk resulteren in een substantieel verschil ten opzichte van het originele ontwerp. Een belangrijke vraag hierbij is of duodenoscopen van de nieuwste generatie hetzelfde infectierisico hebben als die van het allereerste ontwerp en of door dit systeem van semiautomatische 'verlenging' van marktautorisatie geen onnodige risico's worden gelopen. Het is onduidelijk wanneer een bestaande endoscoop na een modificatie wél wordt beschouwd als een nieuw medisch hulpmiddel en het gehele traject van marktautorisatie dus opnieuw doorlopen moet worden.

Duodenoscopen van alle 3 de genoemde fabrikanten waren betrokken bij de internationaal gerapporteerde uitbraken. De FDA waarschuwde in 2015 dat het duodenoscoopontwerp adequate reiniging en desinfectie kon verhinderen.2 Naar aanleiding hiervan hebben de 3 fabrikanten de instructies voor reiniging en desinfectie herzien en aangepast na goedkeuring van de FDA.2, 11 Zowel Olympus als Fujifilm had geen 510(k) aangevraagd voor een nieuw ontwerp met gesloten liftkanaal, dat was gebaseerd op een eerder goedgekeurd ontwerp met open liftkanaal.2 Bij Olympus betrof het de TJF-Q180V duodenoscoop, die was geïntroduceerd in 2010. In 2014 gaf de FDA aan dat de ontwerpmodificaties potentieel van invloed waren op de veiligheid en dat Olympus alsnog een 510(k) moest aanvragen. Olympus heeft daarop het afsluitmechanisme van het liftkanaal aangepast om het risico op transmissie te verminderen. Begin 2016 heeft de FDA verklaard dat het aangepaste ontwerp als

gelijkwaardig wordt beschouwd onder de voorwaarde dat deze aanpassing wordt doorgevoerd.12, 13 Interessant hierbij is dat de FDA in de discussie rond de uitbraken heeft verklaard dat de Olympus TJF-Q180V duodenoscoop niet van de markt gehaald zou worden aangezien dit tot een onaanvaardbaar tekort aan duodenoscopen zou leiden.13 Olympus zal dit jaar wereldwijd alle TJF-Q180V duodenoscopen, waaronder 4400 Amerikaanse duodenoscopen, terugroepen om het liftmechanisme en de O-ring-afsluiting aan te passen.12, 14

Verantwoordelijkheden

Zoals uitgelegd in een leidraad en convenant heeft in Nederland de medisch specialist de eindverantwoordelijkheid voor het gebruik van apparatuur die bij de verleende zorg wordt ingezet. De raad van bestuur is eindverantwoordelijk voor een kwaliteitsborgingsysteem voor medische apparatuur. Samen dienen de raad van bestuur en medische staf voorafgaand aan implementatie van een medisch hulpmiddel te zorgen voor een plan waarin de aanschaf, het gebruik, periodieke kwaliteitsborging en evaluatie op een verantwoorde wijze geregeld zijn. Medische hulpmiddelen dienen hierbij de Europese CE-markering te hebben.15, 16

De eisen omtrent het reinigings- en desinfectieproces in Nederland zijn samengevat in een richtlijn en aanvullend handboek.17, 18 Sinds de jaren 90 worden de normen met betrekking tot het reinigings- en desinfectieproces vastgelegd in richtlijnen door de Werkgroep Infectie Preventie, een samenwerking tussen artsen-microbiologen, internisten-infectiologen en deskundigen infectiepreventie.18 In 2006 hebben verschillende uitvoerende beroepsverenigingen, die zijn verenigd in de Stuurgroep Flexibele Endoscopen Reiniging en Desinfectie, de bestaande regelgeving gebundeld in een dynamisch handboek, dat het proces en de benodigde procedures in detail beschrijft.17 De Inspectie voor de Gezondheidszorg beschouwt de richtlijn en het handboek als veldnormen.18, 19

Maatregelen

Op korte termijn is er behoefte aan betere controles die voortijdig kunnen vaststellen of het reinigings- en desinfectieproces adequaat was. Momenteel ligt in Nederland de focus op procescontrole. Reiniging en desinfectie worden adequaat geacht als het proces is uitgevoerd volgens de fabrikantinstructies. Controle van de flexibele endoscoop met kweken wordt niet periodiek uitgevoerd, alleen bij incidenten zoals een uitbraak.[17, 18] Momenteel wordt op initiatief van de Nederlandse Vereniging voor Medische Microbiologie en met subsidie van de Stichting Kwaliteitsgelden Medisch Specialisten een landelijke richtlijn ontwikkeld waarin wordt beschreven of, hoe en met welke frequentie microbiologische controle uitgevoerd moet worden. Daarnaast wordt gekeken naar de effectiviteit van testen om de voorreiniging te kunnen controleren.

Naar verwachting zullen gecontamineerde endoscopen door microbiologische controles eerder worden geïdentificeerd en kunnen nieuwe uitbraken daardoor sneller herkend of voorkomen worden.

Toekomstige duodenoscoopontwerpen moeten niet alleen effectief en efficiënt zijn, maar tevens goed te reinigen en desinfecteren. Mogelijk zullen nieuwe duodenoscopen gedeeltelijk of in hun geheel voor eenmalig gebruik zijn of gesteriliseerd kunnen worden. Voor verdere innovatie van duodenoscopen en veilig gebruik bij patiënten moeten de controlerende instanties in Europa en in de VS ontwerpmodificaties vóór marktintroductie beoordelen op effectiviteit en veiligheid. Het is de vraag of het initiatief hiervoor moet worden overgelaten aan de fabrikanten. Bij gerede twijfel moeten preklinische of klinische studies uitgevoerd worden. Ook na marktautorisatie zal door ziekenhuizen, controlerende instanties en fabrikanten actieve surveillance moeten plaatsvinden om een patroon van uitbraken vroegtijdig te herkennen. Op deze manier kunnen ERCP-procedures veilig blijven plaatsvinden

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CHAPTER
3

Independent root cause analysis of contributing factors, including dismantling of 2 duodenoscopes, to an outbreak of multidrug-resistant *Klebsiella pneumoniae*

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Abstract

Background and Aims:
Worldwide an increasing number of duodenoscope-associated outbreaks are reported. The high prevalence rate of contaminated duodenoscopes puts patients undergoing endoscopic retrograde cholangiopancreatography (ERCP) at risk of exogenous transmission of microorganisms. The contributing factors of the duodenoscope design to contamination are not well understood. This paper reports on the investigation following the outbreak of a multidrug-resistant *K. pneumoniae* (MRKP) related to two Olympus TJF-Q180V duodenoscopes.

Methods:
We conducted a contact patient screening and microbiological laboratory database search. Reprocessing procedures were audited and both duodenoscopes were fully dismantled to evaluate all potential contamination factors. Outcomes were reviewed by an experienced independent expert.

Results:
In total 102 patients who had undergone an ERCP procedure from January to August 2015 were invited for screening. Cultures were available of 81 patients; yielding 27 MRKP infected or colonized patients. Ten patients developed a MRKP-related active infection. The duodenoscopes had attack rates (the number of infected or colonized cases/number of exposed persons) of 35% (17/49) and 29% (7/24). Identical MRKP isolates were cultured from channel flushes of both duodenoscopes. The review revealed four major abnormalities: miscommunication about reprocessing, undetected damaged parts, inadequate repair of duodenoscope damage and duodenoscope design abnormalities, including the forceps elevator, elevator lever, and instrumentation port sealing.

Conclusions:
Outbreaks are associated with a combination of factors including duodenoscope design issues, repair issues, improper cleaning, and systemic monitoring of contamination. To eliminate future duodenoscope-associated infections, a multi-pronged approach is required including clear communication by all parties involved, a reliable servicing market, stringent surveillance measures and eventually new duodenoscope designs as well as reprocessing procedures with a larger margin of safety.

Introduction

In recent years a rising number of outbreaks of infectious multidrug-resistant organisms (MDRO) caused by contaminated duodenoscopes have been reported worldwide, with at least 400 patient infections and at least 20 deaths.[1-3] Duodenoscopes are mostly used for therapeutic endoscopic retrograde cholangiopancreatography (ERCP) procedures. Being 1%-4%, the post-ERCP infection rate is higher compared to regular gastro-intestinal endoscopic procedures.[4-7] This rate is for the most part rightly attributed to endogenous infections and inherent to the ERCP procedure. However, unique ERCP-related factors including design issues may possibly contribute to exogenous transmission through contaminated duodenoscopes. The total number of outbreaks may be underestimated: registration of outbreaks is imperfect, detected outbreaks may not always be reported, and outbreaks in smaller centers and in particular transmissions of non-MDRO can remain unnoticed and might therefore not be reported as outbreaks.[1, 2, 8] The published outbreaks could only be detected and retrospectively traced because of the distinct features of the causative microorganisms, i.e. MDRO.[1, 2] This was almost only possible in large academic referral centers with the necessary microbiological laboratory alert system capabilities.[1, 2] Recent studies show duodenoscope contamination incidences ranging from 1% to 35%.[9-14] A recent nationwide Dutch study by our group showed that 15% of the patient-ready duodenoscopes were contaminated with gastrointestinal or oral flora,[15] indicating that patients undergoing ERCP have been exposed to contaminated equipment with risk of transmission.

Reprocessing, which is used to prevent transmission of micro-organisms, does not always offer a guaranteed adequate decontamination of duodenoscopes.[15] During endoscopic procedures duodenoscopes can be contaminated with a microbiological load up to 7-10 $\log_{10}$.[16-19] Reprocessing, consisting of flushing, cleaning, high-level disinfection and drying, reduces at maximum 6-12 $\log_{10}$.[16-19] This margin of safety leaves no room for error. However, reprocessing is error-prone,[20-22] as the essential step of meticulous cleaning must be performed manually. Furthermore, duodenoscopes are more difficult to reprocess compared to other endoscopes due to their complex design.[16, 23] This consists of a side viewing tip with a forceps elevator and elevator wire channel, that is sealed off in the current duodenoscope types from Olympus, Pentax and Fujifilm. Contributing to persistent contamination, the complex design may explain why outbreaks still might occur even when reprocessing would be performed exactly according the manufacturers' Instructions For Use (IFU), as was reported in other cases.[24, 25]

The mechanisms behind the duodenoscope design contributing to contamination are not well understood. To the best of our knowledge, only one dismantling of a contaminated Olympus TJF-Q180V duodenoscope was investigated by an independent

expert.[26, 27] One of the conclusions of this investigation was that the specific design including a fixed distal cap hampered adequate cleaning.[26, 27] This led to design modifications and worldwide recall, including 4400 duodenoscopes in the USA.[28] Recent borescope studies have shown that gastrointestinal endoscopes, including duodenoscopes, frequently have damaged working channels;[29-31] possibly impeding adequate removal of organic debris. Dismantling of outbreak-associated duodenoscopes would improve our understanding of duodenoscope factors and may eventually lead to safer endoscopic procedures.

Identification of two patients on the same ward colonized with a multidrug-resistant *K. pneumoniae* (MRKP) infection led to the discovery that two duodenoscopes had been the source for 27 colonized or infected patients for at least eight months. This paper reports on the outbreak investigation, including an extensive reprocessing audit, full dismantling of both duodenoscopes and review of these results by the same independent expert as the previously mentioned report, with the aim to identify all factors contributing to the persistent contamination of the duodenoscopes.

Materials and methods

Setting

University Medical Center Utrecht (UMCU) is a 1042-bed tertiary academic center in The Netherlands with 300 ERCP procedures yearly. At the time of the detection of the outbreak (July 2015), two Olympus TJF-Q180V (Zoeterwoude, The Netherlands) duodenoscopes (A and B) and two older Olympus TJF-160VR models (C and D) were being used. Maintenance and repairs were performed by a single Independent Service Organization (ISO). Duodenoscope A (3.9 years; 571 procedures) had been repaired in May 2014 and twice in May 2015. Duodenoscope B (1.9 years; 287 procedures) had been repaired in January and March 2015. From three years after commissioning, duodenoscopes C (5.9 years) and D (5 years) both were repaired six times. Their number of procedures was not registered from the date of commissioning.

Outbreak investigation

In July 2015, MRKP isolates were detected in clinical cultures from two patients admitted at the same surgical ward on different days. These *K. pneumoniae* were resistant to third-generation cephalosporins (due to the production of Extended-Spectrum Beta-lactamase (ESBL) and/or AmpC beta-lactamase), intermediately susceptible to meropenem and resistant to colistin. A contact investigation was initiated to assess possible transmission of identical MRKP, consisting of screening of patients and a microbiological laboratory database search. Contact patients (n=72) were defined as index patients' roommates, and those patients hospitalized at the same surgical ward for at least 14 days during the index patients' admission period. Contact patients were

asked to take rectal swabs on five consecutive days to screen for multidrug resistant gram-negative bacteria. Additionally, the laboratory database was searched using the following criteria: cultures from January 1st 2015, *K. pneumoniae* identified by MALDI-TOF mass spectrometry, ESBL positive or not interpretable, and resistance to cefoxitin and colistin. This laboratory database search identified 15 patients with phenotypically identical MRKP isolates, analyzed using DiversiLab (bioMérieux, Marcy-l'Étoile, France). Six of these 15 patients did not have a classic (same time, same place) epidemiological link to the index cases, but review of their medical records revealed that all patients had undergone an ERCP procedure with duodenoscopes A or B. Therefore, 24 days after the investigation had started, duodenoscopes A and B were quarantined and subsequent ERCP procedures were performed using duodenoscopes C and D. Cultures taken from duodenoscopes A and B showed persistent contamination with MRKP in both duodenoscopes. Duodenoscope C was also temporarily quarantined due to contamination, but was returned to service after culture results were negative following a second reprocessing cycle. Screening of contact patients was expanded to all 102 patients who underwent an ERCP procedure in the UMCU in 2015. A case was defined as: a patient who was colonized or infected with the MRKP outbreak strain, identical to the index isolates using DiversiLab, identified from a clinical or screening culture AND who underwent an ERCP procedure with duodenoscopes A or B. After finishing the contact investigation in November 2015, the outbreak date range was set to January to August 2015. A patient colonized with MRKP –unknown at that time– may have contaminated duodenoscope A in the fall of 2014. Expansion of the contact investigation was not deemed necessary as a laboratory database search over 2014 did not yield extra MRKP cases. Furthermore, screening of additional patients who had undergone an ERCP more than a year ago was considered ineffective, as spontaneous decolonization may had occurred.

Sampling, culture and molecular typing methods

At first only the quarantined duodenoscopes A and B, but eventually all four duodenoscopes and four Olympus ETD3 automated endoscope reprocessors (AER) were sampled using a uniform sampling protocol according to the Dutch guideline.32 Because of positive culture results, duodenoscopes A, B and C were reprocessed and sampled a second time. Placed on a sterile surface, three to four sites per duodenoscope were sampled. The three common sample sites were: flush of the suction channel, flush of the biopsy channel and swab of the distal tip including the forceps elevator. The unsealed elevator wire channels of the duodenoscopes C and D were flushed as well. Channels were flushed with sterile 0.9% NaCl fluid, of which at least 20ml was collected at the distal tip. Distal tips were sampled with Tubed Sterile Dryswabs (MWE, Wiltshire, England). During the second sampling, smaller Pernasal Dryswabs were used to reach all crevices.

Before dismantling duodenoscopes A and B were sampled again. The distal tip was sampled using Pernasal Dryswabs and BW-412T and MAJ-1888 cleaning brushes; the entrance of the biopsy channel with the BW-412T brush. All channels were flushed; of each channel at least 100 ml was collected at the distal tip. All separate dismantled parts were sampled with Pernasal Dryswabs.

Channel flushes were filtrated over a 0.45µm filter using a Sentino Microbiology pump (Pall, Medemblik, The Netherlands), after which the residue was fixed on R2A-agar. Swabs were inoculated on blood agar. Samples were incubated for 72 h at 35-37°C. Culture results were presented in Colony Forming Units (CFU)/20 ml per microorganism. K. pneumoniae isolates were typed using DiversiLab, a polymerase chain reaction fingerprinting system using repetitive sequences, and with Next-Generation Sequencing.

Other investigations

External review

The outbreak team decided in cooperation with Olympus to invite an experienced independent expert of the Delft University of Technology (TU Delft), who also reviewed the previous outbreak in the Netherlands,[23, 26, 27] to assess all potential factors contributing to the outbreak. This included an extensive audit and dismantling of both TJF-Q180V duodenoscopes A and B by dedicated Olympus technicians at Olympus (Zoeterwoude, The Netherlands) under supervision of the independent expert. An UMCU infection control practitioner specialized in flexible endoscopes audited the reprocessing procedure. Reprocessing was performed according to the at that time current IFU and Dutch guidelines.[32] Traceability of the duodenoscope was guaranteed using Hygienetracker (Star Medical Systems, Montfoort, The Netherlands).

Duodenoscope dismantling

All procedures were documented, filmed and photographed by the independent expert and conducted in the presence of Olympus and UMCU representatives. At the UMCU, first the duodenoscopes were reprocessed and dried according to the IFU, except for the use of the manual cleaner agent Neodisher Mediclean Forte (Dr. Weigert, Assen, The Netherlands). At Olympus secondly, the duodenoscope forceps elevator area and channels were visually inspected using a small diameter Olympus IPLEX-TX borescope. Finally, the distal tip, biopsy channel, instrument channel port, air/water channels and the control section were dismantled using sterilized instruments on a sterile surface. Each part was inspected, sampled and then cleaned with ethanol before removing it from the duodenoscope in order to prevent cross contamination or dislocation of traces.

RESULTS

Outbreak investigation

The outbreak investigation yielded culture results from 81 patients out of the 102 contact patients. Eight patients refused to participate or did not respond to the request for screening, and 13 patients died in 2015 without any screening or clinical cultures available.

An independent committee of medical experts reviewed the medical charts and considered their deaths not to be related to a possible colonization or infection with the outbreak strain. The epidemic curve is shown in Figure 1. In total, 27 cases were identified: one of the two index patients had undergone an ERCP, 15 patients were identified as cases by the laboratory database search, and 11 patients were identified as cases by contact screening. The ERCP characteristics, culture source and culture indication of each patient are shown in Table 1. At least 10 cases developed a MRKP-related active infection; six cases at presentation (five sepsis; one cholangitis) and four sepsis cases at a later moment. At first only duodenoscope A infected patients with an attack rate (number of infected or colonized cases/number of exposed persons) of 35% (17/49 patients). After six months duodenoscope B (attack rate of 29%; 7/24 patients) was also a MRKP vector. Three patients who underwent ERCP procedures with duodenoscope A first, and duodenoscope B later, may have been the possible link between both duodenoscopes.

Culturing of duodenoscopes A and B showed persistent contamination of the channels with identical MRKP isolates (Table 2). The following microorganisms were also cultured: ESBL-producing *E. coli* and *C. freundii*, *E. cloacae* complex, *P. aeruginosa, K. oxytoca* and *S. maltophilia.* Although no *K. pneumoniae* was found in duodenoscopes C and D or the AERs, *S. maltophilia* and *A. pittii* were cultured once from duodenoscope C. Contact patient screening did not detect *S. maltophilia*, ESBL-producing *C. freundii* or phenotypically identical *E. cloacae* complex. In 7/81 (9%) patients an ESBL-producing *E. coli* was found. However, comparing *E. coli* isolates by molecular typing techniques proves to be difficult. As the prevalence was similar to the current estimated population prevalence of 8%, the outbreak team decided not to further investigate possible *E. coli* transmission. As the detected *A. pittii, P. aeruginosa* and *K. oxytoca* isolates were susceptible for all tested antibiotics, the outbreak team decided further investigation was not indicated.

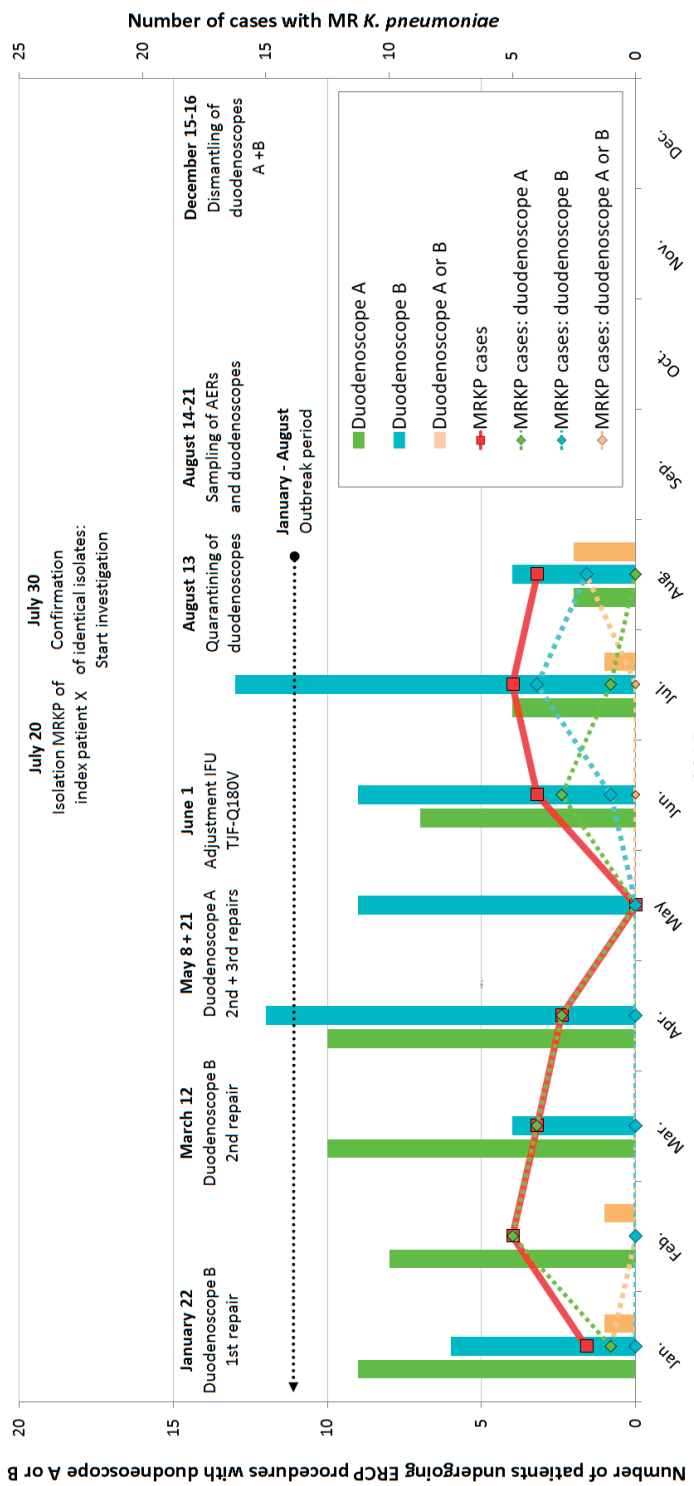

Figure 1. Timeline of the outbreak. Green and blue bars, number of patients that have undergone an ERCP procedure with duodenoscope A or B respectively. Follow-up procedures with the same duodenoscope have been excluded; pink bar, number of patients that have undergone a procedure with duodenoscope A or B; solid red line, all MRKP cases retrospectively detected by clinical or screening cultures.; dashed green line, all cases with MRKP being treated with duodenoscope A; dashed blue line, all cases with MRKP being treated with duodenoscope B; dashed pink line, all cases with MRKP being treated with a TJF-Q180V duodenoscope, either A or B. The outbreak period was set from January–August 2015. Abbreviations: ERCP, endoscopic retrograde cholangiopancreatography; MRKP, Multidrug-resistant K. pneumoniae.

Table 1. Overview of the 27 MRKP case patients.

Patient no.	Scope	Age (y) sex	Indication for ERCP	Intervention	L/S	Culture source	Culture indication
1	A	8/M	Benign biliary stricture (chronic pancreatitis)	PD stent removal and placement	S	Rectal swab	Screening
2	A	66/M	MBS (cholangiocarcinoma)	ES, dilation, biliary stent placement	L	Blood	Sepsis**
3	A	69/M	No ERCP: lower gastrointestinal bleeding (CRC)	Endoscopic clip placement	L	Sputum, wound, blood, rectal swab	Sepsis**
4	A	67/M	MBS (pancreatic cancer)	ES, biliary stent placement	L	Rectal swab	Study sample
5*	A	74/M	Suspected. pancreatitis by MBS (cholangiocarcinoma)	ES, dilation	L	Sputum, rectal swab	Abdominal infection***
6	A+B	15/M	MBS (rhabdomyosarcoma)	ES, biliary stent placement	L	Feces, urine, throat	Abdominal infection***
7	A	80/M	Suspected bile leak (metastatic CRC)	Dilation, biliary stent placement	S	Rectal swab	Screening
8	A+B	10/V	Biliary stricture of unknown cause	Brush, stent removal and placement	S	Rectal swab	Screening
9	A	63/M	Recurrent choledocholithiasis	Dilation, stone removal	S	Rectal swab	Screening
10	A	86/V	Choledocholithiasis	ES, biliary stone removal	L	Rectal swab	Study sample
11	A	67/V	MBS (cholangiocarcinoma)	Dilation, brush	L	Rectal swab	Study sample
12	A	73/M	PD leakage after partial pancreatic resection	ES, PD stent placement	S	Rectal swab	Screening
13	A	70/V	Choledocholithiasis	ES, dilation	L	Sputum	No symptoms
14	A	62/M	Chronic pancreatitis	PD stent placement	L	Blood	Sepsis**
15	A	72/V	MBS (susp. pancreatic cancer)	Biliary stent placement	L	Rectal swab	Study sample
16	A	48/V	MBS (pancreatic cancer)	ES, biliary stent placement	L	Rectal swab	Study sample
17	A+B	57/V	MBS (cholangiocarcinoma)	Dilation, biliary stent placement	L	Blood	Sepsis**
18	B	69/M	MBS (susp. duodenal cancer)	No intervention	S	Rectal swab	Screening
19	A	53/V	Benign biliary stricture (chronic pancreatitis)	ES, biliary stent placement	L	Rectal swab	Study sample
20	B	70/M	Suspected bile leak after hemicolectomy (CRC)	ES	L	Rectal swab	Study sample
21	B	15/V	Suspected biliary stricture	ES	L	Bile	Cholangitis**
22	B	57/V	Suspected pancreatic cancer	ES, Biliary stent placement	S	Rectal swab	Screening
23	B	63/M	Suspected cholangiocarcinoma	ES, dilation	S	Rectal swab	Screening
24	A/B	58/V	MBS (pancreatic cancer)	Biliary stent placement	S	Rectal swab	Screening***
25	B	40/M	Benign PD stricture (chronic pancreatitis)	PD cannulation	S	Rectal swab	Screening
26	A/B	62/M	Suspected cholangitis	Biliary stent placement	S	Rectal swab	Screening***
27	B	72/M	MBS (metastatic CRC)	ES, dilation, biliary stent placement	L	Blood	Sepsis**

Infection: signs and symptoms of an active infection including at least fever (≥38,1 ºC) and other signs such as leukocytosis, sepsis or septic shock. Study samples: rectal swabs were performed as part of another ongoing study which was conducted before the start of the outbreak investigation. L/S: Laboratory database search / Screening of contact patients. A+B: patients underwent a procedure with duodenoscope A first, and duodenoscope B later. A/B: Patients underwent a procedure with duodenoscope A or B. Abbreviations: CRC: colorectal cancer; ES: endoscopic sphincterotomy; MBS, malignant biliary tricture; MRKP, Multidrug-resistant K. pneumoniae; PD: pancreatic duct. *: index patient. **MRKP-related infection at presentation. *** MRKP-related sepsis at a later moment.

Table 2. Overview of cultured microorganisms from suspected duodenoscopes.

Duodenoscope	Date (dd-mm-yyyy)	Sample site	Sample type	Microorganism	Quantity (CFU)
A TJF-Q180V	14-08-2015 After quarantining	Suction channel	Flush	MR-*K. pneumoniae**	>200
				S. maltophilia	>200
				P. aeruginosa	>200
				E. cloacae complex	>200
		Biopsy channel	Flush	MR-*K. pneumoniae**	>200
				K. oxytoca	>200
				S. maltophilia	>200
				P. aeruginosa	>200
		Distal tip	Dryswab	Negative	
	19-08-2015 After 2nd reprocessing	Suction channel	Flush	*C. freundii*	1
				S. epidermidis	12
				S. maltophilia	22
				E. cloacae complex	1
				CNS	1
		Biopsy channel	Flush	MR-*K. pneumoniae**	75
				C. freundii	13
				S. maltophilia	>200
		Distal tip	Dryswab	Negative	
		Distal tip	Pernasal Dryswab	Negative	
B TJF-Q180V	14-08-2015 After quarantining	Suction channel	Flush	MR-*K. pneumoniae**	28
				E. coli	3
		Biopsy channel	Flush	*E. faecium*	1
		Distal tip	Dryswab	Negative	
	19-08-2015 After 2nd reprocessing	Suction channel	Flush	MR-*K. pneumoniae**	6
				E. coli	4
		Biopsy channel	Flush	*E. faecium*	1
		Distal tip	Dryswab	Neg.	
		Distal tip	Pernasal Dryswab	Neg.	
C TJF-160VR	21-08-2015	Suction channel	Flush	*A. pittii*	2
		Biopsy channel	Flush	*A. pittii*	1
		Elevator channel	Flush	*A. pittii*	26
				S. maltophilia	6
		Brush		*Corynebacterium* spp.	23
				Brevibacterium spp.	6
				C. jeikeium	23
	25-08-2015 After 2nd reprocessing	All cultures		Negative	
D TJF-160VR	21-08-2015	All cultures		Negative	

Duodenoscopes A and B were quarantined on August 13th 2015.

CFU, colony forming units; MR, multidrug-resistant.

*Isolates identical to the index isolates detected in clinical and screening cultures.

Reprocessing audit

The reprocessing audit showed that the UMCU protocol (July 2013) had several deviations from the IFU 5.0 (May 2015). After review, the independent technical expert deemed three of the deviations as factors potentially influencing reprocessing efficacy.33 First, the UMCU protocol did not explicitly state that the forceps elevator had to be moved in the upright and bent position during manual cleaning. Secondly, in June 2015, five months after the start of the outbreak, Olympus made the MAJ-1888 forceps elevator brush mandatory. The use of this brush was not implemented yet; duodenoscopes were still brushed with the formerly mandatory BW-412T brush. Finally, leakage testing was not routinely performed under water, but only if there was a suspicion of a leak.

Dismantling of the duodenoscopes

The following results are a summary of the original extensive investigation report.[33] On December 15th and 16th 2015 duodenoscopes A and B were dismantled. No MRKP isolates were found in the 15 and 16 samples taken from duodenoscopes A and B, respectively. Two microorganisms of concern were cultured from the instrumentation port of duodenoscope B: 10 CFU/100 ml *S. maltophilia* and 10 CFU/100 ml *E. cloacae*. In both duodenoscopes damage and improper repairs were observed: brown staining behind the glass covering the light-guide lens (Fig. 2a); brown scale on the distal tip frame underneath the protective cap (Fig. 2b); actuator area cover plates were incorrectly reattached with too little glue, sealing it incompletely (Fig. 2b); and new biopsy channels had been attached to the tip in a manner that deferred from the prescriptions of the duodenoscope manufacturer (Fig. 2c). In duodenoscope B, the following additional damage was observed: brown staining behind the objective lens of duodenoscope B (Fig. 2a); inadequate connection of the replaced protective cap, leaving space between the cap and the tip frame (Fig. 2d); loosened bonding of the cardan rubber, which covers the distal 10 centimeters of the endoscope before the distal tip (Fig. 2e); insufficient lubricant powder underneath the cardan rubber, likely having been the cause of friction damage to the outside of the distal end of the biopsy channel (Fig. 2f); and heavily oxidized electric circuits and connecting parts of the signaling tube in the control section, indicating moist damage (Fig. 2j). In duodenoscope A, a crack at the distal end on the inside of the biopsy channel was observed with the borescope (Fig. 2h).

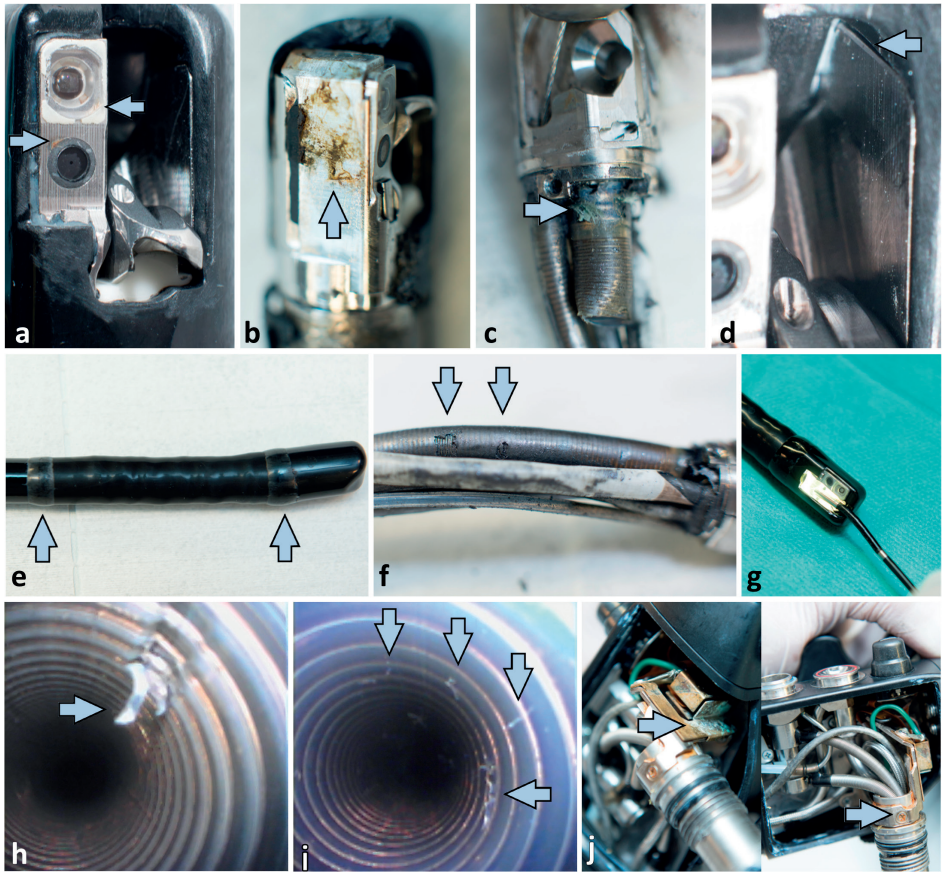

Figure 2. Photographs of the dismantling of duodenoscopes A and B, showing damage, oxidation and incorrect repairs (photos adapted with permission).[33] The observations as shown in photos a and c were present in both duodenoscope A and B. **a.** Duodenoscope B. Close up of the distal tip showing the light-guide lens and objective lens. Sludge was observed behind the glass that covers both lenses (arrows). **b.** Duodenoscope B. Close-up of the dismantled distal tip showing a brown layer on the frame of the distal tip and the cover plate of the actuator area that was incorrectly reused and reattached by soldering after repairs. **c.** Duodenoscope B. Close-up of the dismantled distal tip showing the incorrect fastening of the biopsy channel to the distal tip. **d.** Duodenoscope B. Close up of the distal tip showing unwanted space between the tip frame and the protective cap (arrow). **e.** Duodenoscope B. Photo showing the cardan rubber at the distal 10 centimeter of the duodenoscope and the distal tip. At the arrows loosening of the cardan rubber bonding was observed. **f.** Duodenoscope B. Outside of the distal part of the biopsy channel with damaged parts caused by friction (arrows). **g.** Borescope investigation. Both duodenoscopes had replaced biopsy channels with a ribbed structure instead of the original smooth structure. **h.** Duodenoscope A. Borescope showing a crack at the distal end of the biopsy channel near the tip (arrow). The biopsy channel was used for 20 procedures in total. **i.** Duodenoscope B. Borescope showing fibers at the distal end of the biopsy channel near the tip (arrows). **j.** Duodenoscope B. Control section: oxidation of electric circuits (left) and the connecting parts of the signaling tube (right).

Figure 3. **Photographs of the dismantling of duodenoscopes A and B, showing residue resulting from design issues** (photos adapted with permission).[33] The observations as shown in photos a-d were present in both duodenoscope A and B. **a.** Duodenoscope A. Elevator lever with a brown layer on both sides of the O-ring: axis side (patient side) and the channel port side (sealed off by O-ring). **b.** Duodenoscope A. Scanning electron microscopy photograph of the screw that fastens the lever axis to the forceps elevator with a powdery, brown layer with organic characteristics in the screw thread. Detail scans: 255x (left) and 3600x (right). **c.** Duodenoscope A. Elevator lever and axis with the O-ring removed. A brown layer is seen in the groove of the O-ring. **d.** Duodenoscope A. Forceps elevator with brown layer around the axis hole. **e.** Duodenoscope A. White, porous-looking layer in the recess for the forceps elevator. **f.** Duodenoscope B. Instrumentation port: water droplets under the rubber ring that seals the port were observed.

Three design-related abnormalities were observed (Fig. 3). Firstly, in both duodenoscopes brown staining was observed on the distal tips in places on the patient side that were not reachable for brushes and poorly accessible for rinsing or drying: on the internal channel port side and on the patient sided axis of the elevator lever (Fig. 3a); on the screw fastening the forceps elevator to the lever axis (Fig. 3b); in the groove in which the O-ring is situated (Fig. 3c); and in the axis hole of the forceps elevator (Fig. 3d). Secondly, at several places surrounding the forceps elevator that were easily accessible for brushes, white and brown oxidation stains were observed (Fig. 3e). Finally, water droplets were observed under the instrumentation port's rubber sealing ring of duodenoscope B (Fig. 3f).

DISCUSSION

A rising number of reported outbreaks question if reprocessing of duodenoscopes is adequate enough to prevent infection of patients with exogenous microorganisms. In the outbreak described in this report, during eight months two duodenoscopes were persistently contaminated with identical MRKP isolates and infected ≥29% of all patients who underwent an ERCP procedure with one of the two duodenoscopes. In addition to standard outbreak investigations, this investigation included the full dismantling of both duodenoscopes and review of the audit and dismantling results by an independent expert. The investigations indicated a multifactorial etiology of the outbreak and showed that debris and thus possibly patient material was likely to have been transported onto sealed off areas. Four notable points of attention could have contributed to this: design issues hampering adequate cleaning, undetected damaged parts, construction defects after repairs and flaws in the local reprocessing protocol. The results of this report ask for critical evaluation of duodenoscope design, development of reliable maintenance and servicing, and transparent communication. These defensive layers will help to prevent further duodenoscope-associated infections.

High attack rates can lead to a large number of colonized and infected patients, especially if the outbreak continues unnoticed for many months. The eight months duration of this outbreak is no exception as other outbreaks are known to have been noticed after four or even up to twelve months.[23-25, 34-36] During this outbreak, the duodenoscope attack rates of 35% and 29% resulted in 27 case patients. Other outbreak reports describe similar attack rates ranging from 12%-41%,[23, 35, 37-39] and patient counts of similar magnitude.[1, 23, 24, 34, 36] New Dutch and European surveillance strategies, developed in response to the outbreaks, potentially could shorten or even prevent outbreaks.[40, 41] However, negative surveillance culture results do not exclude contamination: outbreaks continued under repeatedly negative surveillance cultures,[36-38, 42, 43] outbreak investigation cultures remained negative,[34, 39, 44, 45] or the microorganism was only cultured after dismantling of the duodenoscope.[23, 42] As the duodenoscope design hinders assessment of contamination, surveillance culturing might not be sensitive enough to prevent outbreaks.

In the TJF-Q180V duodenoscope design areas of concern were observed that hamper adequate cleaning. These included the O-ring sealing that could potentially lead to leakage of moisture as described in 2012 by the same independent expert.[26, 27] After the FDA indicated that this modification of the earlier TJF-160VR design affected patient safety, Olympus revised the O-ring and started a recall of all TJF-Q180V worldwide in 2016.[28] As the duodenoscopes involved in this outbreak had not been revised, this issue could have contributed to persistent contamination. In addition to this, brown deposits

were observed around the lever-axes, forceps elevators and elevator screws of both duodenoscopes. Although located at the patient side of the distal tip, these places could not be reached with brushes and were poorly accessible for rinsing or drying. Scanning electron microscope images showed that the material looked similar to products of erosion or oxidation in presence of bacteria and appeared to have an organic character. However, the exact material composition could not be determined. As these traces may have been remnants of moisture, it could not be ruled out that microorganisms had been present. Furthermore, in one duodenoscope water droplets were observed around the instrumentation port, which contained a non-original O-ring, despite the performance of the drying cycle exactly according to the IFU. This could either point to previous drying not in accordance with the IFU, improper repairs, or the IFU drying process being inadequate. White and brown scales were observed at places around the forceps elevator that were well accessible for brushes. This could have been the result of inadequate brushing or an ineffective rinsing or drying process. Design issues that could hamper adequate decontamination should be critically evaluated.

Undetected damage may have contributed to several outbreaks as duodenoscopes without indications for servicing had critical abnormalities.[12, 25] Dutch guidelines require annual technical endoscope inspections, which are performed by 75% of the centers.[46, 47] Institutional technicians could detect external damage (i.e. concerning the cardan rubber, tip frame or biopsy channel). Recently Fujifilm, Pentax and Olympus recommended annual inspections.[28, 48-50] In this outbreak the biopsy channel must have been damaged in the short time of three months ahead of quarantining, when the duodenoscope was used for only 20 procedures after the last replacement of the biopsy channel. This is in line with recent borescope studies stating that biopsy channels of all types of endoscopes are frequently damaged,[31] even as early as after four weeks of use,[29] which may add to the risk of contamination.[51] The American Society for Gastrointestinal Endoscopy (ASGE) warns that endoscope durability is understood incompletely.[52] Assessment of the critical number of procedures after which to perform inspection or preventive maintenance might help to understand the development of endoscope wear and reduce the chance of using critically damaged endoscopes.

Institutions should be able to rely on repaired duodenoscopes being of similar quality as a brand-new one, regardless if repairs are performed by the manufacturer or by ISOs. This investigation showed several inadequately conducted repairs, including incorrectly attached arm covers and biopsy channels of both duodenoscopes. In some cases parts were reused or replaced with materials not originating from Olympus. In addition to aforementioned O-ring design issues, nearly all inadequate repairs could have contributed to the persistence of microorganisms. However, the investigation could not reconstruct the exact route of contamination. In 70% of the Dutch centers

institutional technicians perform the by Dutch guidelines required inspections of repaired endoscopes; often finding functional irregularities concerning the flexibility of the tip and the position of the spray nozzle.[46, 47] However, institutional technicians may lack expertise or instruments such as borescopes for adequate assessment, and some inadequate repairs can only be revealed after dismantling. Although servicing of medical devices by ISOs is essential to the US healthcare system,[53] the FDA and ASGE acknowledged concerns about the quality of servicing.[53, 54] ISOs may experience difficulties in obtaining servicing manuals, technical specifications, training and replacement parts from original manufacturers.[53, 54] In the Netherlands, Olympus does not sell spare parts of the TJF-Q180V duodenoscopes; as a result, ISOs choose to use non-original materials. Perhaps the repair quality could be improved if ISOs would service devices in agreement with manufacturers, the latter providing access to necessary materials and information.[54] Also communication between all involved parties can be improved.[1] For example, US manufacturers and institutions are not obligated to notify ISOs about adverse events related to servicing of the device.[53] A more transparent market would support reliable and affordable high-quality servicing.

In addition to the duodenoscope-related risks, reprocessing is error-prone by itself.[20-22] In multiple outbreaks reprocessing breaches may have contributed.[35-37, 42, 55] In response to the finding that the TJF-Q180V design hampered adequate cleaning, Olympus issued a Safety Advice in 2013.[23, 56] The advice indicated, amongst other warnings, detailed forceps elevator brushing instructions to reach all crevices. Although not explicitly stated in the UMCU protocol, during the audit these actions were performed by disinfection assistants.[33] Olympus also suggested the use of the new designated MAJ-1888 brush. This was made mandatory in June 2015, five months after this outbreak started. As in the UMCU leakage testing was not performed underwater unless a leak was suspected, leaks may have been missed. The repair history of duodenoscope B listed the assessment of a potential leak, which may explain the oxidation around the electrical connection in the control section. During the external review both the IFU leakage test and the Olympus AER automatic leakage test did not detect any aberrations. Recently, the European guideline questioned if leakage testing was accurate enough as micro-defects were often not detected.[40] To ensure direct implementation of recommendations, the independent expert advised manufacturers to communicate new reprocessing clearly and to make critical recommendations mandatory right away.[33] Hospitals should, in addition to direct implementation, also perform recurring audits. This was essential in our center to minimize protocol breaches after the outbreak investigation.

This is the second report that describes the dismantling of duodenoscopes in an outbreak setting.[23] Both hospital and manufacturer were open to critical review by an experienced independent expert, enabling the investigation of all potential causes for

contamination. The procedure described in this report has limitations. Dismantling took place four months after quarantining, which may have contributed to culture results negative for MRKP in any of the dismantled parts. Therefore, the exact location of the persistent contaminant could not be traced. Furthermore, the reprocessing audit took place after the outbreak. This may have influenced the responses of the disinfection assistants. Lastly, not all findings may apply to other centers. Duodenoscope contamination incidences differ between hospitals,[11] possibly because of differing control rigidity, surveillance and maintenance strategies.

This report describes how a combination of factors including duodenoscope design issues, undetected damaged parts, inadequate repairs, nontransparent communication and inadequate hospital protocols may have contributed to the outbreak. The reliability of the defensive layers of the current system around reusable duodenoscopes seems to show room for improvement due to several factors: reprocessing with small margins of safety while human errors are to be expected,[16-22] imperfect maintenance strategies, duodenoscope designs that can hamper adequate cleaning,[23, 57] unclear communication and imperfect adverse event reporting.[1, 8] To develop better defensive layers and avoid unreported internal assessment by the manufacturer,[25, 57] we would suggest independent reviews of future outbreaks including a timely full dismantling of the duodenoscope. Furthermore, adapted duodenoscope designs may currently be marketed without additional clinical testing, if sufficiently based on previously approved designs. Peer-reviewed validation tests are only obligatory for radically altered designs, which is assessed by manufacturers themselves. But as successive adjustments can result in a substantial different design, standard peer-reviewed design validation tests could contribute to safer duodenoscope designs. In the short term, the number of duodenoscope-associated outbreaks could be reduced by direct implementation of critical reprocessing measures, a reliable servicing market, critical review of current monitoring methods, and introduction of surveillance measures. Eventually new duodenoscope designs as well as reprocessing procedures with a larger margin of safety are required.

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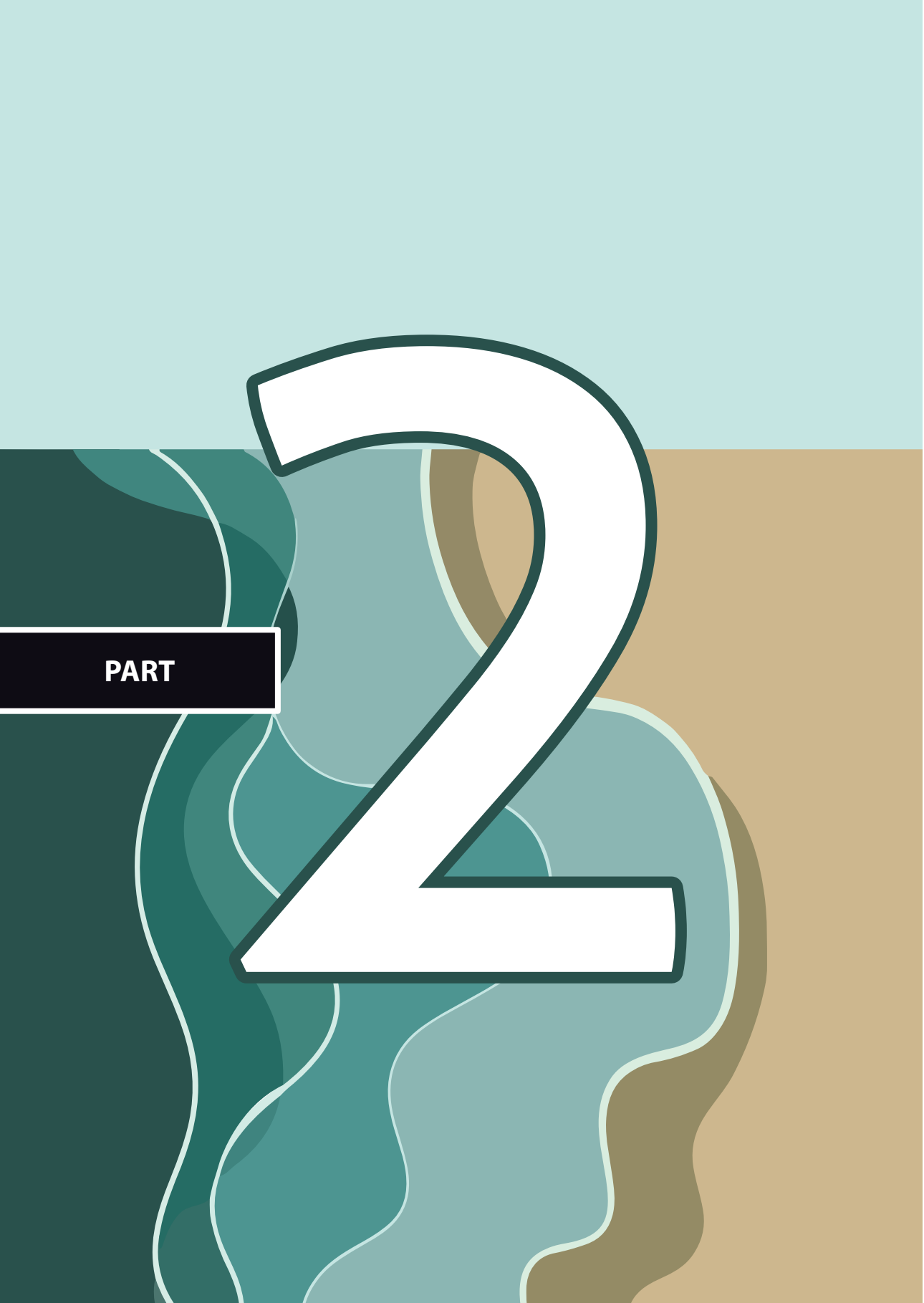
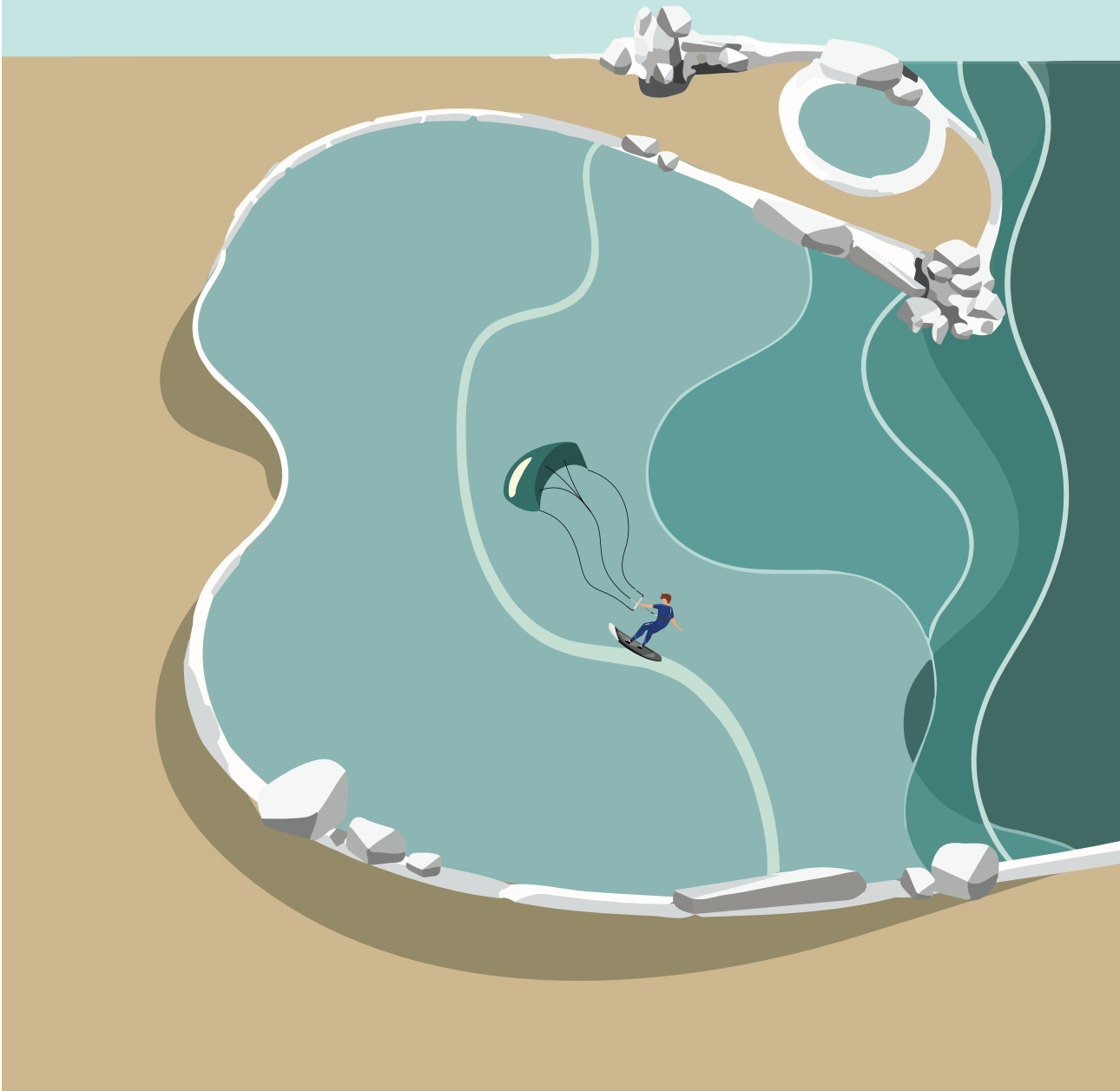

PART
2

Contamination of complex gastrointestinal endoscopes: prevalence and risk factors




CHAPTER
4

High prevalence rate of digestive tract bacteria in duodenoscopes: a nationwide study

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Abstract

Objective

Increasing numbers of outbreaks caused by contaminated duodenoscopes used for Endoscopic Retrograde Cholangiopancreatography (ERCP) procedures have been reported, some with fatal outcomes. We conducted a nationwide cross-sectional study to determine the prevalence of bacterial contamination of reprocessed duodenoscopes in The Netherlands.

Design

All 73 Dutch ERCP centres were invited to sample ≥2 duodenoscopes using centrally distributed kits according to uniform sampling methods, explained by video instructions. Depending on duodenoscope type, four to six sites were sampled and centrally cultured. Contamination was defined as 1) any microorganism with ≥20 colony forming units (CFU)/20mL (AM20) and 2) presence of microorganisms with gastrointestinal or oral origin, independent of CFU count (MGO).

Results

Sixty-seven out of 73 centres (92%) sampled 745 sites of 155 duodenoscopes. Ten different duodenoscope types from three distinct manufacturers were sampled including 69 (46%) Olympus TJF-Q180V, 43 (29%) Olympus TJF-160VR, 11 (7%) Pentax ED34-i10T, eight (5%) Pentax ED-3490TK and five (3%) Fujifilm ED-530XT8. Thirty-three (22%) duodenoscopes from 26 (39%) centres were contaminated (AM20). On 23 (15%) duodenoscopes MGO were detected, including *Enterobacter cloacae, Escherichia coli, Klebsiella pneumonia* and yeasts. For both definitions, contamination was not duodenoscope type dependent (*P* values: 0.20 and higher).

Conclusion

In 39% of all Dutch ERCP centres at least one AM20 contaminated patient-ready duodenoscope was identified. Fifteen percent of the duodenoscopes harboured MGO, indicating residual organic material of previous patients, i.e. failing of disinfection. These results suggest that the present reprocessing and process control procedures are not adequate and safe.

Introduction

Very recently, an increasing number of infectious outbreaks involving multidrug-resistant organisms (MDRO) caused by contaminated duodenoscopes, used for Endoscopic Retrograde Cholangiopancreatography (ERCP) procedures, have been reported in both Europe and the United States (US).[1-5] These include outbreaks of infections with carbapenem-resistant Enterobacteriaceae, such as *Escherichia coli* and *Klebsiella pneumoniae,*[3, 4] of which some have been associated with fatal outcomes.[6] Post-ERCP infections typically range between 2% and 4%.[7] It is not clear to what extent these infections are caused by the procedure itself (i.e. endogenous infections) or to what extent contaminated duodenoscopes are the source of infection (i.e. exogenous infections). For example, in one specific outbreak with a persistently contaminated duodenoscope, 14.4% of all patients who underwent an ERCP were found to be colonised or infected.[8] Outbreaks can be traced by bacterial typing. Especially when MDRO strains are involved, detection is easier as laboratories usually store these resistant strains and (retrospective) typing can be performed. This raises the question whether outbreaks with duodenoscopes are a new and emerging problem, or whether outbreaks are only detected more frequently because of increased awareness facilitated by recognisable MDRO in patients.[3, 9]

During procedures in the gastrointestinal tract, all flexible endoscopes including duodenoscopes become heavily exposed to gastrointestinal flora.[10] Therefore flexible endoscopes are reprocessed after each procedure: a multistep process involving flushing, manual cleaning, automated cleaning, high-level disinfection and drying. Duodenoscopes are more difficult to reprocess compared to other flexible endoscopes.[10] This is due to their complex design, which includes a side viewing tip, forceps elevator and elevator channel. Patient-ready duodenoscopes can be contaminated because of breaches in the reprocessing protocol, inadequate handling or because the current technique of reprocessing may be inadequate for the currently available duodenoscope design.[11] Recent outbreaks have been documented to occur even when manufacturers' Instructions For Use (IFU) for reprocessing were followed to the letter.[2, 3, 9]

In the Netherlands, as in many other parts of the world, process control is used. This means that reprocessing is considered to be adequate when it is performed according to the IFU and according to the standard handbook of the Dutch Steering Group for Flexible Endoscope Cleaning and Disinfection (SFERD).[12] This handbook is based on regulations applicable in the Netherlands, as well as the guidelines of the European Society of Gastrointestinal Endoscopy (ESGE).[13] Despite international outbreaks and outbreaks in Dutch ERCP centres,[14, 15] both the IFU and SFERD do not include microbial surveillance after disinfection as a routine practice. Recently, contamination of duodenoscopes has

been assessed in several studies.[16-18] Most studies were performed in a single university centre,[16, 17] making it difficult to extrapolate their results and estimate the true burden on a national level. A study among 21 centres was conducted by Brandabur et al,[18] showing contamination rates with a wide variability across centres. To date no such study has been conducted in a nationwide setting using a uniform sampling and culture method as well as examining all possible contamination sites.

Given the increase in the number of publications pertaining duodenoscope contamination and the potentially severe consequences for patients, there is an urgency to develop a more thorough understanding of the scale of the problem. Therefore, the aim of this study was to determine the prevalence of microbial contamination of patient-ready duodenoscopes in all ERCP centres in the Netherlands.

Materials and methods

Setting

We conducted a prospective nationwide cross-sectional study amongst all Dutch ERCP centres. In the Netherlands, over 16.000 ERCP procedures are performed in 73 ERCP centres yearly.[19] All 73 Dutch ERCP centres were asked to sample at least two duodenoscopes at their own choosing and, if present, to include the newest Olympus TJF-Q180V (Olympus, Zoeterwoude, The Netherlands). Duodenoscopes were eligible for sampling if they were reprocessed and ready for patient use, e.g.: after high-level disinfection or after drying in the storage cabinet. No data was recorded about the moment of sampling, surveillance methods or adherence to reprocessing or sampling protocols. No patient data was included in this study; therefore there was no need for approval by the Medical Ethical Research Committee.

Sample collection

Sampling was performed independently by local staff of the included ERCP centres, using a centrally distributed sample collection kit, according to a strict and uniform sampling protocol (See online supplementary files). This method was developed by a multidisciplinary team of reprocessing staff, medical device experts, infection control professionals, medical microbiologists and gastroenterologists based on the SFERD standard handbook.[12] The sampling protocol was explained using twelve instruction videos available online (See online supplementary videos). As examples, the sampling and labeling procedure was shown in detail using one Olympus TJF-160VR and one Pentax ED34-i10T (Pentax, Dodewaard, The Netherlands) duodenoscope. Duodenoscopes were sampled while placed in the Automated Endoscope Reprocessor or on a sterile surface. Depending on the duodenoscopes type, four to six sites were sampled. The

four sites present in all duodenoscope types were; 1) a flush of the biopsy channel, 2) a flush of the suction channel, 3) a swab from the forceps elevator, 4) and a single brush through the biopsy and suction channel. Type dependent samples were; 1) a swab of the removable protection cap, 2) and a flush of the elevator channel or air/water channel, if these channels were unsealed. Channels were flushed with sterile physiological saline solution of which at least 20mL was collected at the distal tip in a sterile container. The flush fluid was aspirated with a sterile needle and injected in two 9.5mL BD Vacutainers without additives (Becton Dickinson, Etten-Leur, The Netherlands). Forceps elevator and protection cap were sampled with ESwabs (Copan Italia S.p.A., Brescia, Italy). Type dependent, Olympus BW-412T or Pentax CS6021T single-use endoscope cleaning brushes were used to brush the biopsy and suction channel. Both ESwabs and the brush tip were transported in ESwab medium. Instructions were to swab first, secondly to flush the channels and finally to brush the channels. The decision to reprocess the endoscope after sampling was up to the respective centres and was not documented for the purpose of the current study. Samples were sent to the Erasmus MC department of Medical Microbiology and Infectious Diseases for culturing.

Culturing and interpretation

Samples were cultured on the day of receipt. Channel flushes were filtrated over a 0.45 µm filter of which the filtrate was forced on R2A agar. ESwabs and brush tips were vortexed in their ESwab medium of which 0.75mL was poured on a blood agar. Samples were incubated at 35°C, examined for growth for 72 hours and read at 24h, 48h and 72h. Culture results were presented in Colony Forming Units (CFU)/20mL per microorganism. Results were sent to the respective ERCP centres without further interpretation: further action was up to the respective ERCP centre and was not documented for the purpose of the current study. At the time of study conduct, Dutch guidelines for endoscopy centres stated that in case of contamination with a subset of indicator microorganisms with ≥20CFU/20ml or in case of persistent contamination, endoscopes should be quarantined and possible causes be investigated.[12] Cultured microorganisms were categorised depending on their origin into gastrointestinal, oral, skin and waterborne flora. Contamination was defined according to 2 definitions: 1. microbial growth with ≥20CFU/20mL of any type of microorganism (AM20) as used by the ESGE guideline and Dutch SFERD handbook,[12, 13] or 2. presence of microbial growth (≥1CFU/20mL) of gastrointestinal and/or oral microorganisms (MGO).

Statistical analysis

Categorical data are presented in percentages. Mean (range) and median (interquartile range (IQR)) are given for continuous and skewed data respectively. The chi-square test was used to compare categorical data and Student's T-test or Mann Whitney U-test was used to compare continuous data. Contamination rates of duodenoscope types

and sample sites were compared according to a logistic regression model, using the SAS procedure GENMOD. This model adjusted for the multiple samples of each unique duodenoscope, with each duodenoscope clustered within their respective ERCP centre. Duodenoscope types were compared to the newest Olympus TJF-Q180V type as a reference and sample sites were compared to the flush of the biopsy channel. For both analyses, duodenoscope types or sample sites could be included if there was at least one contamination case and one non-contamination case. Analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA) and SPSS, version 21.0 (IBM Corp., Armonk, New York, USA).

Results

Between June 2015 and March 2016, 67 out of 73 (92%) Dutch ERCP centres sampled 745 sites of 155 endoscopes. Five endoscopes were excluded: four duodenoscopes from one centre whose samples were cultured in their own microbiology department and one gastroscope from another centre as this type of endoscope does not have a forceps elevator, that is, no duodenoscope (Figure 1). Twenty-six samples from 17 duodenoscopes were excluded, as these sites did not correspond with the specified duodenoscope type. This resulted in an inclusion of 150 duodenoscopes with a total of 701 samples from 66 (92% of all centres) ERCP centres (Figure 1). The median time between local sampling and culturing in the Erasmus MC was one day (IQR 1-2). Table 1 provides an overview of the contamination prevalence per duodenoscope type and sample site for AM20 and MGO contamination definitions. Contamination according to the AM20 definition was found in 33 (22%) out of the 150 reprocessed and patient-ready duodenoscopes. Duodenoscopes were most often contaminated with skin flora (n=17; 11%) and to a lesser extent with water-borne flora (n=12; 8%), gastrointestinal flora (n=10; 7%) or oral flora (n=4; 3%). Contamination according to the MGO definition was found in 23 (15%) duodenoscopes. Table 2 shows all different microorganisms that were cultured, among others E coli, K pneumoniae, and Pseudomonas aeruginosa.

Ten different duodenoscope types from three distinct manufacturers (i.e. Olympus, Pentax and Fujifilm) were sampled. Contamination as defined by AM20 was identified in five different duodenoscope types and contamination as defined by MGO was identified in four different types. As shown in figure 2, contamination for AM20 (four duodenoscope types included) as well as MGO (two duodenoscope types included) was shown not to be type dependent (all P values >0.05).

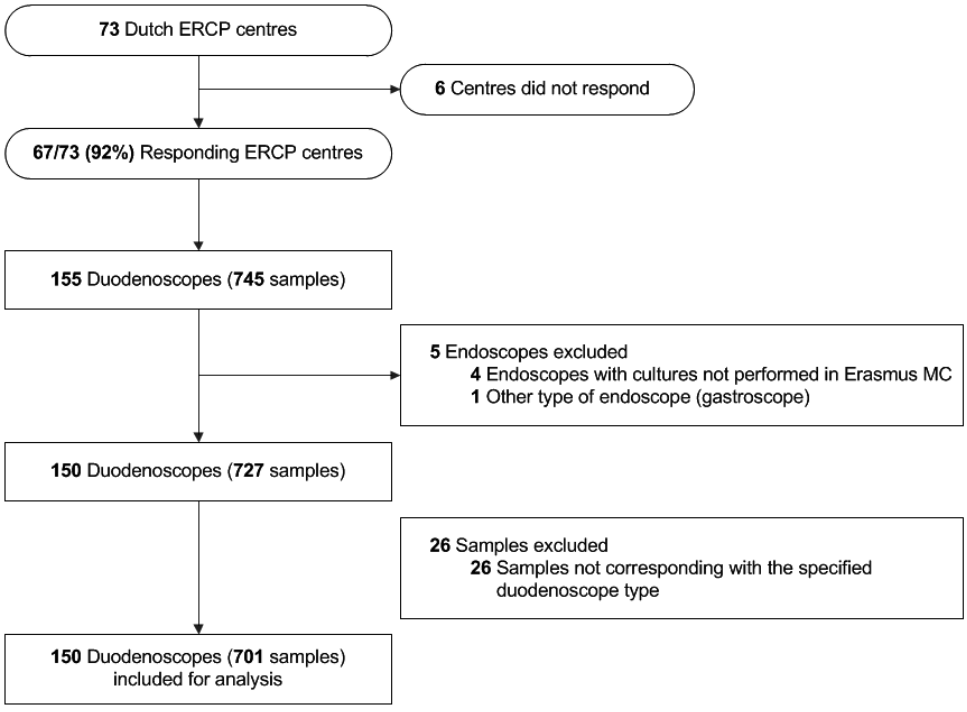

Figure 1. Flow diagram.

ERCP, Endoscopic Retrograde Cholangiopancreatography.

The AM20 contaminated duodenoscopes originated from 26 (39%) centres across the Netherlands. No difference (*P*=0.10) was shown in contamination prevalence between academic tertiary medical centres (n=3/8; 38%), specialised peripheral medical centres (n=13/23; 57%), or general peripheral medical centres (n=10/35; 29%). This was also the case for MGO contaminated duodenoscopes originating from 19 (28%) centres. No difference was found (*P*=0.25) between academic tertiary medical centres (n=3/8; 38%), specialised peripheral medical centres (n=9/23; 39%), and general peripheral medical centres (n=7/35; 20%).

Table 1. Prevalence of AM20 and MGO contamination for duodenoscopes and sample sites

Duodenoscope type	N	AM20		MGO	
		Contam.	Not contam.	Contam.	Not contam.
All duodenoscopes	150	33 (22%)	117 (78%)	23 (15%)	127 (85%)
Olympus TJF-Q180V	69	15 (22%)	54 (78%)	15 (22%)	54 (78%)
Olympus TJF-160VR	43	13 (30%)	30 (70%)	6 (14%)	37 (86%)
Olympus TJF-160R	8	1 (13%)	7 (87%)	0	8
Olympus TJF-140R	2	0	2	0	2
Olympus TJF-145	2	0	2	0	2
Pentax ED34-i10T	11	3 (27%)	8 (73%)	0	11
Pentax ED-3490TK	8	0	8	0	8
Pentax ED-3680TK	1	0	1	1 (100%)	0
Fujifilm ED-530XT8	5	0	5	0	5
Fujifilm ED-530XT	1	1 (100%)	0	1 (100%)	0
		AM20		**MGO**	
Sample site		Contam.	Not contam.	Contam.	Not contam.
All sample sites	701*	47 (7%)	654 (93%)	35 (5%)	666 (95%)
Biopsy channel	146	5 (3%)	141 (97%)	6 (4%)	140 (96%)
Suction channel	137	4 (3%)	133 (97%)	5 (4%)	132 (96%)
Forceps elevator	148	14 (10%)	134 (90%)	7 (5%)	141 (95%)
Brush	139	17 (12%)	122 (89%)	14 (10%)	125 (90%)
Protection cap	56	6 (11%)	50 (89%)	3 (5%)	53 (95%)
Elevator channel	53	0	53	0	53
Air/water channel	26	1 (5%)	21 (95%)	0	22

*Sampling of all possible sites would have yielded 745 samples: 44 (6%) sites were not sampled. This included 4/150 (3%) biopsy channel, 13/150 (9%) suction channel, 2/150 (1%) forceps elevator, 11/150 (7%) brush, 9/65 (13%) protection cap, 2/55 (4%) elevator channel and 3/25 (12%) air/water channel samples. AM20, Microbial growth with ≥20CFU/20mL of any type of microorganism; MGO, Presence of any microbial growth of gastrointestinal or oral microorganisms; Contam., contaminated. Not contam., not contaminated.

Microorganisms were cultured from 166 (24%) sample sites of 97 (65%) duodenoscopes. Additionally, 54 (8%) sample sites of 41 (27%) duodenoscopes contained two or more microorganisms, in some cases up to five different microorganisms. As shown in table 1, all sample sites, except the flush of the elevator channel were found positive for AM20 or MGO contamination. The flush of the biopsy channel was used as a reference to compare the contamination prevalence of all sample sites. Three sample sites had a higher probability of being contaminated (Figure 3). According to the AM20 definition the swab of the elevator (OR 2.93, 95% CI 1.13-7.61; *P*=0.03) and the swab of the protection cap (3.38, 95% CI 1.08-10.55; *P*=0.04) were more often contaminated. The brush of the biopsy/suction channel was more often contaminated for both AM20 (OR 3.87, 95% CI 1.13-7.61; *P*=0.006) and MGO (OR 2.64, 95% CI 1.14-6.14; *P*=0.02) definitions.

Table 2. Cultured microorganisms of 150 duodenoscopes.

Gastrointestinal flora independent of CFU count			Oral flora independent of CFU count		
	No. of duodenoscopes	**Quantity range**		**No. of duodenoscopes**	**Quantity range**
Yeasts	7	6 - 100 CFU	*Moraxella* spp.	4	1 CFU
Klebsiella pneumoniae	4	100 - >100 CFU	*Streptococcus salivarius*	4	1 – 15 CFU
Enterobacter cloacae	3	100 - >100 CFU	*Moraxella osloensis*	3	1 CFU – 100 CFU
Escherichia coli	2	50 and 100 CFU	*Streptococcus mitis*	2	30 and 50 CFU
Klebsiella oxytoca	2	100 CFU - >100 CFU	*Neisseria flavescens*	1	1 CFU
Enterococcus faecium	1	1 CFU	*Rothia* spp.	1	10 - 30 CFU
Enterococcus faecalis	1	100	*Streptococcus mutans*	1	2 CFU
Pseudomonas aeruginosa	1	100 CFU	*Streptococcus oralis*	1	5 CFU
Staphylococcus aureus	1	>100 CFU	*Streptococcus* spp.	1	10 CFU
	Skin flora ≥20 CFU			**Water-borne flora ≥20 CFU**	
	No. of duodenoscopes	**Quantity range**		**No. of duodenoscopes**	**Quantity range**
Bacillus spp.	5	40 - 100 CFU	*Stenotrophomonas maltophilia*	3	100 - >100CFU
Micrococcus luteus	5	100 CFU	*Acinetobacter* spp.	2	80 and 100 CFU
Staphyloccocus epidermidis	4	50 - 100 CFU	*Agrobacterium radiobacter*	2	20 and 100 CFU
Kocuria spp.	2	25 and 100 CFU	*Paraoccus yeeii*	2	30 and 100 CFU
Staphyloccocus hominis	2	25 and 100 CFU	*Achromobacter xylosoxida*	1	100 CFU
Staphyloccocus warneri	2	50 and 80 CFU	*Alternaria* spp.	1	>100 CFU
Kocuria rhizophila	1	>100 CFU	*Pseudomonas monteilii*	1	100 CFU
Micrococcus spp.	1	30 CFU	*Pseudomonas putida*	1	100 CFU
Staphyloccocus auricularis	1	>100 CFU	*Sphingomonas paucimobilis*	1	100 CFU
Staphyloccocus spp. (CNS)	1	60 CFU	*Rhizobium* spp. or *sphingobium* spp.	1	>100 CFU

CFU, colony forming units; CNS, coagulase – negative staphylococci

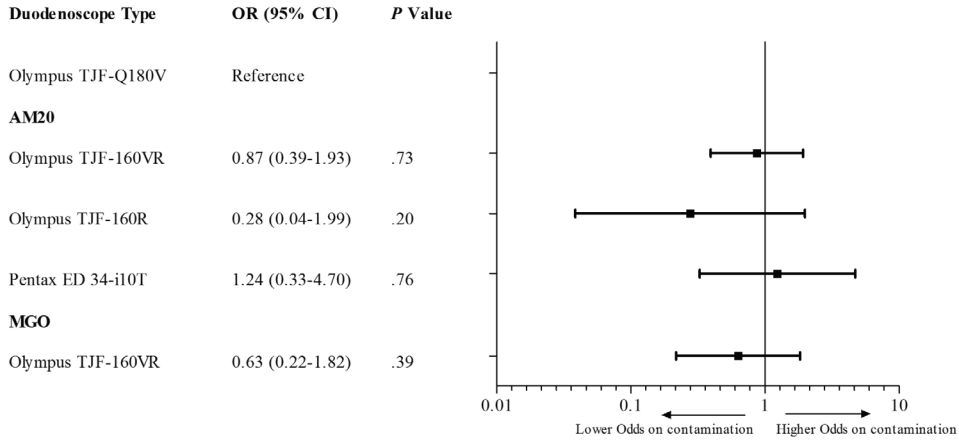

Figure 2. OR for each duodenoscope type on contamination.

Abbreviations: AM20, Microbial growth with ≥20CFU/20mL of any type of microorganism; CFU, colony forming units; MGO, presence of any microbial growth of gastrointestinal or oral microorganisms

DISCUSSION

In our nationwide prevalence study, we found that over one-fifth of sampled duodenoscopes were contaminated according to AM20 definition, with 39% of Dutch ERCP centres having at least one contaminated duodenoscope intended to be ready for patient use. Furthermore, MGO were cultured on 15% of the sampled duodenoscopes, indicating the presence of organic residue of previously treated patients. Our observations coincide with worldwide reported outbreaks indicating that exogenous transmission of bacteria and associated infections and even viral infections related to contaminated duodenoscopes continue to threaten patients undergoing ERCP.[1-4, 20] Therefore, stringent measures are required to lower the number of contaminated duodenoscopes in order to minimize the risk of interpatient microbial transmission during ERCP and to prevent future outbreaks.

The prevalence of duodenoscope contamination in this study was in line with reports from several retrospective single tertiary centre studies.[21-23] Recent studies by Brandabur et al and Ross et al performing post-procedure or everyday morning cultures reported remarkably lower contamination rates.[16, 18] This could be explained by the fact that continuous feedback of microbial surveillance resulted in a raised alertness, resulting in lower contamination rates over time. In the centres included in the present study it is not common practice to perform surveillance cultures, especially no daily or post-procedure cultures, as Dutch guidelines do not demand these.[12, 24] Other contributing factors could be differences in sampling and culture methods. For example, we used a

more sensitive contamination cut-off and a longer incubating time than Brandabur et al and Ross et al.[16, 18] The present study was conducted in 2015-2016 after multiple MDRO-outbreaks were reported (inter)nationally, including reports of outbreaks in Dutch ERCP centres as early as 2009 and 2012.[14, 15] Despite current national awareness about the potential consequences of contamination, our results were concordant with a cross-sectional multicentre (n=37) Canadian study published in 2002 in which a contamination prevalence of 30% was reported using a contamination cut-off of 10 CFU/mL.[25]

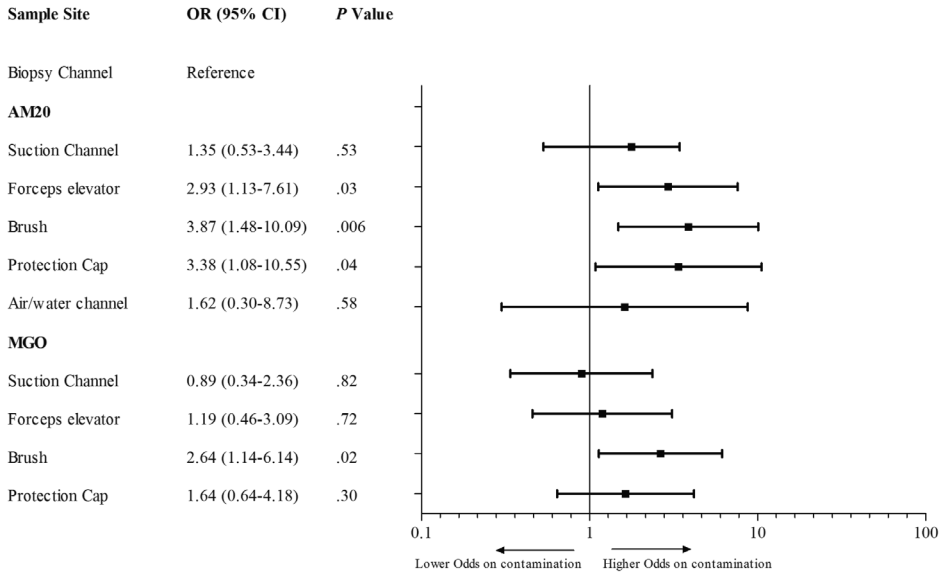

Figure 3. Odds ratio for each sample site on contamination.

Abbreviations: AM20, Microbial growth with ≥20CFU/20mL of any type of microorganism; MGO, Presence of any microbial growth of gastrointestinal or oral microorganisms; OR, odds ratio; 95%CI, 95% confidence interval.

The most recent duodenoscope types introduced into the market have distinct design changes, including sealing of the elevator channel and a sealed protection cap, aimed at preventing contamination and the need for reprocessing at these locations. In 2012, an outbreak in our hospital was linked to the newest Olympus TJF-Q180V duodenoscope.[2] After the outbreak, the duodenoscope was investigated by Olympus and an independent expert. One of the conclusions was that TJF-Q180V's specific design features hampered adequate cleaning and disinfection.[15] To further investigate these matters, we asked participating centres to include the TJF-Q180V duodenoscope, if present. The current study shows that contamination for both AM20 and MGO were not restricted to certain duodenoscope types. This is in line with outbreaks that have been reported involving various duodenoscope types from all three manufacturers.[6] More-

over, Brandabur et al also reported that culture positivity was not affected by scope type.[18] Despite differences in design, none of the available duodenoscope types seem excluded from the risk of contamination.

The differences in the type of cultured flora can give an indication where in the reprocessing process the duodenoscopes were contaminated. Several guidelines that advocate active microbiological surveillance give guidance on how to interpret culture results.[26, 27] In this study a substantial number of duodenoscopes were contaminated with skin and water-borne flora. Contamination with skin flora is thought to arise from handling and therefore could potentially easily be reduced by improved handling during reprocessing and transport. However, the presence of skin flora could be due to contamination during sampling. We cannot rule out this cause as sampling on site was not audited. Dutch centres have to use filtered water for reprocessing facilities and process control involves quarterly microbiological control of the rinse water.[12] In our view, persistent contamination with water-borne flora demands a thorough investigation as it can be caused by several factors, including contamination of the water supply, inadequate filtering of the water supply and inadequate drying of the endoscope during storage. Contamination with MGO indicates inadequate reprocessing as originating from the gastro-intestinal tract. This type of contamination could be due to a breach in the reprocessing procedure or because the reprocessing procedure cannot be adequately performed due to reprocessing, endoscopic or procedure specific risk factors. Currently, we are working on a Dutch guideline in which actions following positive cultures will be described extensively. The guideline will be submitted for international publication in the near future. Differences in Automated Endoscope Reprocessors, endoscope hang time and different reprocessing methods do not seem to affect contamination rates.[18, 28, 29] Beside the complex design of the duodenoscope,[2, 6, 30] endoscope age has also been suggested as a risk factor,[2, 21, 28] with Brandabur et al. proposing the number of procedures as a better indicator for endoscope usage.[18] Contamination does not seem to be confined to duodenoscopes: single center studies show that coloscopes and gastroscopes can have similar contamination rates.[21, 23] However, compared to duodenoscopes other gastrointestinal endoscopes are far less the reason of recent reported outbreaks.[5] We hypothesize that this could be due to differences between types of procedures as ERCP procedures tend to be more invasive, entering sterile body cavities and could have a more compromised patient population. The latter defines the more serious and therefore detectable clinical outcome of transmission of microorganisms by ERCP compared to other gastrointestinal endoscopes.

In the present study the brush, the forceps elevator and the protection cap had the highest probability of detection of contamination. The forceps elevator is a site known to be prone to persistent contamination.[2, 3, 16, 18] The brush is also noted as a site that can

harbour the involved microorganism during an outbreak.[16] Borescope channel inspections of gastro- and coloscopes performed by Ofstead et al, revealed that all reprocessed endoscope channels contained fluid, discoloration and debris.[31] This underlines that the biopsy channel is subject to heavy wear and tear: devices are introduced frequently, causing soiling of the channel which adds to the risk of contamination.[32] Remarkably, in the present study, the elevator channel was not contaminated in any duodenoscope and the air-/water channel in only one duodenoscope. Sampling of these specific channels is often not performed during surveillance and often not even in the case of an outbreak.[16]

In current guidelines and studies there is no international consensus on a uniform sampling and culturing method, although several differences could potentially affect culture outcomes. The location and the number of sample sites differ greatly: in some instances, a channel brush[21, 33] or swab of the forceps elevator[12, 25] is omitted. When the channel brush or the forceps elevator would not be cultured in the present series, 19% (6/32) or 9% (3/32), respectively, of the AM20 contaminated duodenoscopes would have been missed. Some studies and guidelines advocate a different order of sampling, such as retrograde sampling or the flush-brush-flush method, as it might have a higher sensitivity.[14, 26, 27, 34] The cleaning brush that is used for sampling could disrupt present biofilms and affect subsequent samples. However, in this study the brush sample was performed last. A sample flush with a neutralizer instead of saline solution can prevent false negative outcomes due to the biocidal activity of residual disinfectants, [35, 36] and is advocated by the French guideline and several French studies.[17, 21, 35, 37] The toxicity of the neutralizers might also cause false negatives, [38] and theoretically the endoscope should not contain any residual disinfectant after a successful reprocessing cycle. Other guidelines including the Dutch guideline, according to which our sampling protocol was designed, do not require a neutralizer based on current evidence.[12, 13, 26, 27] However, if a neutralizer effectively prevents false negative outcomes, the contamination rates in this study could be even higher. A longer incubation time is associated with a higher culture positivity rate. Saliou et al state that endoscope samples should be incubated for at least one week. In their study after 48h only 55.5% of the final number of contaminated endoscopes were found positive.[21] Some studies and guidelines use an incubation time of 48h.[16, 18, 26, 27] In this study we have chosen for a 72h period: the microorganisms of concern would be detected and the study results could by compared to the centres' previous microbiological surveillance results. Also the choice of growing media for incubation of flush samples can affect the culture positivity rate. R2A agar, as used in this study, has a high sensitivity, especially for slower growing microorganisms.[39, 40] To be able to compare test results and omit false negative test results, standardised and uniform instructions for sampling, culturing, and interpretation of culture results should

be devised which, based on results in this study, should include a channel brush and a swab of the forceps elevator as these sites pose the highest risk of contamination.

To the best of our best knowledge, this is the first study assessing contamination of duodenoscopes nationwide. Another strength of our study is that we cultured all samples in one microbiology laboratory using a standardised protocol. Finally, because of the extensive sampling method we were able to analyse all possible contamination sites. This study has some limitations. This study could only be conducted nationwide as a cross sectional study without follow-up samples of the duodenoscopes: improvement of contamination rates or persistent contamination was not assessed. Furthermore, sampling was conducted independently by local staff. Although we provided strict sampling protocols with clear video instructions on how the culture procedure should be performed, we were not able to check for adherence to the sampling protocol. Also the conditions in which the endoscopes were sampled (i.e. just disinfected, or after drying with or without alcohol flush or positive air flow) were not recorded. Potential differences in culture outcomes between sampling post-disinfection or post drying, differences in drying times or other storage or reprocessing parameters could not be assessed. However, all assessed duodenoscopes were ready for use in patients and should not be contaminated, regardless of the moment of reprocessing. We hypothesize that the effect of these factors on the presence of especially gastrointestinal and or oral flora is rather small as we see this as a failure of the reprocessing process. Lastly, a small amount of sites were not sampled, which could cause underestimation of the total number of contaminated duodenoscopes.

The observed nationwide high prevalence of contamination of patient-ready duodenoscopes is a clear indication that the current combination of reprocessing and process control is not sufficient. All participating hospitals are dedicated endoscopy centres following the national guideline that underlines process control. This includes reprocessing exactly according to the manufacturer's instructions and extensive yearly audits.[12, 24] As adherence to reprocessing protocols was not observed, this study shows real-life outcomes of patient-ready duodenoscopes with little bias. Regardless whether the precise cause of contamination was a breach in the reprocessing process or the complex duodenoscope design: process control was not able to identify and prevent such large scale inadequate reprocessing. This calls for concerted action by all parties involved i.e.: manufacturers, regulatory bodies, government agencies, gastroenterologists, and medical microbiologists. Nowadays, ERCP has evolved into a minimally invasive interventional procedure having replaced more invasive and complicated surgical procedures. It is an essential procedure practiced all over the world with over 650.000 procedures performed in the US annually.[41] During revision of the market clearance of the Olympus TJF-Q180V duodenoscope, the U.S. Food and Drug

Administration (FDA) stated that a decrease in ERCP capacity would be unacceptable.[42] However, contaminated duodenoscopes put patients at risk of developing clinically relevant infections by transmission of microorganisms.

In 2015, the FDA issued a warning that some parts of duodenoscopes may be extremely difficult to access and adequate cleaning of all areas may not be possible.[30] Since then additional measures have been suggested,[11] including alternative reprocessing methods or implementation of microbial surveillance as proposed by Centres for Disease Control and Prevention.[10, 33] Eventually, radical changes in the design of duodenoscopes should ensure thorough cleaning and disinfection. However, development and market introduction of such newly designed duodenoscopes will require substantial time. A complicating factor is that standardised procedures to test duodenoscopes in their ability to be adequately cleaned and disinfected are not available. Therefore, in the short term we should not solely rely on process control as there is no scientific proof that this serves as a reliable proxy for safe and clean duodenoscopes. Uniform guidelines and instructions for microbial surveillance should be developed. Also, an international registry for contaminated scopes should be instituted in order to truly estimate the scale of the problem and track its impact and revolution over time.

To conclude, this nationwide cross-sectional study shows high prevalence rates of contamination of duodenoscopes in Dutch ERCP centres. The recent reports on infections due to contaminated endoscopes will probably be due to involvement and alertness on highly resistant micro-organisms, but also the more and more complex designs of endoscopes can play a role in this emergence. Additional preventive measures including microbial surveillance strategies are needed to reduce the number of contaminated duodenoscopes.

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CHAPTER
5

Nationwide Risk Analysis of Duodenoscope and Linear Echoendoscope Contamination

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Introduction

Worldwide, a rising number of reports describe outbreaks of multidrug-resistant organisms (MDRO) caused by contaminated duodenoscopes.[1-6] Duodenoscopes are used for endoscopic retrograde cholangiopancreatography (ERCP) procedures, of which approximately 650,000 are performed in the United States annually.[7] Contaminated duodenoscopes and the subsequent outbreaks are commonly detected by transmission of MDRO bearing distinct features that enable retrospective tracing. Often, these outbreaks are not properly reported, registered and/or communicated by manufacturers, hospitals and governmental bodies.[1, 2, 4] Although 400 patient infections and 20 deaths are officially reported between 2012-2017,[1, 2, 7] the actual number of patients affected by transmission of exogenous microorganisms and the corresponding burden of disease, is likely to be much higher.[1]

Patients undergoing ERCP are exposed to exogenous microorganisms when duodenoscopes are not properly cleaned, and therefore remain contaminated. Recent studies show that duodenoscope contamination incidences range from 0.3% to 30%.[8-14] The first nationwide PROCESS (Prevalence of contamination of complex endoscopes in the Netherlands) study showed that 15% of the patient-ready duodenoscopes were contaminated with gastrointestinal or oral microorganisms, i.e. bacteria originating from previous patients.[15] Contamination of reprocessed duodenoscopes is attributed to their complex design; which includes a side viewing tip, forceps elevator and elevator wire channel.[16] Linear echoendoscopes, used for endoscopic ultrasound (EUS) procedures, have a similarly complex design with an additional balloon channel. As several studies reported contamination of linear echoendoscopes,[9, 17] it raises the question if duodenoscopes and linear echoendoscopes (DLEs) have a similar contamination prevalence at a nationwide level.

The margin of safety of endoscope reprocessing is very small and does not leave any room for error.[18-21] In clinical practice however, reprocessing procedures are error-prone and adequate decontamination is not guaranteed.[15, 22-28] Large multicenter studies show that contamination is independent of duodenoscope manufacturer,[9, 15] type,[15] or endoscope age;[9] implying that all DLEs seem to have a similar risk for contamination. Risk factors for DLE contamination and potential subsequent interventions are still unknown, and require additional investigation. Therefore, we conducted a second nationwide study, the PROCESS 2 study, to (re-)assess the level of contamination of DLEs. We combined the data of the PROCESS 1 and 2 studies to identify potential DLE and reprocessing risk factors for contamination of DLE.

Materials and methods

Setting and design

We conducted two prospective nationwide cross-sectional studies among the 74 Dutch centers using DLEs: the PROCESS 1 and 2 studies. While the prevalence data from PROCESS 1 has been published,[15] the data on endoscope age and usage has not been published before. During PROCESS 1 we invited centers to sample at least two reprocessed duodenoscopes and to include the newest Olympus TJF-Q180V (Olympus, Zoeterwoude, The Netherlands) as one of the two duodenoscopes if possible. During PROCESS 2 we invited centers to sample all reprocessed DLEs present at the endoscopy department.

Reprocessing, the multistep process of post-procedure flushing, manual cleaning, automated cleaning, high-level disinfection (HLD) and drying, was performed according to each endoscope's Instructions for Use (IFU) and according to the standard handbook of the Dutch Steering Group for Flexible Endoscope Cleaning and Disinfection (SFERD).[29] At the time of the PROCESS studies, microbiological surveillance was only recommended after repairs,[29] but centers could perform routine surveillance on their own initiative. No patient data or patient samples were collected and/or included in this study; therefore there was no need for approval by the Medical Ethical Research Committee.

Sample collection and culture methods

The sampling, culturing and interpretation methods were the same for both studies and described extensively for PROCESS 1 (See online supplementary files).[15] In PROCESS 2, we provided additional sampling protocols for linear echoendoscopes which included sampling of the balloon channel (See online supplementary files). Contamination was defined as: (i) microbial growth with ≥20CFU/20mL of any type of microorganism (AM20) as used by the then current ESGE guideline and Dutch SFERD handbook,[29, 30] or (ii) presence of microbial growth (≥1CFU/20mL) of gastrointestinal and/or oral microorganisms (MGO).

Risk factors for contamination

Data on endoscope age and usage were recorded using questionnaires for both PROCESS studies. For PROCESS 2 an extended set of DLE and reprocessing factors was recorded. Age was defined as the time between the date of purchase of the endoscope and the sampling date. Usage was defined as the number of procedures for which the endoscope was used since the date of purchase until the date of sampling. Only first-hand purchased endoscopes with usage registries at the time of purchase were included, but not second-hand endoscopes, loan endoscopes and endoscopes whose usage was not recorded directly from the construction date. Risk factors recorded for

PROCESS 2 included: biopsy channel replacement, reprocessing characteristics (manual cleaning detergent, automated cleaning detergent, disinfectant and type of automated endoscope reprocessor (AER)), moment of sampling (drying cabinet or AER), and microbiological surveillance frequency.

Statistical analysis

Categorical data were presented in percentages. Mean (standard deviation) and median (interquartile range (IQR)) were given for continuous and skewed data respectively. Contamination rates were analyzed by multilevel logistic regression. This modeling technique allowed to take into account the hierarchical structure of the data (and the correlation between measurements possibly caused by it): samples were taken at multiple locations per DLE, DLEs could be investigated in both PROCESS studies, and DLEs were grouped within their respective centers.

Using PROCESS 2 data we assessed reprocessing characteristics. Variant types of each reprocessing characteristic could be included if there was at least one contamination case and one non-contamination case. The most frequently observed category was used as a reference. If possible, we categorized different factors to enable analysis of groups with larger power. Odds ratios with 95% confidence intervals (CI) were calculated for each characteristic. To correct for the increased possibility of a type I error as a result of testing in multiple subsets using two outcome definitions we applied the Bonferroni correction, giving $\alpha=0.05/10=0.005$.

We pooled data from both PROCESS studies to analyze the factors endoscope age and usage. The model was adjusted for the factors age and usage while analyzing duodenoscopes and linear echoendoscopes separately. In a second analysis using data from PROCESS 2 only, age and usage were reset if the biopsy channel was replaced. Odds ratios with 95% confidence intervals were calculated per year and per 100 procedures. We applied the Bonferroni correction for the increased possibility of a type I error as a result of using both AM20 and MGO as outcome definitions, giving $\alpha=0.05/2=0.025$. We performed analyses in SPSS V21.0 (Chicago, Illinois, USA) and in R V3.4.1 (Vienna, Austria) using the package lme4.[31]

Role of the funding source

A grant of the Dutch Ministry of Health funded the PROCESS studies. The funder was not involved in any part of this study, including study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Section I: PROCESS 2

The PROCESS 2 study was conducted between October 2016 and May 2017 in a total of 61 of the 73 (84%) centers in the Netherlands performing ERCP and/or EUS procedures during this time period. Across these 61 centers, a total of 159 duodenoscopes and 64 linear echoendoscopes were included in the study. Contamination according to the AM20 definition was found on 21 (13%) duodenoscopes and 8 (13%) linear echoendoscopes (Table 1), originating from 20 (33%) centers (Supplementary table 1). Prevalence rates per contamination category are shown in supplementary table 2. Contamination according to the MGO definition was found on 24 (15%) duodenoscopes and 9 (14%) linear echoendoscopes, originating from 24 (39%) centers. The median age and usage were 5.5 (2.7-6.7) years and 266 (162-532) procedures for duodenoscopes, and 3.6 (1.3-5.8) years and 270 (128-443) procedures for linear echoendoscopes (Table 2). In 30% of the DLEs the biopsy channel was replaced (40 (30%) duodenoscopes and 16 (30%) linear echoendoscopes). Table 3 shows the adapted age and usage which was reset to zero in case of biopsy channel replacement.

Table 1. PROCESS 1 and 2: Prevalence of AM20 and MGO contamination

	PROCESS 2			PROCESS 1*			PROCESS 1&2 pooled		
	N	**AM20**	**MGO**	**N**	**AM20**	**MGO**	**N**	**AM20**	**MGO**
All DLE							373	62 (17%)	56 (15%)
Duodenoscopes	159	21 (13%)	24 (15%)	150	33 (22%)	23 (15%)	309	54 (17%)	47 (15%)
Olympus									
TJF-Q180V	68	9 (13%)	8 (12%)	69	15 (22%)	15 (22%)	137	24 (18%)	23 (17%)
TJF-160VR	45	6 (13%)	6 (13%)	43	13 (30%)	6 (14%)	88	19 (22%)	12 (14%)
TJF-160R	6	1 (17%)	1 (17%)	8	1 (13%)	0	14	2 (14%)	1 (7%)
TJF-140R	1	0	1	2	0%	0	3	0	1 (33%)
TJF-145	-	-	-	2	0%	0	0	0	0
Pentax									
ED34-i10T	14	0	2 (14%)	11	3 (27%)	0	25	3 (12%)	2 (8%)
ED-3490TK	11	3 (27%)	3 (27%)	8	0	0	19	3 (16%)	3 (16%)
ED-3680TK	-	-	-	1	0	1	1	0	1
Fujifilm									
ED-530XT8	7	1 (14%)	2 (29%)	5	0	0	12	1 (8%)	2 (17%)
ED-530XT	7	1 (14%)	1 (14%)	1	1	1	8	2 (25%)	2 (25%)
Linear echoendoscopes	64	8 (13%)	9 (14%)						
Olympus									
GF-UCT180	28	4 (14%)	5 (18%)						
GF-UCT140-AL5	3	0	0						
GF-UCT140P-AL5	1	0	0						
Pentax									
EG-3870UTK	17	3 (18%)	3 (18%)						
EG-3270UK	10	1 (10%)	1 (10%)						
FG-36UX	1	0	0						
Fujifilm									
EG-580UT	4	0	0						

*PROCESS 1 contamination results have been published before.[15] DLE, duodenoscopes and linear echoendoscopes; AM20, Microbial growth with ≥20CFU/20mL of any type of microorganism; MGO, Presence of any microbial growth of gastrointestinal or oral microorganisms.

Table 2. PROCESS 1 and 2: Age and usage

	N	All endoscopes	AM20		MGO	
			Contam.	Not contam	Contam.	Not contam.
Duodenoscopes PROCESS 2						
Age	148	5.5 (2.7-6.7)	5.7 (5.0-7.1)	5.3 (2.5-6.7)	6.3 (4.8-7.2)	5.3 (2.5-6.7)
Usage	118	266 (162-532)	257 (196-614)	269 (138-530)	344 (212-590)	260 (149-520)
PROCESS 1						
Age	142	4.4 (2.2-6.6)	4.9 (3.6-7.0)	4.2 (2.1-6.6)	4.4 (2.7-7.1)	4.4 (2.1-6.6)
Usage	111	180 (88-385)	400 (88-701)	175 (88-349)	279 (94-530)	175 (88-373)
PROCESS 1&2 pooled						
Age*	290	4.9 (2.5-6.7)	5.4 (3.7-7.1)	4.7 (2.2-6.7)	5.6 (3.4-7.1)	4.9 (2.2-6.6)
Usage*	229	231 (105-450)	287 (130-670)	228 (101-441)	282 (282-567)	230 (101-445)
Linear echoendoscopes PROCESS 2						
Age**	58	3.6 (1.3-5.8)	5.6 (0.8-6.5)	3.5 (1.3-5.7)	2.9 (1.8-4.9)	3.7 (1.3-6.0)
Usage**	50	270 (128-443)	405 (34-841)	243 (134-424)	305 (147-411)	250 (112-450)

Age presented in years (median; IQR); Usage presented in number of procedures (median, IQR). AM20, Microbial growth with ≥20CFU/20mL of any type of microorganism; MGO, Presence of any microbial growth of gastrointestinal or oral microorganisms; Contam., contaminated; Not contam., not contaminated.

*Information on age was missing of 19 (6%) duodenoscopes; on usage of 80 (26%) duodenoscopes.
**Information on age was missing of 6 (9%) linear echoendoscopes; on usage of 14 (22%) linear echoendoscopes.

Table 3. PROCESS 2: Age and usage reset in case of biopsy channel replacement

	N	All endoscopes	AM20		MGO	
			Contam.	Not contam.	Contam.	Not contam.
Duodenoscopes*						
Replaced biopsy channel	40		8 (20%)	32 (80%)	9 (23%)	31 (77%)
Original biopsy channel	95		9 (10%)	86 (90%)	12 (13%)	83 (87%)
Age**	132	3.4 (1.4-6.0)	4.7 (1.6-6.0)	3.4 (1.4-6.0)	4.7 (1.4-6.3)	3.4 (1.4-5.8)
Usage**	109	203 (61-440)	213 (38-362)	200 (64-447)	219 (31-510)	197 (63-437)
Linear echoendoscopes*						
Replaced biopsy channel	16		3 (19%)	13 (81%)	2 (13%)	14 (87%)
Original biopsy channel	38		4 (11%)	34 (89%)	6 (16%)	32 (84%)
Age**	51	2.4 (1.1-4.2)	1.5 (0.4-5.1)	2.5 (1.1-4.1)	2.4 (1.7-3.9)	2.5 (0.9-4.9)
Usage**	42	188 (61-386)	55 (34-515)	198 (75-378)	305 (147-411)	163 (43-378)

Age presented in years (median; IQR); Usage presented in number of procedures (median, IQR). AM20, Microbial growth with ≥20CFU/20mL of any type of microorganism; MGO, Presence of any microbial growth of gastrointestinal or oral microorganisms; Contam., contaminated; Not contam., not contaminated. *Information on biopsy channel replacement was only recorded during PROCESS 2 and was missing in 24 (15%) duodenoscopes and 10 (16%) linear echoendoscopes. ** Age and usage were reset to zero on the date of the biopsy channel replacement if the channel was replaced.

Reprocessing characteristics

Reprocessing characteristics, assessed only during PROCESS 2, are shown in Table 4. In the included Dutch centers (n= 61), over 50% of the 217 DLEs we cleaned and disinfected with Neodisher products (Dr. Weigert, Assen, The Netherlands), and 48% were disinfected in Wassenburg AERs (Wassenburg Medical, Dodewaard, The Netherlands). Contamination rates of AM20 and MGO for DLEs did not depend on the different reprocessing characteristics (Table 4, all *P* values ≥0.01). This outcome did not change when the detergents and disinfectants were categorized into two groups (i.e. detergents in alkaline and non-alkaline variants, and disinfectants in peracetic acid (PAA) or glutaraldehyde (all *P* values ≥0.22)). In total 138 (63%) DLEs of 30 (51%) centers were subject to surveillance cultures, of which 106 (48%) of the DLEs were sampled monthly or quarterly. Contamination, however, was not shown to be surveillance dependent (all *P* values ≥0.41).

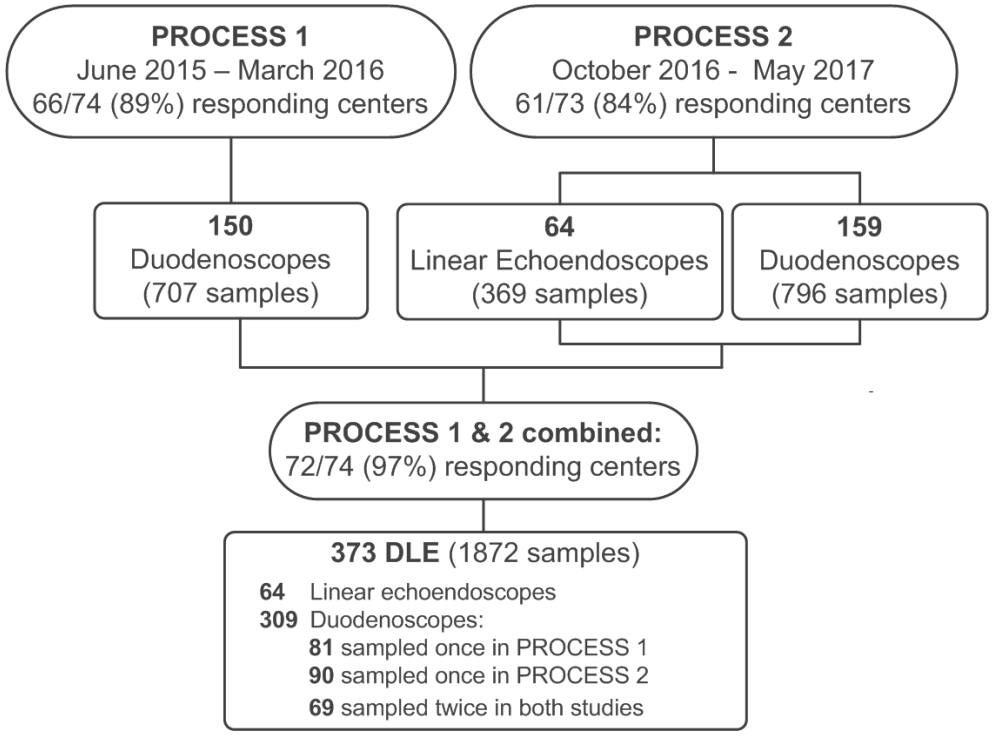

Figure 1. Flow diagram.

PROCESS, Prevalence of contamination of complex endoscopes in the Netherlands; DLE, duodenoscopes and linear echoendoscopes.

Section II: PROCESS 1

PROCESS 1 was conducted between June 2015 and March 2016.[15] In total 66 out of the 74 (89%) eligible centers during this time period participated in the Netherlands. The centers included in total 150 duodenoscopes. We have presented the contamination prevalence results (AM20: 22% (n=33); MGO: 15% (n=23)) of these duodenoscopes in a previous publication.[15] The endoscope age and usage data of PROCESS 1 as shown in Table 2 has not been presented before. The duodenoscopes had a median age of 4.4 (2.2-6.6) years and had been used for a median of 180 (88-385) procedures.

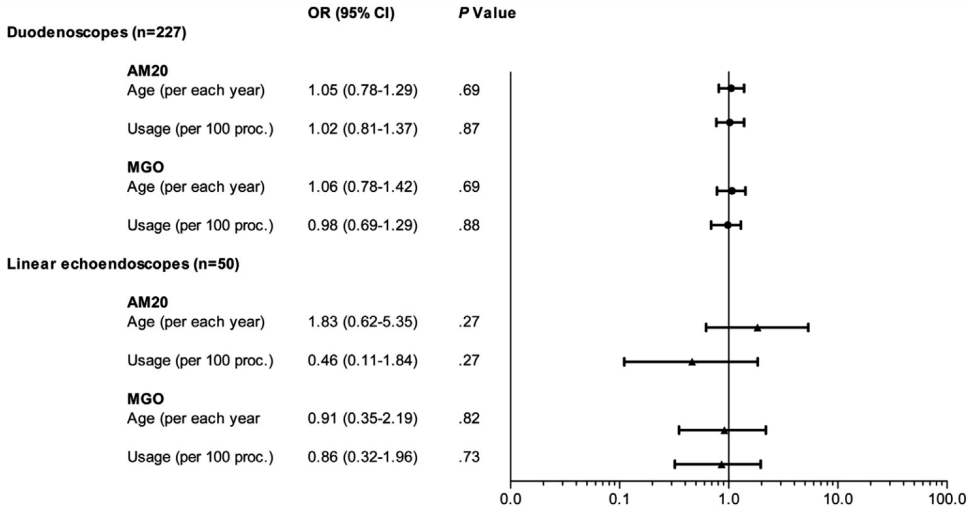

Figure 2. PROCESS 1 and 2: OR for age and usage on AM20 and MGO contamination in DLEs.

Analysis of age and usage using pooled data from PROCESS 1 and 2. DLE, duodenoscopes and linear echoendoscopes; AM20, microbial growth with ≥20 colony forming units/20 mL of any type of microorganism; MGO, presence of any microbial growth of gastrointestinal or oral microorganisms.

Section III: age and usage

PROCESS 1 and 2: pooled data

Overall, 97% (72/74) of all eligible Dutch centers participated in at least one of the two studies. In the PROCESS 1 and 2 studies pooled together 373 DLEs were included and tested, consisting of 309 (83%) duodenoscopes and 64 (17%) linear echoendoscopes. Eighty-one duodenoscopes were tested only once in PROCESS 1, 90 duodenoscopes were tested only once in PROCESS 2, and 69 duodenoscopes originating from 36 centers were tested in both PROCESS studies (Figure 1). Ten different duodenoscope and seven linear echoendoscope types were included from three distinct manufacturers (i.e. Olympus, Pentax and Fujifilm). In total 1866 sites were sampled (Supplementary Table 3). Table 1 shows the contamination prevalence of the pooled duodenoscopes (AM20: 17% (n=54); MGO: 15% (n=47)) and all DLE collectively (AM20: 17% (n=62); MGO: 15% (n=56)). The contaminated DLE originated from 48 (67%) centers (supplementary table 1). The analysis of the pooled data from both PROCESS studies showed that contamination by AM20 and MGO in both duodenoscopes and linear echoendoscopes were not age or usage dependent (all *P* values ≥0.27, Figure 2).

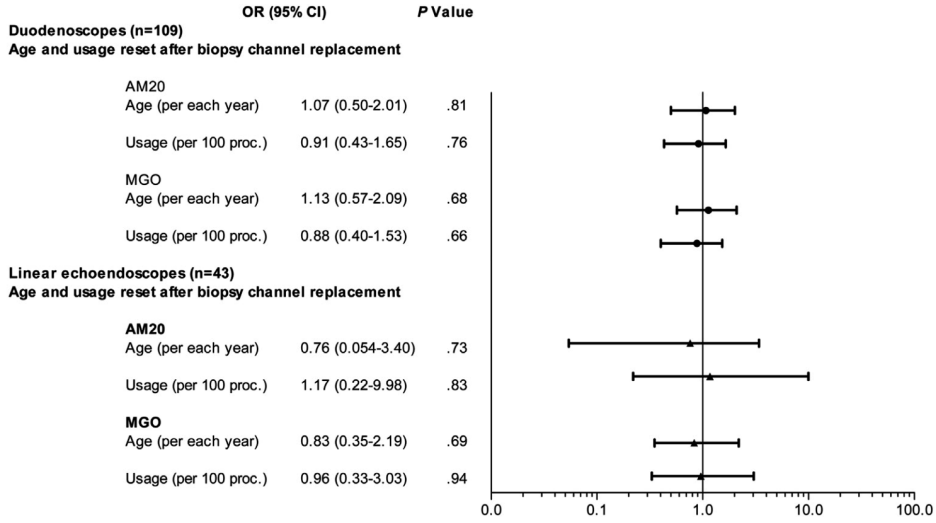

Figure 3. PROCESS 2: OR for reset age and usage on AM20 and MGO contamination in DLEs with information on biopsy channel replacement. Analysis of reset age and usage using data from PROCESS 2. DLE, duodenoscopes and linear echoendoscopes; AM20, microbial growth with ≥20 CFU/20 mL of any type of microorganism; CFU, colony forming units; MGO, presence of any microbial growth of gastrointestinal or oral microorganisms.

PROCESS 2: reset age and usage

Analysis of reset age and usage using data from PROCESS 2 only did not demonstrate contamination was age or usage dependent (all *P* values ≥0.66, Figure 3).

Discussion

In the PROCESS 1 and 2 studies, we found that contamination of DLEs according to the MGO and AM20 definitions was independent of endoscope age and usage. These results suggest that older and heavier used DLEs, if maintained correctly, have a similar risk for contamination as brand-new DLEs. Furthermore, the high MGO contamination prevalence of ~15% was comparable for duodenoscopes and linear echoendoscopes, rendering both patients undergoing ERCP as well as EUS at risk for transmission of microorganisms. These results are in line with previous reports showing that duodenoscopes of all manufacturers and types can be a source for outbreaks.[1, 2] Our results also support the notion that outbreaks are inevitable when current-design DLEs are processed using error-prone reprocessing procedures with an insufficient margin of safety. Effective control measures, such as feasible sterilization instead of disinfection, and eventually radical redesign of DLEs are required.

In the current study we found that contamination was not age or usage dependent. Other studies, including a large multicenter study, also found that contamination was not age-dependent,[9, 32] although in two single-center studies contamination of gastrointestinal endoscopes was either age or usage associated.[10, 33] DLEs are subject to heavy wear and tear including 1) repeated bending of the vulnerable distal end, 2) damage caused by endoscope accessories (e.g. forceps or baskets), and 3) mechanical as well as chemical strain by each reprocessing cycle. Undetected damage in duodenoscopes is known to cause outbreaks.[8, 34, 35] Recent borescope studies show that biopsy channels are frequently damaged,[36-38] which adds to the risk of contamination.[39] In this study, adequate and timely servicing is a plausible explanation as to why older and more often used DLEs had the same risk of contamination as brand-new endoscopes. Fujifilm, Olympus and Pentax recently recommended yearly technical inspections in their IFU for specific duodenoscope types, [40-43] as is required by the Dutch guidelines.[44] However, time-based inspections still do not give clear guidance as yearly usage varies greatly between DLE (PROCESS studies median yearly usage: 65(41-109 IQR) procedures, similar to usage reported in other studies).[32] Therefore, manufacturers should assess the possibility of usage-based maintenance and inspections and their impact on the prevention of contamination.

Table 4. PROCESS 2: Reprocessing characteristics

	N	AM20			MGO		
		Contam.	Not contam.	P-value	Contam.	Not contam.	P-value
Manual cleaning detergent	217*						
Neodisher MediClean Forte[a,e]	145	23 (16%)	122 (84%)	Ref.	27 (19%)	118 (81%)	Ref.
Neodisher endo Clean[a,e]	33	2 (6%)	31 (94%)	.47	2 (6%)	31 (94%)	.38
Neodisher endo DIS active[a,e]	4	0	4		1 (25%)	3 (75%)	.89
Neodisher Mediclean[a,e]	4	0	4		0	4	
Neodisher Steelco[a,e]	4	2 (50%)	2 (50%)	.37	0	4	
Medivators Intercept Detergent	11	1 (9%)	10 (91%)	.68	1 (9%)	10 (91%)	.60
Dr. Peppe Instru Zym[e]	7	0	7		0	7	
Wassenburg EndoHigh Detergent[a,e]	5	1 (20%)	4 (80%)	1.0	1 (20%)	4 (80%)	.93
Olympus EndoDet	4	0	4		0	4	
Automated cleaning detergent	216*						
Neodisher MediClean Forte	81	10 (12%)	71 (88%)	Ref.	12 (15%)	69 (85%)	Ref.
Neodisher endo Clean	42	3 (7%)	39 (93%)	.66	1 (2%)	41 (98%)	.33
Neodisher SC	9	2 (22%)	7 (78%)	.65	1 (11%)	8 (89%)	.87
Getinge Poka-Yoke DLC	30	7 (23%)	23 (77%)	.30	10 (33%)	20 (67%)	.14
Olympus EndoDet	35	5 (14%)	30 (86%)	.81	5 (14%)	30 (86%)	.81
Medivators Intercept Detergent	11	1 (9%)	10 (91%)	.82	1 (9%)	10 (91%)	.73

Wassenburg EndoHigh Detergent	8	1 (13%)	7 (88%)	.96	1 (13%)	7 (88%)	.89
Disinfectant	220*						
Neodisher endo SEPT PAC	65	9 (14%)	56 (86%)	Ref.	9 (14%)	56 (86%)	Ref.
Neodisher endo SEPT GA	45	4 (9%)	41 (91%)	.60	2 (4%)	43 (96%)	.38
Neodisher Septo DN (GA)	16	2 (13%)	14 (88%)	.95	1 (6%)	15 (94%)	.61
Getinge Aperlan Poka-Yoke (PAA)	30	7 (23%)	23 (77%)	.40	10 (33%)	20 (67%)	.14
Olympus PAA	35	5 (14%)	30 (86%)	.95	5 (14%)	30 (86%)	.79
Olympus GA	4	0	4		1 (25%)	3 (75%)	.85
Medivators Rapicide PAA	15	1 (7%)	14 (93%)	.63	3 (20%)	12 (80%)	.84
Wassenburg EndoHigh PAA	5	0	5		0	5	
Wassenburg EndoHigh GTA	5	1 (20%)	4 (80%)	.81	1 (20%)	4 (80%)	.81
AER	220*						
Wassenburg WD440 PT	68	8 (12%)	60 (88%)	Ref.	8 (12%)	60 (88%)	Ref.
Wassenburg WD440	38	4 (11%)	34 (89%)	.93	2 (5%)	36 (95%)	.40
Getinge ED-FLOW	24	7 (29%)	17 (71%)	.11	9 (38%)	15 (62%)	.01
Getinge Poka-Yoke AER	6	0	6		1 (17%)	5 (83%)	.86
Olympus ETD3	21	5 (24%)	16 (76%)	.35	5 (24%)	16 (76%)	.16
Olympus ETD Double	11	0	11		1 (9%)	10 (91%)	.82
Olympus ETD4+	7	0	7		0	7	
Steelco EW2	19	2 (11%)	17 (90%)	.96	2 (11%)	17 (90%)	.90
Steelco EW1	3	1 (33%)	2 (67%)	.40	1 (33%)	2 (67%)	.27
Belimed WD 430	8	1 (13%)	7 (87%)	.95	0	8	
Medivators Advantage Plus	11	1 (9%)	10 (91%)	.83	1 (9%)	10 (91%)	.77
Medivators	4	0	4		2 (50%)	2 (50%)	.21
Moment of sampling	216*						
Storage cabinet	196	28 (14%)	168 (86%)	Ref.	31 (16%)	165 (84%)	Ref.
AER	20	1 (5%)	19 (95%)	.58	2 (10%)	18 (90%)	.72
Surveillance cultures	219*						
Only in case of an incident	81	15 (19%)	66 (81%)	Ref.	15 (19%)	66 (81%)	Ref.
At least 1x per month	51	4 (8%)	47 (92%)	.48	7 (14%)	44 (86%)	.80
Every 2 or 3 months	55	10 (18%)	45 (82%)	.87	9 (16%)	46 (84%)	.91
Every 6 or 12 months	32	0	32	-	2 (6%)	30 (94%)	.41

DLE, duodenoscopes and linear echoendoscopes; AM20, Microbial growth with ≥20CFU/20mL of any type of microorganism; MGO, Presence of any microbial growth of gastrointestinal or oral microorganisms; Contam., contaminated; Not contam., not contaminated; AER, automated endoscope reprocessor; [a], detergent with alkaline boosters; [e], detergent with enzymatic boosters; PAC or PAA, peracetic acid; GA, glutaraldehyde; ref, reference. *Information on reprocessing characteristics was only recorded during PROCESS 2.

As adequate preventive maintenance and servicing potentially resets the endoscope, the physical age and cumulative usage might not represent the actual state of the endoscope. Biopsy channel replacement potentially represent the most important part of endoscope maintenance. This channel is subject to heavy wear,[36-38] often replaced during repairs, and frequently contaminated (MGO contamination in the PROCESS studies: biopsy channel flushes 5%, brush samples 8%). However, using PROCESS 2 data with biopsy channel replacement as a surrogate marker for servicing, reset-age and reset-usage were also not associated with contamination. Biopsy channel replacement might not capture the whole story of complex repair histories as the PROCESS studies show that every DLE sampling site can harbor microorganisms. To assess usage as a contamination risk factor, future studies should potentially take the entire servicing history of an endoscope into account.

Guidelines and in-vitro studies indicate potential differences in efficacy between detergents,[45-49] disinfectants,[48, 50, 51] and AERs.[52] In the current study contamination was not shown to be dependent on reprocessing characteristics, which is in line with another multicenter study.[9] Instead of the assessed reprocessing factors, in our opinion the variable manual cleaning step has the greatest impact on the reprocessing outcome. This is additionally complicated by other factors, including the complex DLE design, endoscope damage and biofilm development. We also found that hospitals use different brands of detergents, disinfectants and AERs together. Compatibility between these products and with differing endoscopes is essential. In 2015, 2800 Custom Ultrasonics AERs (~20% of all USA AERs) had to be recalled when it became clear they were not compatible with closed-elevator channel endoscopes, as this led to inconsistencies in duodenoscope disinfection and potentially contributed to outbreaks.[1] Transparent communication of adverse events by manufacturers of endoscopes and reprocessing equipment is essential. Furthermore, new reprocessing measures should be subject to peer-reviewed validation tests while ensuring compatibility with DLEs with adjusted designs.

Using the contamination definition for high-concern organisms by the Centers for Disease Control and Prevention the contamination prevalence for DLE was 8% in this study, similar to the interim results of the postmarket surveillance studies ordered by the US Food and Drug Administration.[53] Recent studies assessing surveillance, [9, 13, 17, 53] culture and quarantine strategies,[8, 9, 54, 55] double HLD,[14, 56] and ethylene oxide (EtO) sterilization[11] have promising lower contamination rates, showing that reduction of contamination is feasible. In addition to the assessed interventions, the lower rates may also be the result of continuous feedback and raised alertness by the studies' culture results,[9, 14, 55, 56] or less sensitive sampling and culture methods. By not sampling all potential sites (e.g. not including a channel brush[54, 55] or channel flushes[14]), incubating cultures for only

48 hours,[14, 54, 56] or focusing only on carbapenem-resistant Enterobacteriaceae as the primary outcome,[11] contaminated endoscopes can be deemed false-negative, while still being a vector for transmission with subsequent infection. In our opinion, interventional measures should focus on the reduction of all MGO. During PROCESS 2, 60% of the centers used a form of microbiological surveillance, however contamination was not shown to be associated with surveillance. This is in line with reported outbreaks that occurred in settings where surveillance cultures were repeatedly negative.[3, 57-60] Although microbiological surveillance will not entirely prevent contamination, it is essential for the identification of persistently contaminated DLEs. As the other proposed measures require extensive financial investments, their value should be proven using sensitive culturing methods in a blinded and preferably multicenter setting before widespread implementation can be definitely recommended.

During both PROCESS studies 15% of the endoscopes were contaminated with MGO, indicating organic residue of previous patients. This suggests that reprocessing remained inadequate, especially as during PROCESS 2 a higher number of centers had at least one MGO contaminated endoscope (PR1: 29%, PR2: 39%). The AM20 prevalence was lower during PROCESS 2, mainly consisting of less contamination with skin and water-borne flora. This may be the result of improvement of endoscope handling and protocol adherence by institutions following the first PROCESS study, (inter-)national alerts and updates of IFU and the Dutch Disinfection handbook.[29, 42, 44, 61] The current study confirms that linear echoendoscopes can also be vectors for transmission,[9, 10, 14, 17] but no echoendoscope-associated outbreaks have been reported to date. This might be because EUS is less invasive compared to ERCP and risk factors for transmission during ERCP such an obstructed biliary system do not play a role.[62, 63] Also patients undergoing ERCP can be sicker and thus more prone to the development of infection if transmission occurs.

To the best of our knowledge, this is the first report to assess the association between DLE contamination and endoscope as well as reprocessing risk factors on a nationwide level. By pooling PROCESS 1 and 2 data, we could assess the factors endoscope age and usage. Confirmed by the similar results of both PROCESS studies, the sampling and culturing method allows for a reliable and sensitive assessment of the DLE contamination rate.

The current study also has some limitations. Information on age and usage was not available for all DLEs, and the recorded repair history was limited to the biopsy channel. Furthermore, some factors that are exemplary of the complexity of reprocessing, e.g. adherence to the multitude of steps, including meticulous manual cleaning, were not assessed in this study. Lastly, generalizability to other countries may be limited

depending on national differences in audit, surveillance and maintenance strategies as well as availability and usage of endoscope types.

The persistent high contamination prevalence for DLEs independent of type, age, usage and reprocessing factors, support the notion that current reprocessing techniques cannot guarantee adequate decontamination. To counter this, easy to apply and effective control measures should be devised and implemented to check for the efficacy of endoscope decontamination. In the short-term reprocessing methods are required with a larger margin of safety counterbalanced with feasibility, welfare for staff and suitable for use with existing model endoscopes. Ultimately, redesigned DLEs that can facilitate sterilization or single-use endoscopes must eliminate the risk of contamination. If not, contamination of DLEs will continue to occur with new outbreaks bound to happen.

Supplementary files

Supplementary Table 1: Centers with ≥1 contaminated endoscope

	N	≥1 AM20 contaminated DLE	≥1 MGO contaminated DLE	≥1 MGO or AM20 contaminated DLE
Centers				
PROCESS 1	66	26 (39%)	19 (29%)	31 (47%)
PROCESS 2	61	20 (33%)	24 (39%)	30 (49%)
PROCESS 1&2 pooled	72	37 (51%)	34 (47%)	48 (67%)

Abbreviations: DLE, duodenoscopes and linear echoendoscopes; AM20, microbial growth with ≥20 CFU/20 mL of any type of microorganism; CFU, colony forming units; MGO, presence of any microbial growth of gastrointestinal or oral microorganisms.

Supplementary Table 2: DLE contaminated with AM20.

	N	AM20	Gut flora ≥20 CFU	Oral flora ≥20 CFU	Skin flora ≥20 CFU	Waterborne Flora ≥20 CFU
PROCESS 1						
Duodenoscopes	150	34 (23%)	10 (7%)	4 (3%)	17 (11%)	12 (8%)
PROCESS 2	223	29 (13%)	13 (6%)	3 (1%)	15 (7%)	4 (2%)
Duodenoscopes	159	21 (13%)	9 (6%)	3 (2%)	12 (8%)	2 (1%)
Linear echoendoscopes	64	8 (13%)	4 (6%)	0	3 (5%)	2 (3%)

Microorganisms categorized by origin. Abbreviations: DLE, duodenoscopes and linear echoendoscopes; AM20, microbial growth with ≥20 CFU/20 mL of any type of microorganism; CFU, colony forming units; MGO, presence of any microbial growth of gastrointestinal or oral microorganisms.

Supplementary Table 3: Prevalence of AM20 and MGO contamination for sample sites

	PROCESS 2			PROCESS 1			PROCESS 1&2 pooled		
	N	**AM20**	**MGO**	**N**	**AM20**	**MGO**	**N**	**AM20**	**MGO**
Duodenoscopes									
All sample sites	796	34 (4%)	42 (5%)	707	51 (7%)	36 (5%)	1503	83 (6%)	78 (5%)
Biopsy channel	154	6 (4%)	8 (5%)	147	5 (3%)	6 (4%)	301	11 (4%)	14 (5%)
Suction channel	158	7 (4%)	8 (5%)	139	6 (4%)	5 (4%)	297	13 (4%)	13 (4%)
Forceps elevator	156	5 (3%)	4 (3%)	149	15 (10%)	7 (5%)	305	19 (6%)	11 (4%)
Brush	156	10 (6%)	11 (7%)	140	18 (13%)	14 (10%)	296	27 (9%)	25 (8%)
Protection cap	65	2 (3%)	5 (8%)	57	6 (11%)	4 (7%)	122	8 (7%)	9 (7%)
Elevator channel	61	3 (5%)	3 (5%)	53	0	0	114	3 (3%)	3 (3%)
Air/water channel	38	0	1 (3%)	22	1 (5%)	0	60	1 (2%)	1 (2%)
Brush air/water channel	8	1 (13%)	2 (25%)	-	-	-	8	1 (13%)	2 (25%)
Linear echoendoscopes									
All sample sites	369	17 (5%)	19 (5%)						
Biopsy channel	63	2 (3%)	4 (6%)						
Suction channel	62	4 (7%)	6 (10%)						
Forceps elevator	64	1 (2%)	1 (2%)						
Brush	64	3 (5%)	3 (5%)						
Elevator channel	58	5 (9%)	2 (3%)						
Air/water channel	27	2 (7%)	2 (7%)						
Brush balloon channel	31	0	1 (3%)						

Abbreviations: AM20, Microbial growth with ≥20CFU/20mL of any type of microorganism; MGO, Presence of any microbial growth of gastrointestinal or oral microorganisms.

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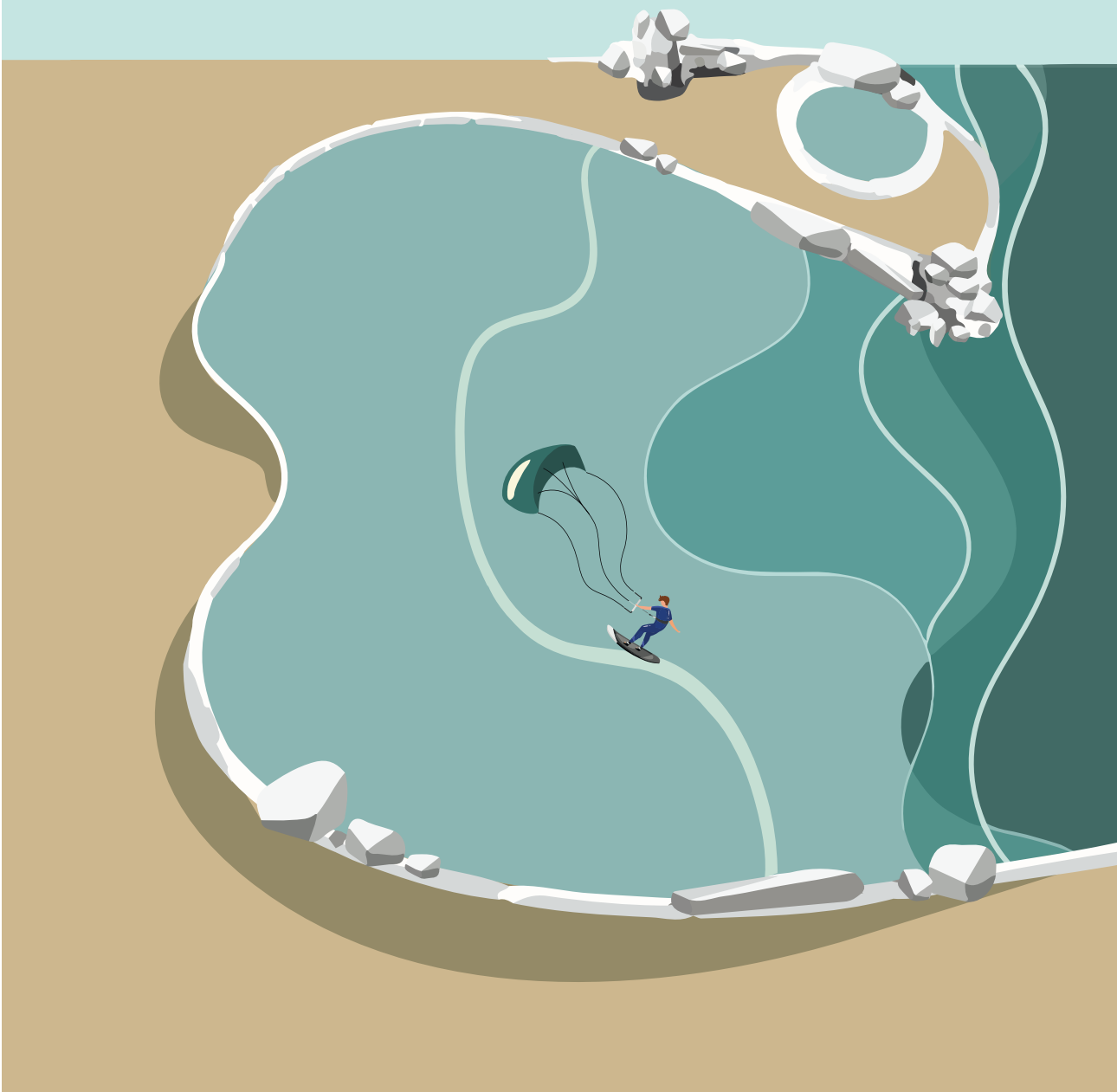
PART
3

Long- and short-term solutions: a role for post-manual cleaning tests?




CHAPTER
6

Assessment of post-manual cleaning adenosine triphosphate tests to prevent the use of contaminated duodenoscopes and linear echoendoscopes: the DETECT study

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Abstract

Background and Aims

We investigated whether use of post-manual cleaning adenosine triphosphate (ATP) tests lowers the number of duodenoscopes and linear echoendoscopes (DLE) contaminated with gut flora.

Methods

In this single-centre before-and-after study, DLEs were ATP tested post-cleaning. During the control period participants were blinded for ATP results: ATP-positive DLEs were not recleaned. During the intervention period ATP-positive DLEs were recleaned. DLEs underwent microbiological sampling after High-Level Disinfection (HLD) with participants blinded for culture results.

Results

Using fifteen endoscopes of five different DLE types, nine-hundred-nine procedures were included (52% duodenoscopes, 48% linear echoendoscopes). During the intervention period the absolute rate of contamination with gut flora was higher (16% vs. 21%). Main analysis showed that contamination was less likely to occur in the intervention period (OR 0.32; 95%CI 0.12-0.85). Secondary analysis showed that this effect was based on one particular duodenoscope type (estimated probability 39%; 95%CI 18%-64% vs. 9%; 95%CI 2%-21%), while no effect was seen in the other four DLE types. In detail, of the four duodenoscopes of this type two had lower contamination rates (69% vs. 39% and 36% vs. 10%). During the control period, both these duodenoscopes had multiple episodes with ongoing contamination with the same microorganism which ended weeks before the start of the intervention period, i.e. they were not terminated by ATP testing.

Conclusion

Post-manual cleaning ATP tests do not reduce post-HLD gut flora contamination rates of DLE. Hence, post-cleaning ATP tests are not suited as a means for quality control of endoscope reprocessing.

Introduction

In recent years, multiple endoscope-associated infectious outbreaks have been reported, in particular related to duodenoscopes used for ERCP.[1-3] Many of these were outbreaks with Multi-Drug Resistant Organisms (MDRO). In several of these outbreaks, it was shown that duodenoscopes were already contaminated for months before transmission was discovered with attack rates (i.e. number of infected or colonized cases/number of exposed persons) up to 40%.[4-8] As outbreaks are shown to be underreported,[1, 2, 9] the published number of 490 patient infections and 32 deaths because of contaminated duodenoscopes between 2008-2018 is considered an underestimation.[1, 3]

After each procedure, endoscopes are reprocessed. This process, which includes flushing, manual cleaning, high-level disinfection (HLD) and drying, has little margin for error.[10-13] Reprocessing nonetheless has been shown error prone.[14-17] Duodenoscopes and linear echoendoscopes (DLEs) are more difficult to clean than other endoscopes due to their complex design, which includes a side viewing tip, forceps elevator and elevator wire channel. Even when manufacturers' Instructions For Use were strictly followed, large outbreaks have occurred.[18, 19]

As current reprocessing techniques do not suffice to achieve reliable decontamination, patients undergoing ERCP are regularly exposed to contaminated duodenoscopes. Duodenoscope manufacturers' postmarket studies show a 5.4% contamination rate with indicator microorganisms (IMO) associated with disease transmission (i.e., *Escherichia coli, Pseudomonas aeruginosa*),[20] which is in line with the 8% contamination prevalence of these microorganisms found in Dutch prevalence studies.[21] A systematic review showed an overall duodenoscope contamination rate of 15%.[22] Patients undergoing EUS may also be exposed to contaminated equipment, as IMO contamination rates of linear echoendoscopes range between 1.1% and 8%.[21, 23, 24] In Dutch hospitals the DLE contamination prevalence with microorganisms from gastrointestinal and oral origin was 15% for two consecutive years.[21, 25] Gastroenterology, microbiology and regulatory agencies have stressed the need for easy to implement and effective control measures to check endoscope decontamination.[26, 27]

Current guidelines advise microbial surveillance to prevent transmission of microorganisms via contaminated endoscopes.[27, 28] However, culturing is labour intensive, expensive and gives delayed feedback due to the 48-to-72-hour incubation period. Real-time audits of 'bacterial load' during reprocessing could drastically improve endoscope safety. The most often proposed alternative is the use of adenosine triphosphate (ATP) assay, a test originating from the food industry, and recently introduced into hospitals to monitor cleanliness of the environment. The ATP test is a

bioluminescence assay using luciferase-catalysed oxidation of luciferin causing ATP-dependent emission of light, measured in Relative Light Units (RLU). Bacteria as well as human cells and secretions contain ATP, and presence of ATP after cleaning may indicate organic residue requiring recleaning.[29]

It is unclear whether the use of ATP tests to guide reprocessing prevents the use of contaminated endoscopes. ATP is found not useful for testing post-HLD because of the poor correlation with terminal reprocessing cultures.[30-33] The correlation with bacterial growth post-cleaning is also questioned.[34, 35] However, with a validated cut-off of 200RLU to differentiate for acceptable levels of protein and bacteria after cleaning,[36-38] it is suggested as a quality control indicator for manual cleaning.[35, 39] As a growing number of endoscopy centres use ATP tests,[40] it is essential to scientifically establish the usefulness and clinical value of ATP. Therefore, the aim of this study was to assess if introduction of post-cleaning ATP tests, with recleaning in case of a positive ATP test, lowers the number of clinically relevant positive cultures of DLE.

Materials and methods

From July 2017 to October 2018, we conducted a prospective single-centre intervention study in a before-and-after design, to assess the utility of ATP testing after manual cleaning. The study was conducted at the 1320-bed tertiary Erasmus MC University Medical Centre in Rotterdam, the Netherlands, which performs approximately 900 ERCP and 750 EUS procedures yearly.

Endoscopes and reprocessing

Multiple DLEs were used throughout the study. Four Pentax ED34-i10T (Pentax Medical, Dodewaard, The Netherlands) duodenoscopes were in use until they were replaced by Pentax ED34-i10T2 duodenoscopes with a disposable elevator cap. One ED34-i10T2 was introduced after 7 weeks, four after week 40. During the entire study, two Olympus TJF-160VR duodenoscopes (Olympus, Zoeterwoude, The Netherlands), three Pentax EG-3870UTK linear echoendoscopes and two Pentax EG-3270UK linear echoendoscopes were in use. Servicing, maintenance, and loan endoscopes were provided by Pentax and Olympus. Reprocessing was performed according to manufacturer's Instructions For Use and the handbook of the Dutch Steering Group for Flexible Endoscope Cleaning and Disinfection (SFERD),[41] and consisted of the following: 1) bedside flush with water, 2) manual cleaning using Neodisher MediClean Forte cleaning agent (dr. Weigert, Assen, The Netherlands), 3) HLD using Neodisher Septo peracetic acid in eight Wassenburg WD440-PT automated endoscope reprocessors (AERs) (Wassenburg, Dodewaard, The Netherlands). In April 2018, the endoscopy department relocated;

ten new Wassenburg WD440-PT AERs were put in use. In December 2017, the original staff of four disinfection assistants was merged with the sterilization unit of in total 15 members. The already existing clinical monthly surveillance cultures were continued during the study; if contaminated with gut flora, endoscopes were quarantined until effectively decontaminated as shown by follow-up cultures.

Study design

This before-and-after study consisted of two parts: a baseline control period followed by an intervention period (Supplemental figure 1). In both periods DLEs were subjected to post-cleaning ATP tests and cultured after HLD by dedicated sampling staff. In the control period, participants were blinded for ATP results: ATP-positive endoscopes were not recleaned. Only in the intervention period, ATP test results were shown to the disinfection assistant; if positive, the endoscope was cleaned and ATP tested again, with a maximum of two repeated cycles. DLEs underwent HLD regardless of the result of a possible positive third ATP test. Sampling staff, disinfection assistants and researchers were blinded for the study culture results. The primary endpoint was the reduction of the percentage of DLE contaminated with gut flora between the control period and the intervention period. We considered the effect of the ATP test as clinically relevant if the gut flora contamination rate was reduced by 50%. Based on Dutch prevalence studies we estimated an 8% gut flora contamination rate for DLEs,[21, 25] without difference between the different DLE brand or types.[1, 2, 21, 23-25] This required a sample size (power: 80%, α=0.05) of 870 procedures. The study was approved by the Erasmus MC Medical Ethical Research Committee (MEC-2017-291); no patients were subject to any study procedures and no patient data were collected.

ATP tests

Depending on DLE type, three to four sites were sampled. First, the distal 10cm of the endoscope, secondly, the forceps elevator, and thirdly, the protection cap (if unsealed and reusable) were swabbed with Clean-Trace ATP surface tests (3M Company, Maplewood, USA). Finally, 40mL sterile water flushed through the biopsy/suction channel was sampled with the Clean-Trace ATP water test. Endoscopes were considered ATP-positive if ≥1 sample tested ≥201RLU. This cut-off has been validated for the distal tip and flush,[36-38] and also used for the elevator and cap for which this was not the case.

Microbiological cultures

Depending on DLE type, three to four sites were sampled. First, the forceps elevator and secondly, the protection cap (if unsealed and reusable) were swabbed with e-Swabs (Copan Italia S.p.A., Brescia, Italy). Thirdly, the biopsy/suction channels were flushed with sterile physiological saline solution of which 20mL was collected in a sterile container at the distal tip. Finally, the biopsy/suction channels were brushed

with either Olympus BW-412T or Pentax CS6021T single-use cleaning brushes. Brush tips and e-Swabs were vortexed in e-Swab 1mL Amies medium of which 0.75mL was poured on blood agar. Channel flushes were filtrated over a 0.22µm filter, of which the filtrate was forced on R2A agar. Cultures were incubated at 35ºC, 5% CO2 and examined for growth after day four. Culture results were presented in Colony Forming Units (CFU)/20mL per microorganism. We used two contamination definitions: (i) presence of microbial growth (≥1CFU/20mL) of gastrointestinal microorganisms (gut flora), and (ii) microbial growth with ≥20CFU/20mL of any type of microorganism (AM20) as used by the European and Dutch guidelines.[41, 42] Endoscopes could be contaminated according either or both definitions.

Statistical analysis

To investigate the effect of the intervention on the probability of contamination measured at any of the sampling sites, we fitted Bayesian logistic mixed models taking into account a correlation between repeated measurements of the same endoscope using endoscope specific (random) intercepts. The models were fitted using the R package JointAI, which performs simultaneous analysis and imputation of incomplete covariates.[43] We used two models. Model 1 is the main analysis, in which we included all covariates potentially influencing reprocessing: study period, study time (per 10 weeks), study procedures (per 50 procedures), transfer to a new endoscopy building and introduction of new disinfection assistants. Model 2 is used for the secondary analysis, in which we assessed differences between endoscope types by adding the endoscopy type and its interaction with the study period to the model. Results are presented as posterior means and 95% credible intervals (CI) of the odds ratios of the covariates. For clinical interpretation of the results of model 2, estimated probabilities were calculated for both study periods while other values were fixed to reasonable reference values. Analyses were performed in SPSS V23.0 (Chicago, USA) and R V4.0.3 (Vienna, Austria).

Funding and registration

This investigator-initiated study (Netherlands Trial Register NL6380) was supported by an unrestricted grant from 3M Health Care, which had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

RESULTS

In total, 909 procedures were included: 431 procedures during the control period of 20 weeks, and 478 procedures during the intervention period of 45 weeks (Table 1). Of these procedures 473 were performed with duodenoscopes and 433 with linear echoendoscopes. Supplementary Figure 2 shows the inclusion and contamination

timelines per endoscope type. Eight procedures, for which it was unknown which endoscope was used, as well as six procedures with unknown ATP test results were excluded from the analyses. Three unknown values for the number of study procedures and seven missing values pertaining which disinfection assistant were involved were imputed during the analysis.

Table 1. Contamination prevalence of duodenoscopes and linear echoendoscopes .

	N	Gut flora % (n)	AM20 % (n)
DLE			
Control period	431	16% (67)	34% (145)
Intervention period	478	21% (102)	39% (185)
- 1 time manual cleaning	315	28% (88)	40% (126)
- ≥2 times manual cleaning	162	9% (14)	36% (59)
Duodenoscopes	473	30% (143)	59% (280)
Control period	224	27% (61)	60% (136)
Intervention	249	33% (82)	58% (144)
Linear echoendoscopes	433	6% (26)	12% (50)
Control period	205	3% (6)	4% (9)
Intervention	228	9% (20)	18% (41)

Abbreviations: AM20, Microbial growth with ≥20CFU/20mL of any type of microorganism; gut flora, presence of microbial growth of gastrointestinal microorganisms; DLE, duodenoscopes and linear echoendoscopes

Gut flora contamination

The main analysis, assessing covariates potentially influencing reprocessing, showed that during the intervention period DLEs were less likely to be contaminated with gut flora (OR 0.32; 95%CI 0.12-0.85) (Figure 1). However, as shown in Table 1, the DLE gut flora contamination rate was higher in the intervention period (21%;n=102), than in the control period (16%;n=67). This difference follows from the performance of two distinct duodenoscopes, explained in the following three steps. First, a secondary analysis (Table 2, Figure 2) assessing the intervention period effect per endoscope type, showed that the effect was based on only ED34-i10T duodenoscopes while no effect was seen in the other endoscope types. ED34-i10T duodenoscopes had during the intervention period a lower estimated probability of contamination with gut flora compared to the control period (Control period: mean 39.0%, 95%CI 17.6%-63.6% vs. Intervention period: mean 9.1%, 95%CI 2%-21%). Secondly, close observation of the four ED34-i10T duodenoscopes showed that duodenoscopes A and B had lower gut flora contamination rates in the intervention period: A (69%;n=29 vs. 39%;n=16) and B (36%;n=13 vs. 10%;n=2). The two other duodenoscopes had very few observations (C:

13%;n=6 vs. 14%;n=1 and D: 20%;n=4 vs. 25%;n=2) and could thus contribute little to the result of the secondary analysis.

	OR (95% CI)
Building	
Gut flora	1.11 (0.40, 3.16)
AM20	0.65 (0.26, 1.73)
ATP test	0.66 (0.25, 1.66)
Disinfection assistant	
Gut flora	1.04 (0.57, 1.90)
AM20	1.13 (0.66, 1.91)
ATP test	2.59 (1.55, 4.37)
Intervention period	
Gut flora	0.32 (0.12, 0.85)
AM20	2.03 (0.77, 5.85)
ATP test	0.37 (0.16, 0.93)
Study procedures	
Gut flora	1.00 (1.00, 1.01)
AM20	1.01 (1.00, 1.02)
ATP test	1.00 (0.99, 1.00)
Study weeks	
Gut flora	1.02 (0.98, 1.07)
AM20	0.99 (0.95, 1.03)
ATP test	0.96 (0.92, 1.00)

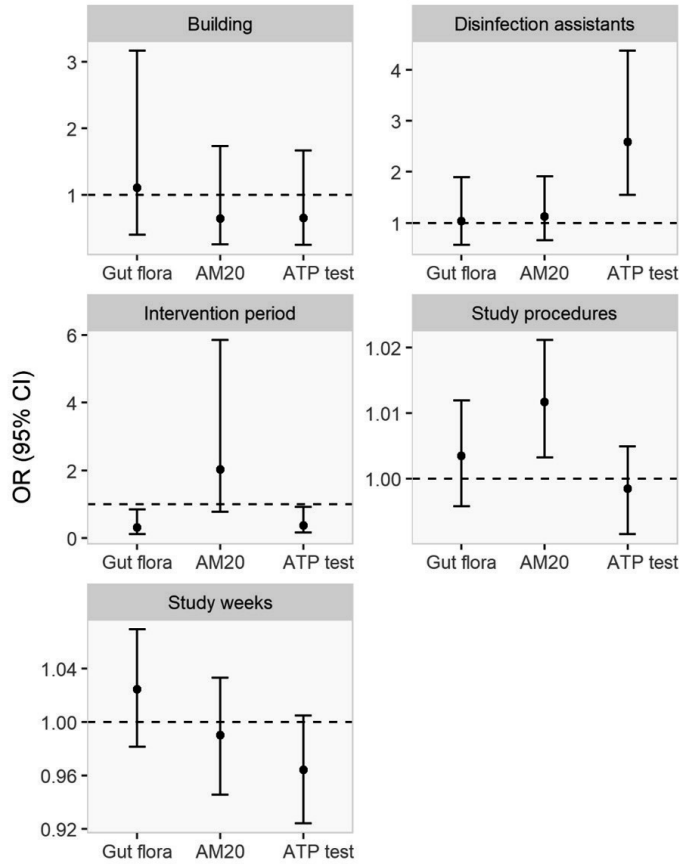


Figure 1. Odds ratios for reprocessing covariates

Abbreviations: AM20, Microbial growth with ≥20CFU/20mL of any type of microorganism; gut flora, presence of microbial growth of gastrointestinal microorganisms, ATP test, positive test result of 1st adenosine triphosphate test: ≥1 sample ≥200RLU; Building, transfer to a new endoscopy unit; disinfection assistant, introduction of new disinfection assistants; study procedures, effect of 50 procedures; effect of 10 study weeks.

Thirdly, it was observed that the control period gut flora rates of duodenoscopes A and B are predominantly caused by episodes of ongoing contamination, which ended before the start of the intervention period (Figure 3). Both duodenoscopes had an episode with *Enterobacter cloacae* complex and *Klebsiella pneumoniae,* and duodenoscope A another episode with *Candida parapsilosis*. The episodes were only detected by regular surveillance cultures after multiple positive blind study cultures, but the *C. parapsilosis*

episode was not detected at all. These episodes ended in November and further study as well as surveillance cultures remained negative for gut flora in the control period. As no gut flora was present at the start of the intervention period, this indicates that ATP testing did not terminate these episodes. Also in the intervention period, new episodes with gut flora emerged among one ED34-i10T duodenoscope and three ED34-i10T2 duodenoscopes. Duodenoscope A had a third episode with *S. maltophilia* in its final month in the intervention period (Figure 3) and three ED34-i10T2 duodenoscopes had up to two-month long episodes with *Enterobacter aerogenes*, *E. cloacae* complex, *Stenotrophomonas maltophilia*, *C. parapsilosis* and yeasts. These new episodes during the intervention period indicate that ATP testing did not prevent ongoing gut flora contamination.

Table 2. Distribution of the estimated probability of gut flora contamination

	Gut flora		
	Control	**Intervention**	**Difference**
Duodenoscopes	**Mean (95%CI)**	**Mean (95%CI)**	**Mean (95%CI)**
Olympus TJF-160VR	15.4 (3.5 - 37.2)	8.8 (2.0 - 22.0)	-6.6 (-27.7 - 8.7)
Pentax ED34-i10T2 DEC	15.6 (0.2 - 60.0)	43.4 (18.4 - 72.1)	27.8 (-18.6 - 63.5)
Pentax ED34-i10T	39.0 (17.6 - 63.6)	9.1 (2.4 - 20.9)	-29.9 (-52.3 - -11.0)
Linear echoendoscopes			
Pentax EG-3270UK	4.7 (0.1 - 23.1)	10.2 (1.4 - 33.4)	5.5 (-10.4 - 26.5)
Pentax EG-3870UTK	4.8 (1.2 - 12.3)	4.2 (1.2 - 10.2)	-0.06 (-7.7 - 5.3)

Estimated probabilities (in %) of gut flora contamination during the control and intervention periods with corresponding 95% credible intervals, under the assumption of reference values (old building, core team, study week 23, 39 procedures) for the other covariates. Pentax ED34-i10T include duodenoscopes A, B, C and D as shown in Figure 3. Abbreviations: DLE, duodenoscopes and

linear echoendoscopes; DEC, disposable elevator cap; CI, confidence interval; gut flora, presence of microbial growth of gastrointestinal microorganisms.

Sample sites that were ATP-positive post-cleaning harboured gut flora after HLD in a selected number of cases. Of all endoscopes, the elevator and cap were the sites which were most often ATP-positive during the control (both sites ≥66%) and intervention (both sites ≥27%) period (Supplementary Table 1). However, these sites had the lowest gut flora contamination rates (elevator 2%;n=16, cap <1%;n=1) (Supplementary Table 2). A similar pattern was seen in the channels of linear echoendoscopes. While 38% tested ATP-positive in the control period, and 16% in the intervention period, the gut flora contamination rates detected by channel flush and brush were lower (control period: 3%, intervention period: 7%). On the other hand, sample sites that did harbour gut flora, were ATP-positive in a low number of cases. Of all sample sites, duodenoscope channels harboured the most gut flora (flush and brush combined: control period: 26%, intervention period: 32%), but the channels tested the least often ATP-positive in the control period (15%) and intervention period (5%). This was in particular the case for ED34-i10T2 duodenoscopes: 52% (n=54) were contaminated with gut flora during the intervention period, but 3% (n=3) tested ATP-positive. This contrast indicates a low correlation between a positive post-cleaning ATP test and presence of gut flora in terminal cultures.

AM20 contamination

The main analysis also showed that the intervention period did not reduce AM20 contamination rates (OR 2.03; 95%CI 0.77-5.85) (Figure 1), which is consistent with the AM20 contamination rates of all DLEs (>34% in both periods) (Table 1). AM20 contamination did became more likely per each 50 procedures performed during the time that the study progressed (OR 1.01; 95%CI 1.00-1.02). In particular ED34-i10T (86%, n=197) and ED34-i10T2 (49%, n=60) duodenoscopes had consistent high AM20 rates (supplementary table 3). The secondary analysis (Table 2, Figure 2), assessing the intervention period effect per endoscope type, shows slightly higher estimated probabilities for all endoscope types in the intervention period, but not large enough to conclude a negative impact with certainty.

Recleaning

In the intervention period, DLEs which underwent extra cleaning due to a positive ATP test had lower gut flora contamination rates (Table 1). This was both the case for duodenoscopes (Gut flora: 37%,n=74 vs. 15%,n=8) and linear echoendoscopes (Gut flora: 12%,n=14 vs. 6%,n=6).

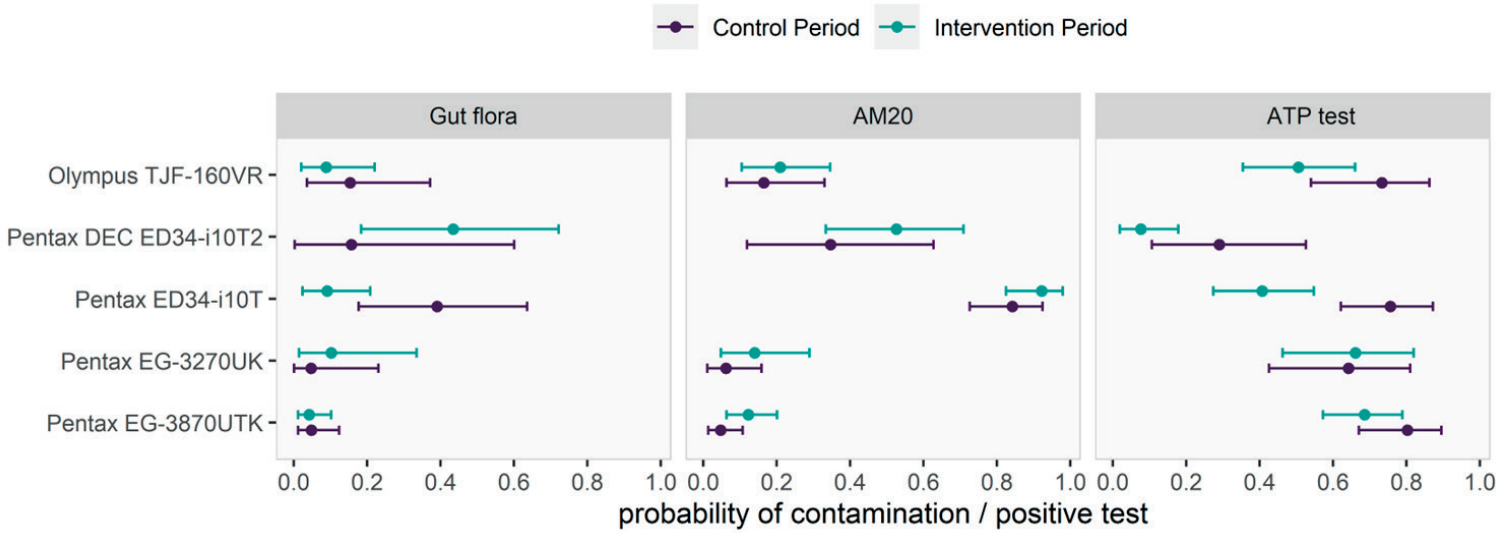


Figure 2. Distribution of the estimated probability of contamination by control period and intervention period as well as endoscope type. Other covariates set to: old endoscopy unit, core disinfection assistant team, study week 23, 39 procedures. Pentax ED34-i10T include duodenoscopes A, B, C and D as shown in Figure 3. Abbreviations: AM20, Microbial growth with ≥20CFU/20mL of any type of microorganism; gut flora, presence of microbial growth of gastrointestinal microorganisms, ATP test, positive test result of 1st adenosine triphosphate test: ≥1 sample ≥ 200RLU.

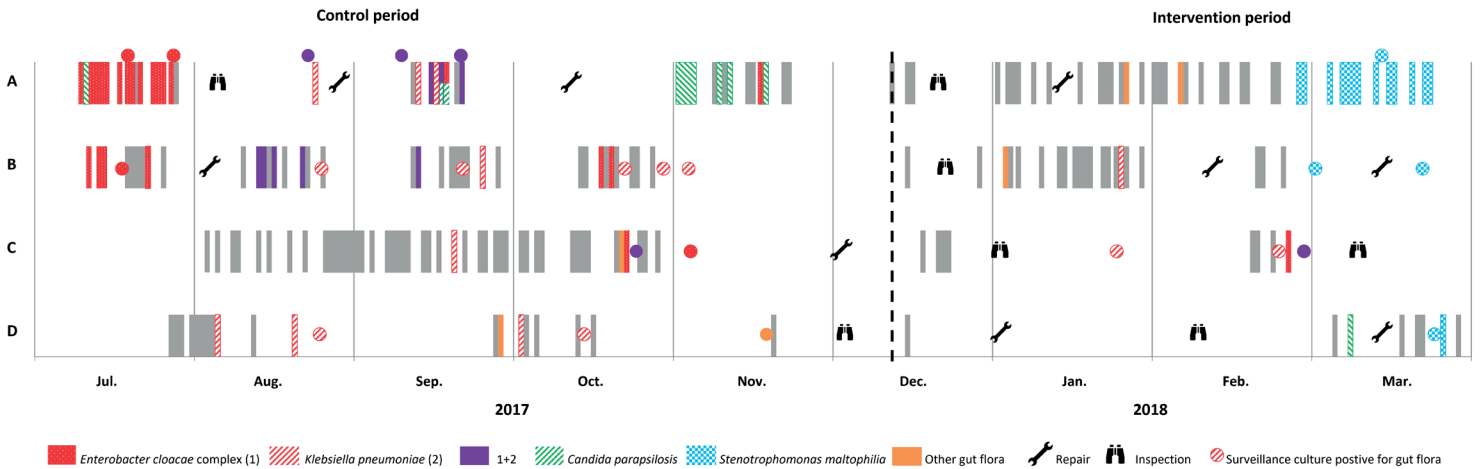


Figure 3. Timeline of Pentax ED34-i10T duodenoscopes. Four Pentax ED34-i10T duodenoscopes (A, B, C and D) were in use until week 40. Microbiological surveillance was performed monthly; if endoscopes were contaminated with gut flora, they were quarantined until they were effectively decontaminated as shown by surveillance cultures. Results of surveillance cultures are delayed due to the 72-hour incubation period. Columns represents study cultures. Both researchers and clinicians were blinded for the result of study cultures. Circles represent surveillance cultures, which are only shown if positive for gut flora. Grey columns are negative for gut flora, coloured columns or circles are positive for gut flora. Pentax inspected endoscopes following ongoing positive surveillance cultures. This is shown as an inspection if no defects were detected and as repair if damage and/or wear required repairs and replacement of parts.

DISCUSSION

In our prospective before-and-after study, introduction of post-manual cleaning ATP tests did not reduce the post-HLD gut flora contamination rate of DLE and thus did not stop or prevent the use of endoscopes contaminated with gut flora. We found a lower odds on gut flora contamination during the intervention period. However, this was based on two duodenoscopes with episodes of ongoing contamination during the control period, which were ended by quarantining and repairs. Until detected by routine clinical surveillance cultures, these episodes could go unnoticed; both researchers and clinicians were blinded for the results of study cultures. The results of this study suggest that the currently used ATP test (i.e. four sample sites with a 200RLU cut-off), is unsuitable to detect inadequately cleaned endoscopes and therefore should not be used as a cleaning quality control indicator. Furthermore, monthly surveillance cultures are inadequate to prevent the use of contaminated equipment. Improvement of the reliability of quality checks and microbiological surveillance regimens is required to prevent the risk of microbial transmission via contaminated endoscopes. Eventually, this risk must be eliminated by radical redesign of DLEs and reprocessing methods.

The current study confirms the results of a small clinical pilot and a simulated-use study, which both show that post-manual cleaning ATP tests are not effective in preventing contamination of pathogenic bacteria in duodenoscopes.[35, 44] In one other small pilot study, endoscope cultures remained negative.[45] However, all previous studies were limited in size and lack a control group, [35, 44, 45] or microbiological cultures,[46, 47] which prevented drawing a final conclusion about the clinical merits of the ATP test. The current study, with a controlled and adequately powered design, shows that post-cleaning ATP tests do not have clinically relevant effect.

We found a discrepancy between a ATP-positive test result and presence of gut flora. The elevator and cap of all DLEs as well as the channels of echoendoscopes had high ATP-positive rates, but only a small number harboured gut flora. On the contrary, ED34-i10T2 duodenoscopes were ATP-positive in only 3 cases. While some studies did found a correlation between ATP and microbial load after manual cleaning,[48] our results are in line with earlier pilot studies which also found no correlation between post-cleaning ATP tests and post-HLD cultures.[34, 35] The discrepancy can be explained by the following; positive ATP results combined with cultures negative for gut flora can be the result of organic residue containing ATP such as human secretions or cells, a high microbial load of non-gut flora or non-cultivable microorganisms. The 200RLU cut-off is validated for the distal tip and flush,[36-38] but for the experimental cap and elevator sites no validation data is known. ATP-negative results in combination with cultures positive for gut flora can be the result of a gut flora microbial load too low to raise the number of RLU.[36]

Another explanation can be that the ATP Water test is not sensitive enough as the material is diluted by the flush water (40 ml), whereas cultures detect all viable CFU in a channel flush as its filter is cultured. Detection is further increased by also sampling channels with a brush.[21] These results imply that the ATP test as used in this study cannot adequately detect gut flora.

The lower ATP test positivity rate in the intervention period can be the result of revised reprocessing routines (i.e. improved cleaning and endoscope handling) and the introduction of disposable caps for ED34-i10T duodenoscopes. Recleaned DLEs had lower gut flora contamination rates, suggesting extra cleaning reduces organic debris. As manual cleaning is error-prone,[14-17, 49] it would benefit a quality control indicator which appropriately detects inadequately cleaned endoscopes. Current evidence does not support the ATP test for this use: improvement of ATP test rates while gut flora rates remain high, is a false negative test result providing an incorrect and false sense of security.

Contamination rates of linear echoendoscopes in this study were in line with previous studies,[21, 24, 25] while duodenoscope rates were remarkably higher. These high rates can be the result of the study design, endoscope-related issues and/or sampling and culture methods. Recent large-scale studies with far lower rates conducted daily or post-procedure surveillance in an open study design,[23, 50, 51] allowing immediate quarantine of contaminated endoscopes which prevented further use. For most hospitals daily surveillance is too labor intense and expensive. High contamination rates in studies blinded for study culture outcomes are perhaps more representative for their clinical practice. High rates were also found in cross-sectional studies,[52, 53] and several outbreak reports show that contamination can persist for months.[6, 8, 18, 19, 54-56] The high rates in this study were mainly based on contamination episodes of a select number of Pentax type duodenoscopes. Recurrent episodes of gut flora and ongoing contamination with water-borne and/or skin flora in both types suggest the presence of biofilms in endoscope channels, including the brand-new duodenoscopes. Once present, a biofilm can be the cause of failure of reprocessing.[57] Duodenoscope damage and wear can contribute to contamination.[19, 50, 54, 58] In duodenoscope A, the first episode ended only after the third servicing, while in duodenoscope B the episode continued despite servicing. Close cooperation and taking joint responsibility by both end users and endoscope manufacturers for reprocessing, strict surveillance and servicing is important in guarding endoscope safety.

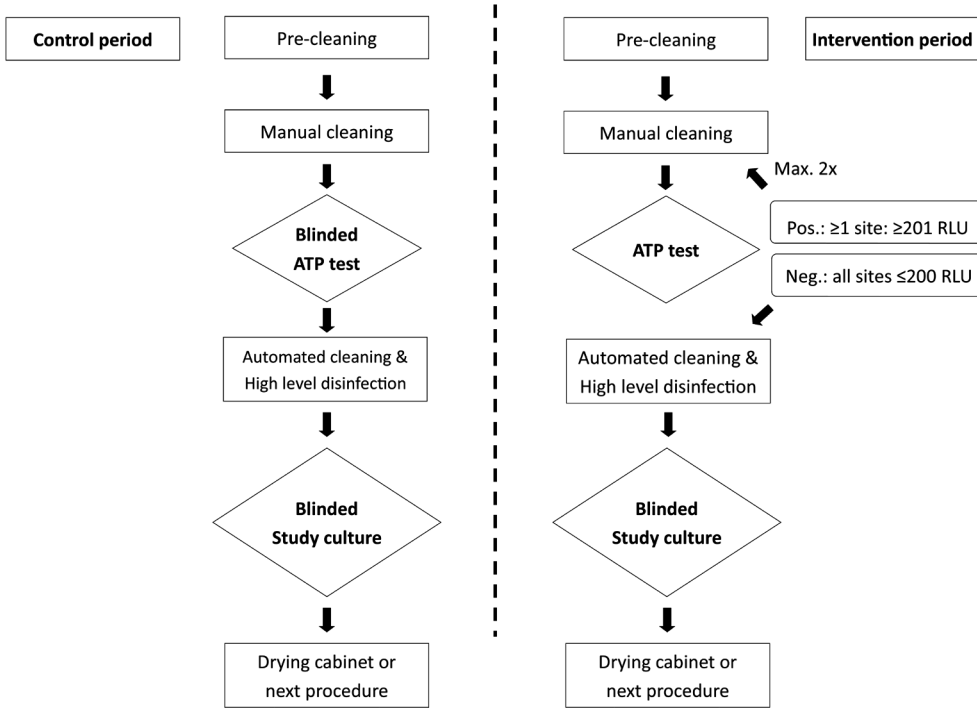
This study shows that monthly surveillance was inadequate for timely detection of contamination. Until detected by surveillance cultures, episodes which lasts multiple weeks continue to expose patients to contaminated equipment. One episode of *C. parapsilosis*

was "missed": i.e., not present in any of the surveillance cultures. This is in line with the fact that during contamination episodes not all consecutive study cultures are positive for the same bacteria spp. Therefore, high-frequency daily or weekly surveillance should be considered to detect ongoing contamination patterns.

To the best of our knowledge, this is the first controlled study with blinded study cultures required to investigate post-cleaning ATP tests. The current study also has some limitations. Generalizability of the results is limited by multiple factors including the single-centre design and susceptibility of distinct endoscopes to contamination. The intervention period had a longer duration than the control period because of a lower inclusion rate. This was because, depending on the number of daily procedures and available endoscopes, not all endoscopes could undergo the longer intervention period ATP-test cycle. Major reprocessing-affecting events that occurred during the study were accounted for by including these factors in the statistical analysis model.

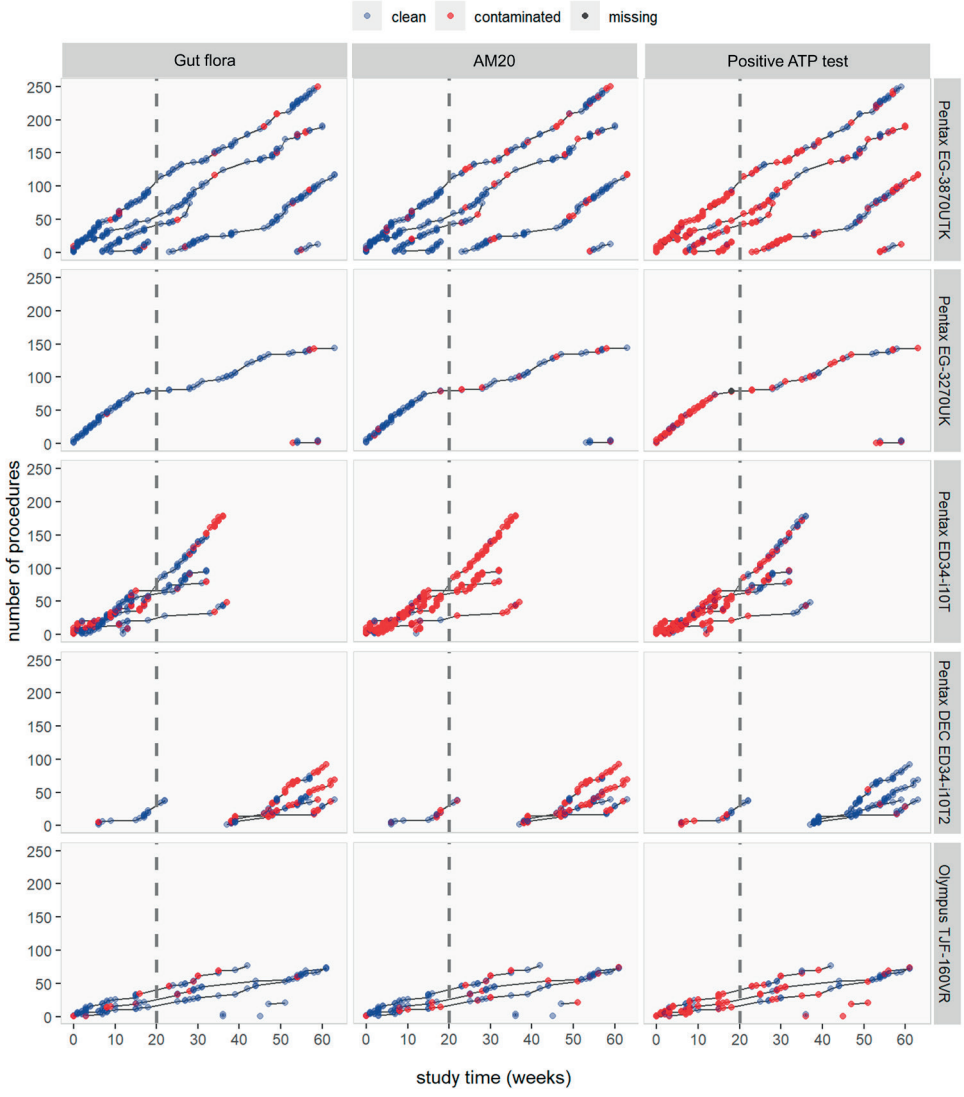
To conclude, this before-and-after intervention study shows that post-manual cleaning ATP tests as used in this study do not reduce the number of contaminated DLE after HLD. To prevent the use of contaminated equipment, reliable control measures are required to assess whether reprocessing of reusable DLE was adequate. Until the risk of contamination is eliminated by sterilization of DLEs or single-use endoscopes, strict and frequent microbiological surveillance is indicated.

Supplementary Tables and Figures



Supplementary Figure 1. Flowchart

Abbreviations: ATP, adenosine triphosphate; RLU, relative light units. ATP negative: test results of all sites were ≤200RLU. ATP positive: ≥1 test site result was ≥201RLU.



Supplementary Figure 2. Timeline of inclusion and outcome rates per endoscope type.

Timeline of measurements per endoscope type. Each line represents one endoscope and each dot marks a measurement. Vertical dotted line: divide between control and intervention period. Blue dot: negative outcome.

First column, red dot: endoscope contaminated with gut flora. Second column, red dot: endoscope contaminated with any microorganism with ≥20 CFU/20mL (AM20). Third column, red dot: endoscope with a positive 1st ATP test.

Supplementary Table 1. Positive ATP test rate per sample site and endoscope type per study period.

		Positive ATP test n (%)				
	N	**≥1 site**	**Distal tip**	**Channel fl.**	**Elevator**	**Cap**
All DLE						
Control	423	344 (81%)	226 (53%)	111 (26%)	280 (66%)	139/204 (68%)
Intervention 1st ATP test	472	162 (34%)	78 (17%)	49 (10%)	127 (27%)	32/114 (28%)
Intervention 2nd ATP test	159	56 (35%)	27 (17%)	8 (5%)	38 (24%)	10/43 (23%)
Intervention 3rd ATP test	53	26 (49%)	10 (19%)	4 (8%)	22 (42%)	5/13 (38%)
Duodenoscopes						
Pentax ED34-i10T						
Control	150	125 (83%)	62 (41%)	23 (15%)	87 (58%)	106 (71%)
Intervention 1st ATP test	77	27 (35%)	7 (9%)	3 (4%)	22 (29%)	13/51 (25%)*
Intervention 2nd ATP test	27	8 (30%)	2 (%)	0	6 (22%)	3/21 (14%)*
Intervention 3rd ATP test	7	3 (43%)	1 (7%)	0	2 (29%)	1/5 (20%)*
Pentax DEC ED34-i10T2						
Control	17	7 (41%)	3 (18%)	2 (12%)	6 (35%)	-
Intervention 1st ATP test	106	3 (3%)	1 (1%)	2 (2%)	2 (2%)	-
Intervention 2nd ATP test	3	1 (33%)	2 (66%)	0	2 (66%)	-
Intervention 3rd ATP test	1	0	0	0	0	-
Olympus TJF-160VR						
Control	54	44 (81%)	29 (54%)	10 (19%)	38 (70%)	32 (59%)
Intervention 1st ATP test	64	24 (38%)	11 (17%)	8 (13%)	20 (31%)	19/61 (31%)
Intervention 2nd ATP test	24	8 (33%)	3 (13%)	2 (8%)	6 (25%)	7/22 (32%)
Intervention 3rd ATP test	8	5 (63%)	2 (25%)	0	4 (50%)	4/8 (50%)
Linear echoendoscopes						
Pentax EG-3870UTK						
Control	145	125 (86%)	106 (73%)	56 (39%)	111 (77%)	-
Intervention 1st ATP test	187	90 (48%)	47 (25%)	27 (14%)	69 (37%)	-
Intervention 2nd ATP test	88	35 (40%)	18 (20%)	5 (6%)	23 (26%)	-
Intervention 3rd ATP test	33	15 (45%)	5 (15%)	4 (12%)	14 (42%)	-
Pentax EG-3270UK						
Control	57	43 (75%)	26 (46%)	20 (35%)	38 (67%)	-
Intervention 1st ATP test	38	18 (47%)	12 (32%)	9 (24%)	14 (37%)	-
Intervention 2nd ATP test	18	4 (22%)	3 (17%)	1 (6%)	2 (11%)	-
Intervention 3rd ATP test	4	3 (75%)	2 (50%)	0	2 (50%)	-

* 27 weeks after the start of the Intervention period the endoscopy department changed to single-use protection caps for the Pentax ED34-i10T. Therefore, the number is lower than the total no. of endoscope. ATP positive if ≥201RLU. Abbreviations: DLE, duodenoscopes and linear echoendoscopes; n/a: not applicable; ATP, adenosine triphosphate test; RLU, relative light units

Supplementary Table 2. Gut flora contamination rate per sample site and endoscope type per study period.

	N	Gut flora contamination: n (%)				
		≥1 site	Brush	Channel fl.	Elevator	Cap
All DLE						
Total	909	169 (19%)	96 (11%)	109 (12%)	16 (2%)	1
Control	430	67 (16%)	42 (10%)	42 (10%)	3 (1%)	1/209 (1%)*
Intervention: 1x cleaning	315	86 (27%)	48 (15%)	57 (18%)	11 (3%)	0/71*
Intervention: 2x cleaning	106	9 (8%)	5 (5%)	6 (6%)	2 (2%)	0/30*
Intervention: 3x cleaning	56	5 (9%)	1 (2%)	4 (7%)	0	0/14*
Duodenoscopes						
Pentax ED34-i10T						
Control	151	53 (35%)	34 (23%)	28 (19%)	2 (1%)	1 (1%)
Intervention: 1x cleaning	50	17 (34%)	12 (24%)	11 (22%)	3 (6%)	0/30**
Intervention: 2x cleaning	19	2 (11%)	2 (11%)	2 (11%)	0	0/15**
Intervention: 3x cleaning	8	2 (25%)	1 (13%)	1 (13%)	0	0/6**
Pentax DEC ED34-i10T2						
Control	17	1 (6%)	1 (6%)	0	0	-
Intervention: 1x cleaning	103	52 (50%)	29 (28%)	39 (38%)	1 (1%)	-
Intervention: 2x cleaning	2	1 (50%)	0	1 (50%)	0	-
Intervention: 3x cleaning	1	1	1	1	1	-
Olympus TJF-160VR						
Control	56	7 (13%)	2 (4%)	5 (9%)	0	0
Intervention: 1x cleaning	40	4 (10%)	1 (3%)	1 (3%)	2 (5%)	0
Intervention: 2x cleaning	16	1 (6%)	0	1 (6%)	0	0
Intervention: 3x cleaning	8	2 (25%)	0	2 (25%)	0	0
Linear echoendoscopes						
Pentax EG-3870UTK						
Control	147	5 (3%)	4 (3%)	1 (1%)	1 (1%)	-
Intervention: 1x cleaning	97	12 (12%)	5 (5%)	4 (4%)	5 (5%)	-
Intervention: 2x cleaning	55	2 (4%)	1 (2%)	2 (4%)	0	-
Intervention: 3x cleaning	35	1 (3%)	0	1 (3%)	0	-
Pentax EG-3270UK						
Control	58	1 (2%)	1 (2%)	0	0	-
Intervention: 1x cleaning	20	1 (5%)	0	1 (5%)	0	-
Intervention: 2x cleaning	14	3 (21%)	2 (14%)	0	2 (14%)	-
Intervention: 3x cleaning	4	0	0	0	0	-

* Not all DLE types have (reusable) protection caps. ** 27 weeks after the start of the Intervention period single-use protection caps were introduced, resulting in a lower number lower of cap samples.

Abbreviations: DLE, duodenoscopes and linear echoendoscopes; n/a: not applicable; channel fl, channel flush.

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CHAPTER

7

No relation between adenosine triphosphate after manual cleaning and presence of microorganisms on endoscopes after automated high-level disinfection

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Abstract

Aim

Adenosine triphosphate (ATP) tests are increasingly used to detect biological material, however, their reliability to detect bacterial contamination in endoscopes is not proven. We investigated the predictive value of ATP tests after manual cleaning for the presence or absence of microorganisms as shown by culture after automated high-level disinfection (HLD) in duodenoscopes and linear echoendoscopes (DLE).

Methods

After manual cleaning, ATP tests were performed on swab samples taken from the detachable cap and forceps elevator, and on flush samples of the DLE working channels. These results were compared to the growth of any microorganisms in cultures acquired after automated HLD. ATP tests with >200 relative light units (RLU) were considered positive. ROC curves were used to compare the RLU levels with microbial presence in cultures.

Results

In total, 903 procedures were performed involving 26 distinct DLEs. Depending on sample site, 20.8% (cap) to 63.8% (channel brush) of the ATP negative samples were accompanied by positive post-HLD cultures. 54.4% of the cap samples with a positive culture (growth of any kind of microorganism) and 91.8% of the channel samples with a positive culture had a negative ATP test after manual cleaning. ROC curves per sample site, DLE type and microorganism type all had area under the curves below 0.6.

Conclusion

In our study, ATP tests performed after manual cleaning could not predict the presence or absence of microorganisms after automated HLD as shown by culture. More than half of the positive cultures were preceded by a negative ATP test.

Introduction

Flexible endoscopes are difficult to decontaminate. High-temperature sterilization is not an option because of heat-sensitive components. Instead, endoscopes are reprocessed, consisting of manual cleaning followed by automated chemical high-level disinfection (HLD). Reprocessing has a very narrow margin of safety and is prone to error which often leads to hazardous situations in which patients are treated with contaminated devices [25, 59]. Multiple outbreaks have been reported describing transmission of multidrug resistant bacteria through contaminated endoscopes, causing patient infections and even death [60]. This study focuses on duodenoscopes and linear echoendoscopes (DLE) since these two endoscope types have a similar complex design and duodenoscopes are most frequently associated with nosocomial infections in gastroenterological endoscopy patients [24].

Currently, microbiological culturing is considered the "gold standard" to assess the effect or even failure of reprocessing of endoscopes. A downside of this method is that cultures are laborious and results are available only after days or up to a week because of the laboratory process time. To minimize the risk for transmission, ideally the endoscope should not be used until it is cleared by negative culture results. This however, has considerable impact on logistics and finances as it would require a multitude of endoscopes. As endoscopes are often used continuously, transmission of microorganisms to the patient can occur before the endoscope contamination is detected. Moreover, microbiological cultures are only representative of the situation at the time of sampling, and their sensitivity to show the presence of bacteria is limited by the sampling and culture methodology. Ideally, presence of microorganisms should be detected within minutes and before each endoscopic procedure.

Point-of-care tests such as the adenosine triphosphate (ATP) test can potentially overcome the long period between culturing and results [31]. As ATP is present in living cells, it can serve as a substitute measurement to detect the presence of microorganisms in endoscopes [61]. These tests detect ATP using a bioluminescence assay, measuring the emitted light in Relative Light Units (RLU). A cutoff value of >200 RLUs has been validated by the manufacturer for the most common used ATP test (Clean Trace by 3M), which should distinguish acceptable post-cleaning organic residue levels. However, to measure 1 RLU, at least 10^2 to 10^3 CFU/mL of a microorganism, without organic soil, needs to be present as was shown in a simulated use study [36].

The correlation between ATP tests and microbiological cultures has been assessed by multiple studies with conflicting results. A recent review by Olafsdottir et al. found that post-HLD ATP results do not correlate with post-HLD microbiological cultures, but the

authors suggested it as a potential quality control measure after manual cleaning [33]. However, the relation between post-cleaning ATP test results and post-HLD cultures has only been clinically investigated in two small (pilot) studies [62, 63]. As ATP tests are being used by a growing number of endoscopy centers [64] and in studies to evaluate manual cleaning efficacy [47, 65], solid scientific data is needed whether this is a reliable and useful measuring method.

In the first part of this study, it was investigated whether the contamination of patient-ready DLEs could be reduced by introducing ATP tests to monitor manual cleaning efficacy. The results to that research question have been reported in a separate article by Rauwers et al. (reference) and showed no reduction in contamination of patient-ready DLEs. These study data are further investigated in the current study in order to assess whether there is a relation between the ATP level after manual cleaning and the presence of viable microorganisms in duodenoscopes and linear echoendoscopes after HLD.

Methods

The study design has previously been described by Rauwers et al.(ref). In short, after manual cleaning ATP samples were acquired and post-HLD microbiological cultures were collected of DLE used in endoscopic procedures in the tertiary care Erasmus Medical Center (Rotterdam, the Netherlands) between July 2017 and October 2018. In April 2018, the endoscopy center was relocated to another building. In the new building, new automated endoscope reprocessors (AER) were installed (WD440 PT, Wassenburg, Dodewaard, The Netherlands) which were connected to reverse osmosis water instead of tap water. The study consisted of two phases: 1) the control period during which reprocessing personnel was blinded for ATP test results and 2) the intervention period in which manual cleaning was repeated if an endoscope tested ATP positive. In the intervention period, endoscopes underwent the cycle of cleaning and ATP testing up to a maximum of three times before being subjected to automated HLD.

ATP was tested immediately after manual cleaning using the Clean-Trace™ Hygiene Management System for endoscopes (3M Company, Maplewood, USA). The following sites were sampled: all reachable surfaces of the forceps elevator and cap (if detachable and reusable) were swabbed with a Surface Test, and a 40 mL flush of the biopsy and suction channel was tested with the Water Test. Following the IFU (instructions for use), a site was considered positive if an ATP test passed the 200 RLU threshold [36, 66].

Directly after automated HLD and prior to drying, cultures were acquired from the forceps elevator and the detachable cap (if present) using a flocked swab (eSwab, COPAN, Brescia, Italy). The biopsy/suction channels were flushed with 20 mL sterile

saline solution. After the flush, a brush was pulled through the biopsy/suction channel. This brush was collected in a separate container (eSwab, COPAN, Brescia, Italy). After vortexing, 0.75 mL of the liquid Amies medium (eluent) of the eSwab used for the forceps elevator, detachable cap and brush samples was poured onto Tryptic Soy Agar. The flush samples were filtered through a 0.22 µm filter and placed on an R2A agar plate. All samples were incubated at 35°C and reviewed after four days for growth, presented in Colony Forming Units (CFU)/20mL per microorganism. Colonies were determinated by using Matrix Assisted Laser Desorption Time of Flight Mass Spectrometry (MALDI-TOF MS).

Statistics

For ATP test results, the range and medians per sample site are given, as these results do not follow a normal distribution. Four different contamination definitions are presented as number and percentage of positive samples per site: 1) gut microorganisms (without oral bacteria), 2) gastrointestinal microorganisms (gut and/or oral bacteria), 3) any growth of any type of microorganism and 4) growth of ≥1CFU/20 mL of gut microorganisms and/or ≥20CFU/20 mL of any other type of microorganism (AM20) as is used in Dutch and European guidelines [42, 67].

We made Receiver Operator Characteristic (ROC)-curves for each sample site to investigate whether ATP values could predict the presence of microorganisms. The ATP results were compared to the culture results of the same sample site. As the working channel was cultured by flush as well as a brush, both of these results were independently analyzed by comparing both of them to the ATP flush sample of the working channel. To calculate the sensitivity and specificity, we compared the ATP results after manual cleaning per sample site with the growth of any kind of microorganisms in the accompanying cultures collected post-HLD of the same sample site.

From the procedures performed during the intervention period, we only used the last ATP test results prior to HLD, since the ATP results leading to extra manual cleaning might no longer be related to post-HLD cultures due to the extra manual cleaning. Additionally, separate ROC-curves were produced to investigate an effect of the different study periods and the four different categories of microbiological presence.

Table 1. Presence of gut microorganisms, gastrointestinal microorganisms (gut and/or oral microorganisms), overall microorganisms and AM20 in cultures defined by sample site.

	No. of samples	Gut microorganisms		Gastrointestinal microorganisms		Any growth of microorganisms		AM20	
	N	N	%	N	%	N	%	N	%
Detachable cap	322	1	0.3	15	4.7	68	21.1	5	1.6
Forceps elevator	901	16	1.8	49	5.4	304	33.7	37	4.1
Channel flush	896	102	11.4	105	11.7	377	42.1	260	29.0
Channel brush	897	92	10.3	126	14.0	548	61.1	157	17.5
Total	3016	211	7.0	295	9.8	1297	43.0	459	15.2

N = number of positive samples, % = percentage positive samples per sample site. AM20: growth of ≥1CFU/20 mL of gut microorganisms and/or ≥20CFU/20 mL of any type of microorganism.

Results

ATP results

In total, 903 reprocessing procedures were performed including collection of ATP samples and cultures, involving 26 distinct DLEs. The 3016 collected cultures consisted of 322 detachable cap swabs, 901 forceps elevator swabs, 896 channel flushes and 897 channel brushes (Table 1). Five channel flush samples and four channel brush samples were lost. The same numbers of ATP samples were collected from the detachable cap, forceps elevator and working/suction channel (Table 2). The cap samples were taken from two distinct duodenoscopes which had a detachable cap. The majority (73.2%) of the ATP results were below the threshold of 200 RLU. The RLU range for the detachable cap samples was between 0 and 400.120 (median 163), for the elevator samples between 0 and 242.829 (median 113) and for the flush samples between 2 and 19.813 (median 42). The samples of the detachable cap had the most positive ATP test results with 146 (45.3%) of the tests exceeding the threshold of 200 RLUs, followed by 306 (34.0%) of the forceps elevator samples and 116 (12.9%) of the channel flush samples.

Table 2. Range of ATP values per sample site.

	No. of samples	Lowest value	Highest value	Median	No. of positive ATP samples (> 200 RLU), N(%)
Detachable cap	322	0	400120	163	146 (45.3%)
Forceps elevator	901	0	242829	113	306 (34.0%)
Channel flush	896	2	19813	42	116 (12.9%)
Total	2119	-	-	-	568 (26.8%)

Of the channel, only a flush sample was acquired for the ATP test. ATP: adenosine triphosphate test, RLU: relative light units.

Culture results

Flush and brush cultures showed that the suction/biopsy channel was most often contaminated, according all four categories of microorganisms (table 1). Growth of any microorganism was shown in 42.1% (n=377) of the flush cultures and in 61.1% (n=548) of the brush cultures. The detachable cap was the least often contaminated sample site (21.1%; n=68) followed by the forceps elevator (33.7%; n= 304). See table 1 for the contamination rates of the other microorganism categories per sample site.

Discrepancy ATP and culture results

For the majority of the cultures that were positive for growth of any kind of microorganism, the corresponding ATP test was negative. This was the case for the detachable cap (54.4%; 37/68), forceps elevator (72.0%; 219/304), flush (91.8%; 346/377) as well as the brush (91.2%; 500/548). To a lesser extent, cultures that were negative for growth were preceded by a positive ATP test in the detachable cap (45.3%; 115/254), forceps elevator (37.0%; 221/597), flush (16.4%; 85/519) and brush (19.5%; 68/349).

Of the detachable cap, 21.0% (37/176) of the negative ATP samples was accompanied by a positive culture, for the forceps elevator this was the case in 36.8% (219/595) of the negative ATP samples and 44.4% (346/780) and 64.0% (500/781) for the flush and brush samples. ATP positive samples were accompanied by negative cultures in 78.8% (115/146) of the detachable cap samples, 72.2% (221/306) of the forceps elevator, 73.3% (85/116) of the flush and 58.6% (68/116) of the brush samples.

Of the 903 complete tests performed, 379 (42.0%) had at least one positive ATP sample, in the other 524 (58.0%), all sample sites had ATP values below 200 RLU. Of the aforementioned 379 tests with at least one positive ATP sample after manual cleaning, 125 (33.1%) had post-HLD cultures without any form of bacterial growth. In 234 (61.7%) of the cases with at least one positive ATP sample, the cultures were AM20 negative (no growth of gut bacteria and other microorganisms only < 20 CFU). In 429 (81.9%) of the 524 endoscopes that were ATP negative on all sample sites, at least one culture was positive for any growth of microorganisms, and 258 (49.2%) had at least one AM20 positive culture.

ROC curves

When comparing the post-manual cleaning ATP levels to the post-HLD culture results in ROC curves, we found poor AUC values (figure 1): none of the four main ROC curves had an AUC above 0.5. The AUC of the detachable cap samples was 0.495 (0.411-0.578 95%CI), of the forceps elevator 0.444 (0.405-0.483 95%CI), of the channel flush 0.362 (0.326-0.399 95%CI) and of the channel brush 0.431 (0.392-0.470 95%CI). ROC-curves of the three other contamination categories (gut only, gastrointestinal bacteria and AM20)

showed similar outcomes as all accompanying AUCs were below 0.550. Separate ROC curves dividing the two study phases and the two endoscope types all showed AUCs below 0.6.

Sensitivity and specificity

The sensitivity of the ATP test of samples taken from the detachable cap was 45.6%, with a specificity of 54.7%. In samples of the forceps elevator, the sensitivity was 28.0% and the specificity 63.0%. The ATP samples of the channel had a very low sensitivity when compared to the flush and brush cultures (8.2% and 8.7% respectively), but the specificity in these samples was high (83.6% and 80.5% respectively).

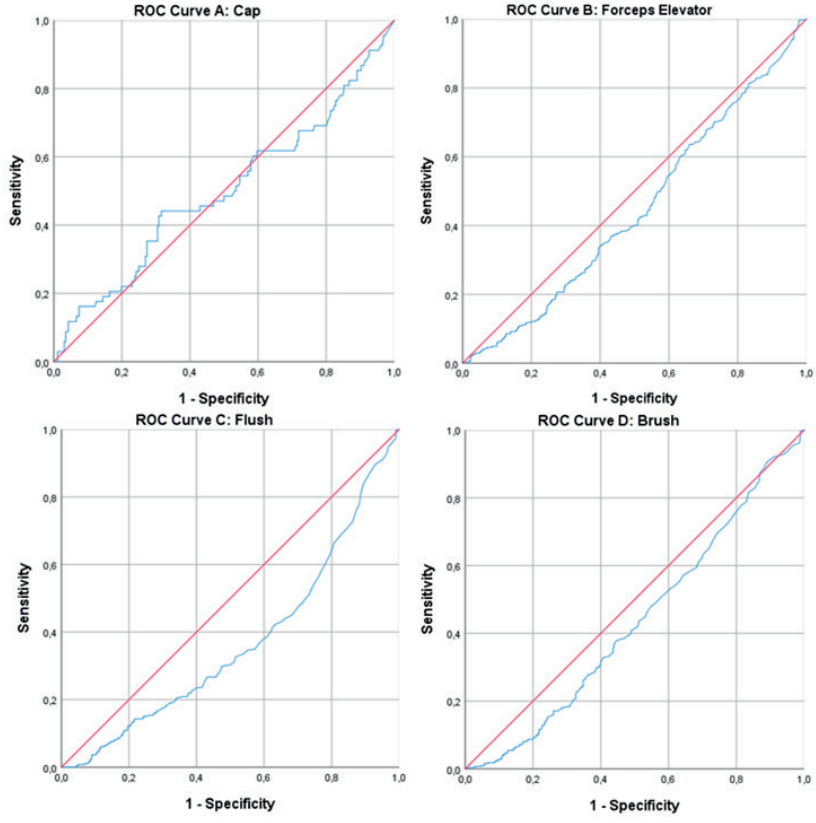

Figure 1. ROC curves correlating ATP outcomes with growth of microorganisms in cultures taken from four sample sites.

A. Detachable cap. AUC 0.498 (0.415-0.582) Sensitivity: 0.456, Specificity: 0.547

B. Forceps. AUC: 0.447 (0.408-0.486) Sensitivity: 0.280, Specificity: 0.630

C. Flush. AUC 0.368 (0.331-0.404) Sensitivity: 0.082, Specificity: 0.836

D. Brush. AUC: 0.436 (0.397-0.475). Sensitivity: 0.087, Specificity: 0.805

Discussion

This prospective study shows that ATP test results after manual cleaning do not predict post-HLD contamination of DLEs as detected by microbiological cultures. Also, no RLU cut off value was found to be of clinical value since the highest AUC achieved was 0.6 with a low sensitivity and in most sample sites a low specificity as well.

Numerous incidents have been reported in which endoscopes remained contaminated despite being reprocessed exactly according to the IFU and subsequently caused infectious outbreaks among patients [60]. A recent meta-analysis found that approximately 15% of patient-ready duodenoscopes were contaminated after adequate reprocessing in non-outbreak settings [68]. However, there was much heterogeneity in this meta-analysis, with only 40% of the included studies reporting the used CFU thresholds to define contamination (>1 to >100 CFU) and no differentiation between the types of bacteria found on these duodenoscopes was mentioned. In two nationwide studies in the Netherlands we also found 15% of the reprocessed duodenoscopes to contain gastrointestinal and/or oral microorganisms (≥1CFU/20mL) [59]. As no method has yet been developed to guarantee a zero contamination rate when using re-usable endoscopes, measures to test and control the reprocessing efficacy are urgently needed. The gold standard of microbiological culturing is expensive, laborious and results are known only after multiple days. In contrast, ATP tests are relatively cheap, easy to perform and give feedback within minutes and therefore would be an ideal alternative to culturing. A recent review already demonstrated no correlation between ATP test results and microbial load found in endoscopes with samples collected at the same time after HLD [33]. Several studies use ATP tests as a surrogate of cultures, with [69-71] or without [47, 65] comparing the ATP results to culture results collected at the same moment during reprocessing. In this study we used ATP tests as an in-process control and analyzed whether this could predict the final presence of microorganisms in cultures acquired after complete reprocessing. The results of our current study are in line with studies by Washburn [34] and Visrodia [62], in which no correlation between post-manual cleaning tests and post-HLD cultures were found. Visrodia et al. performed a pilot study with a low number of tests in which they also performed ATP tests after manual cleaning and culturing after HLD [62]. They also could not find a relation between ATP and culture outcomes.

We add to this body of evidence that RLU levels post-manual cleaning are not related to the presence of viable microorganisms after reprocessing. Therefore, we believe ATP tests after manual cleaning cannot be used as a substitute for microbiological culturing after HLD to evaluate adequate decontamination of endoscopes. This study shows that if ATP tests would be used, depending on the cut-off values used to define unacceptable growth of microorganisms, 33.1% (no growth of any microorganisms) to 61.7% (AM20 negative)

of the ATP positive endoscopes would undergo unnecessary extra cleaning. Contrarily, 49.2% (AM20 positive) to 81.9% (any form of bacterial growth) of the ATP negative endoscopes would be wrongly considered clean enough to continue towards HLD.

The ATP tests in this study were acquired after manual cleaning, whereas the microbiological samples were acquired after automated HLD. The difference between a positive ATP test and a negative culture could be explained by the effectiveness of HLD. Importantly, ATP tests are not designed to specifically identify living microorganisms, but can also reflect the presence of other forms of biological debris containing ATP, such as blood or biofilm components, which are not detected by microbiological cultures [33]. An explanation for negative ATP tests in endoscopes found to be contaminated post-HLD, might have been the presence of microorganisms in such a low concentration and not accompanied by organic soil, that they could not be detected by the ATP test [36, 61]. Contamination due to the disinfection process itself could also be an explanation. However, in endoscopes that were ATP negative but with positive cultures, not only environmental but also gut specific microorganisms were detected. Furthermore, cultures of the final rinse water of the AERs collected during the study did not reveal growth of any microorganisms within these machines.

We found large differences in positive cultures per sample site. The detachable cap had only 21.1% positive cultures throughout the entire study. The forceps elevator, flush and brush samples resulted in 33.7%, 42.1% and 61.1% positive cultures, respectively. This confirms the added value of channel sampling using a friction technique (not only flushing, but also pulling a brush through the channel for physical removal of microorganisms) [72, 73], as the brush samples had a 19% higher yield than the flush samples collected from the same channels. However, this higher yield was largely due to growth of small numbers of environmental microorganisms (skin and water microorganisms); for the other microorganism categories this higher yield by brushing was not found. Interestingly, the distribution of the ATP results per sample site was in the opposite direction, with the channel testing the least often and the detachable cap the most often ATP-positive. Also, the maximum and median ATP values were remarkably lower in the channel samples compared to those of the detachable cap and forceps elevator.

This corresponds with the systematic review by Olafsdottir et al. [33] in which higher ATP levels were found after manual cleaning in the elevator samples compared to the channel samples. A possible explanation might be the difference in sampling methods. While the forceps elevator and detachable cap are swabbed to test for presence of ATP, channels are flushed with 40 mL of sterile water. This means that any biological material from the channels is strongly diluted compared to the swab samples. Furthermore, channel flushes used for cultures are filtrated which also contributes to detection of all microorganisms in the channel.

Limitations

A limitation of this study was the single center design. In comparison with other ATP studies, we observed high contamination rates and high RLU values [61]. Therefore, the setting might not be comparable to other centers with lower contamination rates, however, this is an ideal setting to test the relation between ATP and culture results. One explanation for the high contamination rate might be that sample collection was performed prior to the drying of the endoscopes. In previous studies it was shown that effective drying is an essential step in reducing contamination levels [74, 75]. We found some very high maximum RLU levels, but these were mostly incidental outliers. Median RLU levels were still below the threshold of 200 RLUs and compared to some other studies our median RLU levels were comparable or even lower [62, 71]. Some of the DLEs with an extremely high ATP result still had negative cultures after HLD, strengthening the conclusion that positive ATP results after manual cleaning cannot predict post-HLD microbial presence. Lowering the threshold to 40 RLU, as is advocated by Ridtitid et al. [69], would lead to even more positive ATP tests with negative cultures, and thus to more unnecessary repeated manual cleaning.

Conclusion

ATP tests have been advocated to monitor the effectiveness of manual cleaning of endoscopes. By selecting endoscopes that would require an extra cleaning cycle, the ATP test should lead to less contaminated DLEs. Although no evidence for this use and effect has been established, the use of ATP tests after cleaning has increased in endoscopy centers. This large-scale prospective study shows a low diagnostic accuracy of ATP levels measured on DLEs after manual cleaning compared to the presence of viable microorganisms after HLD. Therefore, we conclude that use of ATP tests after manual cleaning will not lead to properly disinfected endoscopes and are of no added clinical value to improve the effectiveness and outcome of reprocessing of DLEs.

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CHAPTER
8

Endoscope-associated infections: A brief summary of the current state and views toward the future

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Abstract

World-wide reported duodenoscope-associated outbreaks of multi-drug resistant microorganisms are an indication that transmission of infection via contaminated endoscopes occurs more often than previously thought. To reduce the incidence of endoscope contamination, open communication between manufacturers, institutions and government agencies is urgently needed. Endoscope risk factor studies and thorough investigation of outbreaks by experts are instrumental to lower and ultimately annihilate infections by improving endoscope design, endoscope reprocessing, and hospital surveillance and control measures. As current reprocessing methods have a very small margin of safety, there is no room for error. However, strictly following the manufacturer's instructions regarding reprocessing does not sufficiently guarantee complete removal of microorganisms. Additional reprocessing measures to reduce contamination show promising results, but are costly to implement and do not assure zero contamination risk. Redesign of endoscopes to facilitate better cleaning and ultimately sterilization instead of disinfection might hold an important solution. Redesigning endoscopes should not only focus on the forceps elevator but on all parts of the endoscope, as all parts of the duodenoscope can be contaminated despite reprocessing. Single-use duodenoscopes would completely eliminate the risk of transmission of exogenous microorganisms, but come at a cost. Indeed the cost-effectiveness of all available solutions in relation to the true scale of transmission of exogenous microorganisms and increasing burden of world-wide antibiotic resistance patterns will ultimately determine which solutions hold the future.

1. Introduction

This issue of Techniques in Gastrointestinal Endoscopy is dedicated to raising awareness for the existence and extent of endoscope-related infections. In this article we will discuss future directions and opportunities that may limit and eventually eliminate endoscopes-related infections. Short-term measures to reduce the chance of endoscope contamination with current-design re-usable endoscopes are essential. Further development of endoscope design, reprocessing techniques and control measures to prevent contamination are needed to eventually eliminate endoscopes-related infections.

2. The current state

Endoscope-associated infections due to contaminated endoscopes continue to be reported worldwide [1-3]. Although endoscope-associated infections are in particular duodenoscope-related, recent reports also discuss outbreaks related to gastroscopes [4,5], colonoscopes [6], and bronchoscopes [7-9]. Patients infected via endoscopes are mostly detected during outbreak investigations or carriage by epidemiologically linked patients. Infections with multidrug-resistant microorganisms (MDRO) are easily recognizable and thus most frequently reported. It is needless to state that these infections are only the tiny tip of the iceberg as persistent contamination of antibiotic sensitive (non-resistant) microorganisms and contamination lasting only one or two procedures, remain unnoticed. A better estimate of the problem is the number of contaminated endoscopes despite 'adequate' reprocessing. Recent studies have mainly assessed duodenoscope contamination incidence rates ranging from 0.3% to 30% [10-16], although linear echoendoscopes with a similar complex design [11, 12, 17], gastroscopes [12, 18, 19], and colonoscopes can also be contaminated [12, 18, 19]. *Klebsiella pneumoniae* and *Pseudomonas aeruginosa* are frequently involved in endoscopy-related outbreaks, probably due to their persistence in biofilms. Subject to heavy wear and tear, damaged parts such as biopsy channels are vulnerable to biofilm formation. The actual risk for a patient of becoming infected (i.e. transmission) by a contaminated endoscopes is not yet known. Duodenoscope-associated outbreaks showed attack rates (the number of infected or colonized cases/number of exposed persons) from 12%-41% [20-24]. However, in a non-outbreak setting it is unclear what the actual risk of transmission of exogenous microorganisms is when using a contaminated endoscope. Outbreaks have been reported to be associated with multiple factors, including reprocessing protocol breaches [4, 24, 25], inadequate endoscope maintenance [10, 26], duodenoscope design issues [22], and ineffective or even absence of microbiological surveillance [20, 21, 27, 28]. Moreover, the true extent of the problem is unknown as detected outbreaks are not adequately reported, registered and/or communicated by manufacturers, hospitals and governmental bodies [1, 2]. A worldwide survey reported that nearly one fifth of the responding institutions experienced at least one endoscope-associated outbreak [29]. Providing minimal invasive diagnosis and therapeutic options, endoscopy has established itself as an essential

part of contemporary medicine with low procedural risks and costs. The total volume, complexity and invasiveness of endoscopic procedures are expected to keep rising in the coming decades. Safe endoscopic procedures without avoidable microbiological transmission risk in this day and age of increasing reports of antibiotic resistant bacteria and attributable deaths [30] are only possible if all parties involved (gastroenterologists, medical microbiologists, government agencies, regulatory bodies and manufacturers) acknowledge the issue and act concertedly.

3. Future view 1: Short-term measures

3.1. Transparent communication

More transparent communication and thorough assessment of adverse events (i.e. outbreaks, device failures and reprocessing risks) by hospitals and manufacturers, whether involving endoscopes or reprocessing equipment, is essential. Recently, Olympus pleaded guilty to failing to adequately report TJF-Q180V duodenoscope-associated outbreaks in Europe. The US Food and Drug Administration (FDA) stresses that if adverse events are not reported in a proper and timely manner, patient safety may be put at risk [31]. Investigation of the outbreaks by experts, including dismantling the persistently contaminated endoscope, is instrumental to assess and improve endoscope design, scope reprocessing and surveillance measures. Although up to 40 duodenoscope-associated outbreaks have been reported [2, 32], few reports describe investigation of the endoscope concerned [22, 23, 26, 33-35]. One independent investigation led to a design modification and worldwide recall of the Olympus TJF-Q180V duodenoscope [22, 34, 35], including 4400 duodenoscopes in the US [36]. Already in 2015, the FDA demanded post-market surveillance studies by Fujifilm, Olympus and Pentax [37]. After all three manufacturers initially failed to conduct these studies [31], the first interim results show a higher-than-expected contamination rates of up to 3% for high concern organisms [37]. In response to this, the FDA stated that reprocessing is not sufficient to avoid duodenoscope-associated infections [31]. Awareness that endoscope contamination is a clinical reality and cannot be neglected should enforce a proactive attitude of all relevant professionals working with endoscopes. Close and regular communications are required between reprocessing staff, medical device experts, infection control professionals, medical microbiologists and gastroenterologists in order to control endoscope-related infections.

3.2. Endoscope risk factors

To develop tailored measures to control endoscope contamination attributable to its design, more information about endoscope-specific risk factors such as vulnerable design issues, endoscope durability and optimal inspection frequency are needed. Currently, attention focuses on complex design endoscopes, as persistent contamination of the forceps

elevator [10, 24, 26, 38], and the protection cap [22, 33], have been a source for multiple outbreaks. Although several type specific design issues have been raised [22, 33], contamination of duodenoscopes and linear echoendoscopes does not seem to depend on manufacturer or type [11, 39]. Moreover, not only the forceps elevator but the whole endoscope should be critically assessed. All endoscope sites including channels can be contaminated [39], and all endoscope types are at risk of contamination [12]. Borescope studies show that the inside of all types of gastrointestinal endoscopes are often damaged [40, 41], which can affect the risk of contamination [42], as damage to internal parts may facilitate biofilm formation. The American Society for Gastrointestinal Endoscopy (ASGE) warns that endoscope longevity and durability are understood incompletely [43]. Several outbreak investigations show that normal functioning duodenoscopes had critical abnormalities [10, 26, 33], which may have contributed to contamination. Timely inspections and preventive maintenance could prevent use of damaged endoscopes. Affected centers and professional societies advocate that guidelines should become available pertaining endoscope evaluation and maintenance schedules [7, 10, 17, 26, 44]. Nowadays manufactures advice yearly inspections of duodenoscopes [36, 45-47]. Contamination of duodenoscopes and linear echoendoscopes however, is independent of physical age and therefore usage-based inspections could be considered [11](unpublished data). We advocate the implementation of an endoscope specific log file in which users and manufacturers keep track of previous endoscope repairs and culture results. This facilitates early recognition of specific risk factors including possible endoscope design flaws.

3.3. Process control

Although improvements of endoscope designs and reprocessing techniques are to be expected, the majority of hospitals will continue to use current-design endoscopes and High-Level Disinfection (HLD) reprocessing, at least in the decade to come. Therefore strict process control, regular intensive training of cleaning personnel and regular audits remain essential [48], as the current reprocessing technique has a very small margin of safety [49-52] and is error-prone [53-55]. Surveys show a large variation of compliance with reprocessing practices [14, 29, 56, 57]. A worldwide survey among 163 institutions showed that manual cleaning of endoscopes is not routinely performed in 20% of institutions [29]. This is alarming because without manual cleaning adequate disinfection of the endoscope is not possible. Repeated surveys can help to identify persistent reprocessing flaws and create a critical awareness as well as promote knowledge-sharing among institutions [56, 58]. Endoscope manufactures may develop tools to assess (and thereby enhance) compliance with Instructions For Use (IFU) after they have completed the FDA-ordered human factors studies [31]. Even when novel reprocessing techniques including sterilization become available, protocol adherence including meticulous manual cleaning will remain a cornerstone to eliminate endoscope related infections.

3.4. Control measures

According the FDA, following current reprocessing practices is not sufficient to avoid all duodenoscope-associated infections [31]. Therefore, the efficacy of scope decontamination should be verifiable with easy to apply and effective control measures. Microbiological surveillance is the gold standard and considered as the bare minimum by the majority of the international guidelines to prevent the use of persistently contaminated endoscopes [44, 59-61]. Negative culture results however, do not guarantee a total absence of microorganisms. Several outbreak investigations were not able to retrieve the concerning microorganism from the contaminated endoscope [23, 33, 62, 63]. Furthermore, there is no (international) consensus on the sampling and culturing method of endoscopes. This complicates the comparison of culture outcomes from studies around the globe. The optimal culture frequency is also subject of debate, varying between weekly to yearly cultures. Culture-and-quarantine strategies may be challenging for some centers from the viewpoint of economics: obtaining culture results takes at least 48-72 hours and quarantining endoscopes while awaiting these culture results thus requires the purchase of extra endoscopes to overcome scope downtime. Other tests of which the result is readily available, such as adenosine triphosphate (ATP) tests and bioburden assays measuring protein, hemoglobin, or carbohydrates, have several limitations. Testing is performed mainly after manual cleaning to allow the endoscope to proceed to HLD, as post-HLD testing is not sensitive enough to negate the presence of microorganisms. Although the correlation between ATP test results and culture outcomes seems poor [64], these tests could also prove useful to enhance manual cleaning protocol adherence and thereby reduce the incidence of post-HLD endoscope contamination.

4. Future view 2: New reprocessing methods for current-design heat labile endoscopes

4.1. Spaulding criteria: still applicable?

The Spaulding classification has been used for decades and categorizes reusable medical devices in three classes based on the risk of transmission of microorganisms. Duodenoscopes are classified as "semi-critical" devices, meaning that they come in contact with non-intact skin or mucous membranes, requiring HLD [65]. However, the Spaulding classification may be outdated for flexible endoscopes since the procedures for which these devices are being used have become more invasive. Endoscope reprocessing including HLD has a very small margin of safety. Endoscopes are contaminated with a microbiological load up to 7-10 $\log_{10}$ [49-52], while reprocessing reduces this load at a maximum of 6-12 $\log_{10}$ [49-52]. This means that reprocessing leaves no room for error and hence it is an error-prone procedure [53-55], in particular for duodenoscopes which are even more difficult to reprocess due to their complex design [22, 49]. Sterilization reduces a much higher load of microorganisms, but is only required for critical instruments that come in

contact with sterile tissue [65]. ERCP procedures have become more time consuming and more invasive while breaching more often natural mucosal barriers, for example through papillotomy or ampullectomy. Also, patients are becoming more elderly including additional comorbidity and are sometimes immune compromised. The possibility of an infection due to translocation of endogenous microorganisms, i.e. those originating from the patient him/herself, has always been a potential risk that is inherent to ERCP [66]. Importantly, outbreaks now show that duodenoscopes are vectors for transmission of exogenous microorganism, i.e. those originating from a previously treated patient with that same endoscope. In an outbreak setting it was shown that especially biliary obstruction factors (i.e. cholangiocarcinoma, biliary stent placement) were associated with an increased risk of transmission of exogenous microorganisms [67]. This leads to the question if duodenoscopes are in fact critical devices which should be sterilized to exclude avoidable transmission risks for the patient. Current-design heat liable endoscopes cannot endure regular high temperature sterilization methods. Therefore, reprocessing methods with a larger margin of safety should be developed which are both suitable for use with current design duodenoscopes and safe for cleaning staff personnel.

4.2. Double HDL or low temperature sterilization

In 2015, the FDA suggested four potential measures in addition to regular reprocessing to reduce endoscope contamination rates. These measures including repeat HLD, ethylene oxide (EtO) sterilization [15, 16, 68-70], the use of a liquid chemical sterilant and surveillance culturing [10, 11, 15, 17] have been explored in several studies. Although some of these studies show that a reduction of contamination is feasible, no studies convincingly show a zero contamination rate. Most of the suggested measures require extensive logistical and financial investments including the purchase of extra endoscopes to overcome scope downtime. Double HLD could be easily implemented in daily practice and does not require extensive additional costs. Studies assessing the effect of this method were unable to show a zero contamination rate [13, 16, 69], even if a second manual cleaning step was added as well [69]. Performing two cycles of HLD or EtO sterilization after single HLD has not led to lower contamination rates compared to the standard procedure using single HLD [13]. EtO sterilization uses low temperatures and has been used effectively to clean contaminated duodenoscopes after outbreaks [71] or when contamination persisted despite repeated processing cycles. However, this form of sterilization comes with several limitations. EtO has an increased turn-around time requiring the purchase of additional duodenoscopes, it can damage duodenoscopes and it is toxic and carcinogenic to personnel [72, 73]. Furthermore, complete sterilization has not yet been proven in randomized trials [13, 71] and the addition of EtO does not appear to be cost-effective [74]. Hydrogen peroxide ozone sterilization [75] and disinfection using plasma activated water [76] have both so far only been tested in small studies. Both methods showed promising results, but have yet to be proven in clinical trials. For now,

none of these additional measures to the current reprocessing cycle seem to be able to a guarantee a zero contamination rate of reusable endoscopes.

5. Future view 3: Redesign of endoscopes

5.1. Peer-review is essential

The expectation is that redesigned endoscopes will facilitate improved reprocessing procedures or sterilization thereby preventing the risk of transmission of microorganisms. However, lessons can be learned from the introduction of recently adapted duodenoscope models. The current risk classification of endoscopes in both Europe and the US state that new endoscope models are given market authorization without the need for clinical testing if the modified design is sufficiently technical similar to previously approved designs. Depending whether manufacturers themselves decide if the new design could affect endoscope safety or efficacy, the design should be clinically tested [77, 78]. In 2010, Olympus introduced the TJF-Q180V duodenoscope with a sealed elevator channel, based on a previously approved design with an open elevator wire channel [1]. In 2014, only after the occurrence of multiple outbreaks related to the use of the TJF-Q180V, the FDA indicated that the design modifications had a potential impact on safety. After adaption of the elevator wire channel sealing in 2016, the FDA considered the modified design to be equivalent [36, 79]. To reduce the risk of transmission Olympus recalled thousands of duodenoscopes worldwide [36, 80]. The lesson to be learned is that successive design adjustments of endoscope models can ultimately result in a substantial design change as compared to the original design with a potential safety risk. This questions whether this system of semi-automatic 'renewal' of market authorization isn't outdated and poses safety risks that should be avoided.

5.2. Reusable endoscopes with single-use parts

Newly introduced duodenoscope models have disposable protection caps [81, 82], including models with a disposable forceps elevator or with a sterilizable removable elevator mechanism [83, 84]. These adjustments should facilitate adequate cleaning of crevices surrounding the forceps elevator, but this has not been proven in peer-reviewed studies yet. Current design adjustments have focused on the tip and the forceps elevator but multiple sites within the duodenoscope have shown to be predilection sites for contamination [39]. More innovative designs should also address other parts, in particular the damage-sensitive biopsy channel as this site has shown to be often contaminated. Nevertheless, without improvement of the margin of safety of reprocessing other parts of the endoscope remain at risk of contamination.

5.3. Single-use endoscopes

A very important and relevant issue is the fact that it is still unknown which percentage of post-procedure infections are to be attributed to contaminated endoscopes, that is exogenous rather than endogenous infections. The use of single-use endoscopes would eliminate any risk of transmission of exogenous microorganisms. The use of disposable duodenoscopes, bronchoscopes and ureteroscopes has already been tested in clinical practice [85-87]. Apart from whether single-use endoscopes perform as good as reusable endoscopes, implementation of disposable endoscopes will ultimately depend on their cost-effectiveness. A recent report estimated the total per-procedure costs of reusable duodenoscopes at $297-818, depending on the ERCP volume [88]. Although extrapolation to other practices is limited as the analysis was performed in a US tertiary center, the report stated that the use of single-use instead of reusable duodenoscopes would add significant costs. Furthermore, the costs of the HLD reprocessing infrastructure would remain largely the same because these facilities would still be required for the cleaning and disinfection of gastroscopes and colonoscopes until these are disposable as well. Another cost exploration report conservatively estimated reprocessing costs of one reusable endoscope at $114-$280, excluding purchase and maintenance costs [89]. The bigger picture however, also includes costs for managing colonized individuals and infected patients, infection prevention, and implementation of measures to improve the current reprocessing-process (e.g. as suggested by the FDA [74]). Surveillance costs can vary, as currently there is no consensus on which microbiological surveillance method to use and its frequency. In a US tertiary center performing monthly cultures, annual costs per endoscope were $1500 to which the purchase of extra duodenoscopes to overcome downtime was not included [70]. In addition to the burden patients have to endure because of repeated culturing or isolation measures, outbreak management also poses a large financial strain to the health care system. The costs of other non-endoscope related nosocomial outbreaks ranged from €10,778-€356,754 or even up to $804,263 [90, 91] of which about 50% lost revenues were caused by missed incomes due to closed beds. Future studies incorporating all (hidden) expenses should determine if the costs of single-use duodenoscopes are justified.

6. Conclusion

Endoscope-related infectious outbreaks of microorganisms including MDRO call for stringent control measures and critical assessment of current-design endoscopes in the short term, and for the development of innovative reprocessing techniques and radically different endoscopes designs in the long term. To date, the ideal reprocessing method that guarantees absence of exogenous microorganisms of reprocessed endoscopes with an acceptable turnover time while being safe for staff and endoscopes is not available yet. Newly introduced duodenoscope models with disposable parts are the first step towards the development of durable endoscopes that potentially have

a lower risk of contamination. However, instead of reprocessing reusable endoscopes, another route to consider is the use of single-use endoscopes. This would ultimately eliminate the risk of endoscope transmitted infection, but costs may be insuperable, even for the contamination-prone duodenoscopes. Depending on the actual scale of transmission of exogenous microorganisms through contaminated endoscopes and the development and burden of world-wide antibiotic resistance patterns, in relation to the cost-effectiveness of each potential measure to reduce or abolish the risk of infection, time will tell which solution holds the future.

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CHAPTER
9

Discussion and future perspectives

General summary and discussion

The worldwide surge of duodenoscope-associated outbreaks since the new millennium show that current reprocessing practices do not guarantee adequately decontaminated endoscopes. To prevent future outbreaks, identification of risk factors contributing to outbreaks and endoscope contamination is essential. The discussion of this thesis is divided into three themes. First, it describes the background of reprocessing of duodenoscopes and linear echoendoscopes (DLE), the multiple parties that are involved, and potential pathways leading to an outbreak. Secondly, it gains insight in the true size of the underlying problem of DLE contamination by showing the enduring high prevalence of DLE contamination with digestive tract bacteria in Dutch hospitals. In the third part of this thesis we show the results of a study of a cleaning test as a potential marker to check for residue to lower the contamination rate.

Part I: Duodenoscope-associated outbreaks

In **Chapter 2** we discuss the developing story of duodenoscope-associated outbreaks in 2015 as a call for awareness for Dutch medical doctors of all specializations. Outbreaks reported by high impact media such as the LA times and Washington Post, and in 2018 in the Dutch newspaper *AD,* caused public disturbance, leading patients to question ERCP safety.[1-3] Contamination of endoscopes is a multidisciplinary issue involving manufacturers, regulatory agencies, hospital directors, gastroenterologists, medical microbiologists, infection prevention specialists, disinfection professionals and disinfections assistants, as well as medical specialists such as internists and surgeons whose patients also undergo ERCP procedures. Details of endoscope reprocessing were unknown by this audience and the scale of the problem was unclear. In the Netherlands, at that time, endoscope surveillance cultures were not mandatory as only process control was used,[4] which considers reprocessing to be adequate if performed according the manufacturer's instructions for use (IFU). Outbreaks of MDRO were only reported by large tertiary centers which were able to detect and trace the outbreak using the distinct features of the MDRO. It is very likely that transmission of microorganisms occurs regularly while not recognized. Duodenoscope-associated infections (DAI) can also occur non-clustered, and a DAI with susceptible microorganisms can easily be mistaken for an endogenous infection as a result of the ERCP procedure.[5] In addition, DAI are also under-reported and inadequately registered,[6] leading to gross underestimation of the prevalence. An adequate registration system of outbreaks and of transmission by endoscopes, including susceptible microorganisms, is still lacking. A recent review assessing published reports, identified up to almost 500 infected patients and over 30 deaths caused by contaminated duodenoscopes between 2008 and 2018,[7] but this is still considered to be the tip of the iceberg. Positively, hospitals are currently more aware about the possibility of endoscope-associated infections, as shown by two recall actions

by Dutch and Belgian hospitals in 2021 reported by local layman media.[8, 9] We also paid attention to current legislation which grants endoscopes with new designs market access based on their presumed similarity with previous models without the need for clinical trials.[10, 11] This led to patients being treated with equipment which design modifications affected patient safety. Furthermore, manufacturers failed to timely register adverse events of their medical devices.[12] This led to the criminal persecution of Olympus as they did not timely filed the outbreak reported by the Erasmus MC in 2012.[13] In reaction to the surge of outbreaks, the FDA proposed several solutions to reduce contamination rates including the development of duodenoscopes with disposable parts or single-use endoscopes. Although still not automatically required for new endoscope designs, we believe that studies should be conducted to prove their safety and added value.

In **chapter 3** we performed a root cause analysis of contributing factors to an outbreak of multidrug-resistant *Klebsiella pneumoniae* in a Dutch tertiary academic hospital in 2015. This outbreak is exemplary that the current system of process control is not robust enough. We found that the outbreak was the result of a multitude of factors including the design of the duodenoscope, inadequate repairs, improper cleaning, miscommunication about cleaning protocols and lack of microbiological surveillance. Recurrent outbreaks like these since the initial surge since 2008,[6] show that DAI are an ongoing problem. Alertness by adequate surveillance, end control and recurring audits remains necessary. The attack rates (the number of infected or colonized cases/number of exposed persons) of 35% and 29% were similar to other outbreaks (12%-41%).[14-18] The outbreak period of 8 months show that contaminated endoscopes can remain undetected for months, just as other outbreaks had lengths of four or even up to twelve months.[16, 18-22] Following the outbreaks, half-yearly microbiological surveillance has been introduced in the Netherlands.[23] To reduce the risk of month-long outbreaks as a result of undetected use of contaminated endoscopes, more frequent surveillance could be considered. The FDA has ordered manufacturers to file new admissions tests to reevaluate endoscope designs, and manufacturers now suggest yearly servicing inspections.[24-27] As endoscope biopsy channels are frequently damaged,[28] which can occur within a few months of use,[29] and duodenoscopes without indications for servicing can have critical abnormalities which may contribute to outbreaks,[21, 30] preventive inspections and maintenance must be considered. Clear communication between manufacturers and Independent Servicing Organizations as well as a transparent servicing market should enable hospitals to be sure that their repaired duodenoscopes is of similar quality as a brand-new one. Furthermore, to ensure reprocessing protocol adherence, manufacturers must communicate new reprocessing recommendations right away and hospitals must perform recurrent audits. Lastly, to improve the reliability of the defensive layers around reusable endoscopes and to avoid that internal manufacturer

assessment goes unreported,[21, 31] after future outbreaks hospitals should report and publish their internal review.

Part II: Contamination of complex gastrointestinal endoscopes: prevalence and risk factors

The second part of this thesis focuses on the prevalence and risk factors of contamination of duodenoscopes and linear echoendoscopes (DLE). In **chapter 4** we conducted the first nationwide study to assess the prevalence rate of duodenoscopes contaminated with digestive tract bacteria among all Dutch ERCP centers. We found that 22% of the duodenoscopes, originating from 26 (39%) centers were contaminated were contaminated with any microorganism with ≥20 colony forming units (CFU)/20 mL (AM20). Moreover, we found that 15% of the Dutch duodenoscopes harbored microorganisms with gastrointestinal or oral origin (MGO). These results confirmed our hypothesis that patients undergoing ERCP are regularly being treated with contaminated equipment, and not detected as such. No difference was shown in contamination risk between the different duodenoscope types, which is in line with other studies and with reported outbreaks involving various duodenoscope types.[6, 32] Other studies found lower contamination rates,[30, 32] which could be explained by the continuous feedback of the post-procedure or everyday morning cultures of these studies. Another possibility is that we used a more sensitive sampling and culturing method, including a more sensitive contamination cut-off and a longer incubation time. This study showed that to minimize the risk of t microbial transmission more stringent measures were required including microbiological surveillance

In **chapter 5** we present the results of the second nationwide prevalence study in which we assessed the contamination prevalence of duodenoscopes as well as linear echoendoscopes. The MGO contamination prevalence of 15% found with the PROCESS 2 study was similar to the first PROCESS study which was conducted two years earlier.[33] This shows that not only patients undergoing ERCP but also EUS are being treated with contaminated equipment and that this risk had not lowered since PROCESS 1. The contamination prevalence was 8% if the definition by the Centers for Disease Control and Prevention for high-concern organisms was used. After publication of outbreaks in 2015, the FDA demanded post-market surveillance studies by Fujifilm, Olympus and Pentax which all three initially failed to conduct.[12, 34] Based on the first interim contamination rates of 3% for high concern organisms,[34] the FDA stated that reprocessing is not sufficient to avoid duodenoscope-associated infections.[12] Current interim show a rate of 4.1%-6.1%,[34, 35] which is in line with results of the PROCESS studies. Studies assessing surveillance, [32, 35-37] culture and quarantine strategies,[30, 32, 38, 39] and disinfection interventions found lower rates.[40-42] These lower rates are promising and may be the result of continuous feedback and raised alertness by the studies'

culture results,[32, 39-41] but also less sensitive sampling and culture methods. Assessing the DLEs of both PROCESS studies showed that the age of older and younger endoscopes had similar contamination risks, which suggests that if old and heavily used DLEs are correctly maintained their contamination risk is similar to brand-new DLEs. Furthermore, contamination was independent of reprocessing characteristics. Probably manual cleaning is the most important factor, complicated by factors such as the complex endoscope design, endoscope damage and whether a biofilm has already formed. While initially the forceps elevator was thought to be the culprit as it was the source of contamination in several outbreaks,[18, 20, 21, 30] MGO rates of the biopsy channels flush (5%), suction channel flush (5%), and brush (8%) were higher than the forceps elevator (4%). Both PROCESS studies show that especially the endoscope channels harbor gastrointestinal microorganisms.

Part III: Long- and short-term solutions: a role for post-manual cleaning tests?

In the third and final part we investigated if use of post-cleaning adenosine triphosphate (ATP) tests lowers the number of DLE contaminated with gut flora. Multiple gastroenterology and regulatory agencies have stressed the need for easy control measures to check for adequacy of endoscope decontamination.[43, 44] Microbiological surveillance cultures are the current gold standard to assess if reprocessing was adequate, but have multiple downsides as they are labor intensive, expensive and give delayed feedback due to laboratory process time. The FDA and multiple endoscopy societies have suggested the ATP-test as an alternative as it is relatively cheap, easy to perform, and it gives feedback within minutes.[45] The test is a bioluminescence assay which emits ATP-dependent light measured in Relative Light Units (RLU), while using luciferase-catalyzed oxidation of luciferin. Although presence of ATP may indicate residual organic material which requires cleaning, it is unclear if use of ATP tests actually lowers the number of contaminated endoscopes. Therefore, we initiated the prospective single center before-and-after DETECT study (Duodenoscopes and linear echoendoscopes: Efficacy of ATP TEsts Compared to visual inspection).

In **chapter 6** we present the results DETECT study. DLEs were ATP tested post-manual cleaning after 909 procedures. During the intervention period DLEs were recleaned if positive before proceeding to high-level disinfection (HLD). DLEs underwent microbiological sampling after HLD. Introduction of ATP tests did not reduce the gut flora contamination rate and did not stop or prevent the use of endoscopes contaminated with gut flora. Although contamination with gut flora was less likely to occur during the intervention period (OR 0.32; 95%CI 0.12-0.85), the absolute gut flora contamination rate was higher (16%; n=67 vs. 21%; n=102). The lower odds on gut flora contamination in the intervention period were based on two duodenoscopes. During the control period,

these duodenoscopes had multiple episodes of ongoing contamination with the same microorganism. The episodes were ended by quarantining and repairs before the start of the intervention period and were thus not terminated by ATP testing.

This is the first controlled and adequately powered study with blinded study cultures, which confirms the results of previous smaller studies that post-cleaning ATP tests are not effective.[46, 47] False negative tests may provide a false sense of security, as during the intervention period the number of positive ATP-tests were lower while gut flora rates remained high. The rates in this study, which was blinded for study culture outcomes, were far higher compared to other large-scale open design studies with post-procedure or daily surveillance,[30, 32, 38] but may be more representative for clinical practice. Especially the rates for Pentax duodenoscopes were high, potentially the result of biofilm formation in the channels. The high contamination rates and undetected contamination episodes show that monthly surveillance cultures were inadequate. Until the risk of transmission via contaminated equipment is eliminated or reliable quality checks are introduced, more frequent microbiological surveillance is indicated.

The results of the DETECT study showed a discrepancy between ATP-positive test results and post-HLD presence of gut flora. In **chapter 7** we assess the predictive value of post-cleaning ATP tests for the presence of microorganisms after HLD, using data from the DETECT study. We compared the RLU levels of ATP tests performed after manual cleaning with growth of any microorganism in post-HLD cultures. Nor the RLU cut-off according to the instructions for use, nor any other cut-off was found to be of clinical value: all the ROC curves per sample site, DLE type and microorganism type had an area under the curve of <0.6, with a low sensitivity and in most sample sites also a low specificity. This showed that post-cleaning ATP tests could not predict the absence or presence of microorganisms after HLD. This is in line with earlier pilot studies which also did not found a correlation between post-cleaning ATP tests and post-HLD cultures.[47, 48]

The difference between sites with high ATP test results and negative cultures could be explained by a reduction of debris by HLD. The ATP values can also reflect presence of other debris containing ATP but no microorganisms such as blood. The combination of negative ATP tests and positive cultures could be the result of microorganisms in low concentrations, unable for the ATP test to detect. Another explanation might be the sampling method of the channel which is most often contaminated. The ATP flush of the channel is strongly diluted, while filtration of the culture flush contributes to detection of all present microorganisms. The low diagnostic accuracy of post-cleaning ATP levels for presence of post-HLD microorganisms means that ATP-tests have no clinical value in improving the outcome of DLE reprocessing.

Future perspectives and recommendations

In **chapter 8** we look forward to the future, discussing opportunities and directions which may reduce and potentially eliminate endoscope-associated infections. In the coming years major improvements in reprocessing techniques and endoscope design such as endoscopes with disposable elements or even single-use endoscopes are expected. However, the majority of the hospitals will continue to use reusable endoscopes in at least the coming decade. Therefore, process control as well as regular audits including training of cleaning personnel to follow the IFU to the letter and providing them with ample time to complete all reprocessing steps remain essential.[49] Also microbiological surveillance remains the gold standard and the bare minimum to prevent ongoing transmission of microorganisms, as no bioburden assay has proven useful yet. Endoscopy societies should reach consensus on the sampling and culturing methods, as well as on the optimal culture frequency. The other short-term solutions include clear communication between all parties involved, endoscope risk evaluation and improvement of reprocessing methods. As a result of FDA safety communications, a critical evaluation by the US senate,[6] and updated multisociety guidelines[45, 50] awareness on the subject has improved, leading to better communication between gastroenterologists, medical microbiologists and infection prevention professionals. In the Netherlands in particular, awareness has improved because of participation of all Dutch hospitals in the two PROCESS studies,[51] and introduction of a new Dutch microbiological surveillance guideline in 2018.[23] Members of our research group contributed to this guideline which was supported by all involved Dutch societies. Furthermore, transparent communication, reporting and evaluation of adverse events (i.e. outbreaks, device failures and reprocessing risks) as well as post-market follow-up of endoscope designs remains paramount.

While initially the forceps elevator was seen as the culprit for contamination, evidence now shows the entire endoscope and in particular the channels may harbor microorganisms, independent of physical age or usage.[51] During outbreaks it was shown that normal-functioning duodenoscopes had critical abnormalities,[21, 30, 31] which may affect the contamination risk.[52] Therefore manufacturers should consider usage-based inspections in combination with an endoscope specific log file including previous repairs and culture results. This facilitates recognition of endoscope design specific flaws and the need for preventive maintenance.

To reduce the contamination risk of reusable endoscopes, several reprocessing measures in addition to the manufacturers' IFU have been proposed including ethylene oxide (EtO) sterilization and repeat HLD. They show promising results, but are costly and do not provide zero contamination rates. The current method of reprocessing including

HLD has a very small margin of safety leaving no room for error.[53-56] As ERCP procedures are increasingly more invasive and often natural mucosal barriers are breached, new reprocessing methods should be developed which have a larger margin of safety than currently required for reusable duodenoscopes.

Ultimately, the risk of contamination must be eliminated by radically redesigned endoscopes which can be sterilized or single-use endoscopes. Currently redesigned duodenoscopes are introduced with disposable elements such as disposable protection caps,[57, 58] a disposable forceps elevator or with a sterilizable removable elevator mechanism.[59, 60] These endoscopes will not hold the solution, as the other parts remain unchanged and the endoscope simply cannot be sterilized. Furthermore, these endoscope designs are not peer-reviewed. An important lesson from the failed introduction of the TJF-Q180V duodenoscope, is that successive changes in endoscope design can lead to safety risks. Therefore, the current situation of market authorization of new endoscopes without clinical tests if the modified design is technical similar to a previous approved design, as judged by the manufacturer, needs to change.

Single-use endoscopes show promise in overall technical performance and safety profile comparable to reusable duodenoscopes,[61] but implementation will depend on their cost-effectiveness. The clinical question which is still unanswered is how often transmission of microorganisms via endoscopes occurs and how many times it leads to a clinically relevant infection or colonization of the patient. A first retrospective revision by Kwakman et al., estimated a risk of duodenoscope-associated infections (DAI) of 0.01%:[62] at least 180 times higher than previous estimates.[63] To assess the true incidence, prevalence, patient burden and financial costs of DAI, one would ideally conduct a prospective multicenter study blinded for study cultures and including (pre-endoscopy) patient cultures.

Newly designed (single-use) endoscopes will not be a widespread and readily available solution to eliminate the transmission risk. Therefore the application and decontamination of reusable DLE destined to be in operation for many years to come, must be improved in order to lower contamination rates.

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Appendices

Nederlandse samenvatting

Endoscopen zijn flexibele, herbruikbare instrumenten die worden ingezet bij de diagnostiek en behandeling van aandoeningen in het maag-darmkanaal. Hieronder vallen ook duodenoscopen die worden gebruikt voor endoscopische retrograde cholangiopancreaticografie (ERCP) procedures bij patiënten met galweg- en pancreasziekten. Dit bestaat ondermeer uit de verwijdering van galwegstenen en het behandelen van patiënten met een goed- of kwaadaardige vernauwing van de galwegen of alvleesklierbuis door plaatsing van een endoprothese. Vergeleken met andere endoscopen heeft de duodenoscoop een complex ontwerp. Om vanuit het duodenum in de galwegen en alvleesklierbuis te kunnen werken heeft de duodenoscoop geen tip die standaard voorwaarts is gericht, maar een zijwaarts gerichte tip. Hierin zitten de lichtbron, camera, lucht- en waterkanaalopening, werkkanaalopening en een liftmechanisme. Met het liftmechanisme kan de stand van de instrumenten aangepast worden. Om dit liftmechanisme te bedienen loopt een draad door een separaat, smal liftkanaal. Door het complexe ontwerp bestaande uit de zijwaarts gerichte tip, het liftmechanisme en het liftkanaal zijn duodenoscopen moeilijker te reinigen vergeleken met andere flexibele endoscopen. Voor echo-endoscopie (EUS) procedures wordt onder meer de lineaire echo-endoscoop gebruikt. Deze heeft een soortgelijk ontwerp als de duodenoscoop met daarbij een echokop op de zijwaarts gerichte tip en een extra kanaal voor het opblazen van een ballon rond de tip.

Tijdens procedures raken endoscopen gecontamineerd met darmflora. Door translocatie van een endogeen micro-organisme (een bacterie die hoort bij de darmflora van de patiënt) tijdens de ERCP procedure kan er een infectie optreden; dit is een bekend risico. Als flexibele endoscopen inadequaat gereinigd en gedesinfecteerd worden, kunnen patiënten besmet raken door transmissie met een exogeen micro-organisme via een gecontamineerde endoscoop. In 2012 was er in het Erasmus MC een grote uitbraak via een gecontamineerde duodenoscoop met een bacterie die resistent was voor meerdere antibiotica. Deze uitbraak bleek niet op zichzelf te staan; wereldwijd worden nu uitbraken met resistente bacteriën door gecontamineerde duodenoscopen in toenemende mate beschreven. Om uitbraken te voorkomen, is het noodzakelijk om risicofactoren te vinden die bijdragen aan uitbraken en gecontamineerde endoscopen. Deze thesis is verdeeld in drie onderdelen. In het eerste gedeelte wordt beschreven hoe het reinigings- en desinfectieproces van duodenoscopen en lineaire echo-endoscopen (DLE) zich heeft ontwikkeld, welke partijen betrokken zijn en op welke manieren een uitbraak kan ontstaan. In het tweede gedeelte wordt beschreven hoe groot het onderliggende probleem van gecontamineerde DLE is, op basis van de blijvende hoge prevalentie van contaminatie van DLE met gastro-intestinale bacteriën in Nederlandse ziekenhuizen. In het derde en laatste gedeelte van de thesis laten we de resultaten van

een studie zien die heeft onderzocht of een schoonmaaktest als mogelijke marker voor organisch residu het aantal gecontamineerde endoscopen kan verminderen.

Deel I: uitbraken door gecontamineerde duodenoscopen

In **hoofdstuk 2** beschrijven we voor Nederlandse artsen in 2015 hoe wereldwijd in toenemende mate uitbraken door gecontamineerde duodenoscopen werden gemeld. Op dat moment werden in Nederland endoscopen niet standaard op de aanwezigheid van bacteriën gecontroleerd. Het proces van reiniging en desinfectie werd adequaat geacht als het volgens de instructies van de fabrikant werd uitgevoerd. De uitbraken waren gerapporteerd door grote academische ziekenhuizen die de mogelijkheden hadden om uitbraken te detecteren door middel van de opvallende kenmerken van de resistente bacteriën. Het is zeer waarschijnlijk dat transmissie van micro-organismen regelmatig voorkomt maar niet wordt opgemerkt. Tussen 2008 en 2018 waren er bij de gedetecteerde uitbraken bijna 500 patiënten geïnfecteerd geraakt en zijn er 30 doden gevallen. Echter, dit wordt als het topje van de ijsberg beschouwd omdat veel uitbraken waarschijnlijk niet worden opgemerkt. Als laatste beschrijven we de wetgeving voor nieuwe endoscoopmodellen. Deze krijgen zonder klinisch onderzoek toegang tot de markt als de fabrikant zelf beoordeelt dat ze voldoende op het vorig model lijken. Dit heeft ertoe geleid dat patiënten zijn behandeld met duodenoscopen met een aangepast ontwerp dat adequate reiniging en desinfectie kon verhinderen. Hierdoor zijn vijf jaar na introductie wereldwijd duizenden duodenoscopen teruggeroepen en zijn medewerkers van Olympus strafrechtelijk vervolgd wegens het te laat melden van duodenoscoop gerelateerde uitbraken.

In **hoofdstuk 3** hebben wij een analyse uitgevoerd naar de oorzaken van een uitbraak van een multiresistente bacterie via twee duodenoscopen in een Nederlands academisch ziekenhuis in 2015. Door een onafhankelijke expert werden alle mogelijke oorzaken beoordeeld, inclusief een analyse van de twee gedemonteerde duodenoscopen. De uitbraak was veroorzaakt door verschillende factoren, waaronder het duodenoscoopontwerp, inadequate reparaties, onjuiste reiniging, miscommunicatie over reinigingsprotocollen en een gebrek aan microbiologische surveillance. Het aantal geïnfecteerde of gekoloniseerde patiënten ten opzichte van het aantal blootgestelde personen was met 35% en 29% vergelijkbaar met andere uitbraken (12%-41%). Het duurde 8 maanden voordat de uitbraak werd opgemerkt. Bij andere uitbraken duurde dat 4 tot 12 maanden. Om toekomstige uitbraken te wordt geadviseerd om frequente microbiologische surveillance, endoscoopinspecties en preventief onderhoud te overwegen. Verder zouden fabrikanten aanpassingen van het reinigings- en desinfectieprotocol direct moeten communiceren en ziekenhuizen deze aanpassingen direct overnemen. Daarnaast zouden ziekenhuizen met frequente audits moeten controleren of het reinigings- en desinfectieprotocol goed wordt uitgevoerd.

Deel II: contaminatie van complexe gastro-intestinale endoscopen

Hoofdstuk 4 laat de de resultaten zien van de PROCESS studie. Dit was een landelijke prevalentie studie waarin alle Nederlandse ziekenhuizen minimaal 2 duodenoscopen hebben bemonsterd om te bepalen hoeveel er gecontamineerd waren met bacteriën. Van de 155 duodenoscopen was 22%, afkomstig van 26 (39%) ziekenhuizen, gecontamineerd met minimaal één micoorganisme met ≥20 colony forming units (CFU)/20 mL. Bovendien bevatten 15% van de Nederlandse duodenoscopen micro-organismen met een gastro-intestinale of orale oorsprong. Deze resultaten laten zien dat patiënten die een ERCP procedure ondergaan regelmatig worden behandeld met besmette duodenoscopen. Er was geen verschil in contaminatie tussen de verschillende duodenoscooptypen.

In **Hoofdstuk 5** presenteren we de resultaten van de PROCESS 2 studie: de tweede landelijke prevalentie studie waarin alle Nederlandse ziekenhuizen zowel duodenoscopen als ook lineaire echoendoscopen hebben bemonsterd. Net zoals in de vorige studie was 15% van de DLE's gecontamineerd met micro-organismen met een gastro-intestinale of orale oorsprong. Dit laat zien dat zowel patiënten die een ERCP als een EUS ondergaan regelmatig met gecontamineerde apparatuur worden onderzocht en dat dit risico hetzelfde is als tijdens de eerste studie. Als de definitie van de Amerikaanse 'RIVM' (Centers for Disease Control and Prevention) voor zorgwekkende micro-organismen wordt gebruikt is de contaminatie prevalentie 8%. Dit komt in de buurt van de 4,1%-6,1% percentages die zijn gevonden in de surveillance studies van endoscopenfabrikanten. Oudere en jongere DLE's hadden dezelfde contaminatierisico's, wat suggereert dat als oude en intensief gebruikte DLE's correct worden onderhouden, hun besmettingsrisico vergelijkbaar is met gloednieuwe DLE's. Contaminatie was verder onafhankelijk van het type desinfectieapparaat of reinigings- en desinfectievloeistoffen. Aanvankelijk werd gedacht dat het liftmechanisme het meest vaak gecontamineerd was, omdat dit onderdeel de besmettingsbron was bij verschillende uitbraken. Echter de twee landelijke PROCESS onderzoeken laten zien dat met name endoscoopkanalen gastro-intestinale micro-organismen bevatten.

Deel III: lange en korte termijn oplossingen: is er een rol voor reinigingstesten?

We hebben onderzocht of het gebruik van de adenosinetrifosfaat (ATP) test na het reinigen leidt tot een lager aantal met darmflora gecontamineerde DLE. Met microbiologische kweken als de gouden standaard wordt beoordeeld of de reiniging en desinfectie adequaat is. Echter kweken zijn arbeidsintensief, duur en de uitslag is pas na meerdere dagen bekend. De ATP-test is relatief goedkoop, makkelijk uit te voeren en geeft binnen enkele minuten de uitslag. Het is een bioluminescentietest die licht uitzendt afhankelijk van de hoeveelheid ATP, middels een luciferase-gekatalyseerde

oxidatie van luciferine. De mate van licht wordt gemeten in relatieve lichteenheden (RLU). De aanwezigheid van ATP kan duiden op resterend organisch materiaal dat nog moet worden gereinigd. Om te beoordelen of het gebruik van ATP-testen daadwerkelijk het aantal besmette endoscopen vermindert hebben wij de prospectieve voor-en-na DETECT studie uitgevoerd in het Erasmus MC.

In **hoofdstuk 6** presenteren we de resultaten van deze studie. Na 909 procedures werden DLE's ATP-getest na handmatige reiniging. Tijdens de controleperiode werden DLE's ongeacht de ATP uitslag gedesinfecteerd. Tijdens de interventieperiode werden ze opnieuw gereinigd als de ATP-test positief was. Na desinfectie werden de endoscopen microbiologisch bemonsterd: alle onderzoekers waren geblindeerd voor de kweekuitslagen. Het invoeren van ATP-testen verhinderde niet dat DLEs die gecontamineerd waren met darmflora werden gebruikt en verminderde ook niet hun aantal. Hoewel contaminatie met darmflora minder waarschijnlijk was tijdens de interventieperiode (OR 0,32; 95% CI 0,12-0,85), was de absolute besmettingsgraad van de darmflora hoger (16%; n=67 vs 21%; n=102). De lagere kans op darmfloracontaminatie in de interventieperiode was gebaseerd op twee duodenoscopen. Tijdens de controleperiode hadden deze duodenoscopen meerdere episodes van voortdurende besmetting met hetzelfde micro-organisme. De episodes werden voor aanvang van de interventieperiode beëindigd door quarantaine en reparaties: ze werden dus niet beëindigd door het invoeren van de ATP-testen. Dit onderzoek bevestigde de resultaten van eerdere kleinere onderzoeken dat ATP-tests na het reinigen niet effectief zijn.

In **hoofdstuk 7** analyseren we met de data van de DETECT studie de waarde van de ATP reinigingstest om de aanwezigheid van darmflora na het desinfectieproces te voorspellen. We hebben de RLU-waardes van ATP testen vergeleken met de aanwezigheid van elke type micro-organisme na desinfectie. Geen enkele RLU-afkapwaarde was bruikbaar voor het detecteren van micro-organismen. Dit gold voor alle plekken van de endoscoop die waren bemonsterd, endoscooptypen en elk type micro-organisme. Deze resultaten laten zien dat ATP testen na het reinigen niet de aan- of afwezigheid van micro-organismen na desinfectie kunnen voorspellen. Dit komt overeen met eerdere kleine test studies die ook geen correlatie vonden.

Toekomstperspectief en aanbevelingen

In **Hoofdstuk 8** kijken we vooruit naar de toekomst en beschrijven we potentiële oplossingen om het aantal endoscoop gerelateerde infecties te verminderen. Op korte termijn worden verbeteringen verwacht op het gebied van reinigings- en desinfectietechnieken en endoscoopontwerpen inclusief endoscopen met onderdelen voor eenmalig gebruik en zelfs endoscopen voor eenmalig gebruik. Echter de meerderheid van de ziekenhuizen zal in het komende decennium nog herbruikbare endoscopen

blijven gebruiken. Daarom blijft controle van het reinigings- en desinfectieproces inclusief het trainen van het personeel en microbiologische surveillance essentieel. Hierbij zouden beroepsorganisaties overeenstemming moeten bereiken over de beste kweekmethoden en -frequentie. Verder zouden alle betrokken partijen (fabrikanten, controlerende instanties, overheid, mdl-artsen, artsen-microbiologen) met elkaar duidelijker moeten communiceren. Momenteel is er meer aandacht voor contaminatie van endoscopen door meerdere veiligheidswaarschuwingen van de US Food and Drug Administration (FDA), geüpdate richtlijnen en specifiek in Nederland de twee PROCESS studies. Ook dienen uitbraken en het dysfunctioneren van apparaten direct geraporteerd worden en moeten (nieuwe) endocoopontwerpen ook na introductie op de markt geëvalueerd blijven worden.

Tijdens uitbraken bleek dat normaal functionerende endoscopen kritische afwijkingen hadden die mogelijk het risico op contaminatie vergroten. Daarom zouden fabrikanten moeten overwegen om op basis van het aantal uitgevoerde procedures endoscopen te inspecteren. Dit zou fabrikanten kunnen helpen om endoscoopspecifieke ontwerpfouten te ontdekken en zo nodig preventief onderhoud uit te voeren. In aanvulling op de instructies van de fabrikant zijn verschillende extra desinfectieprocedures voorgesteld zoals ethyleenoxide gas sterilisatie en het dubbel uitvoeren van desinfectie. Dit laat veelbelovende resultaten zien maar het is kostbaar en het voorkomt contaminatie niet. Andere methoden met een grotere veiligheidsmarge zullen nog ontwikkeld moeten worden.

Uiteindelijk zal het contaminatierisico geëlimineerd moeten worden door endoscopen met een radicaal ander ontwerp wat sterilisatie mogelijk maakt of door endoscopen voor eenmalig gebruik. Momenteel zijn nieuwe duodenoscoopontwerpen op de markt met een beschermkap en/of tangenlift die na eenmalig gebruik worden vervangen. Deze endoscopen zijn niet de definitieve oplossing, omdat de andere onderdelen nog steeds gecontamineerd raken en de endoscopen niet gesteriliseerd kunnen worden. Bovendien zijn deze ontwerpen niet in studieverband beoordeeld. De eerdere mislukte introductie van duodenoscopen met ontwerpfouten heeft laten zien dat opeenvolgende aanpassingen van oudere ontwerpen kan leiden tot veiligheidsrisico's. Daarom moet de huidige situatie, waarbij endoscopen zonder klinische testen markttoegang krijgen als de fabrikant zelf beoordeelt dat het ontwerp technisch gelijk is aan het vorige ontwerp,veranderen. Het invoeren van duodenoscopen voor eenmalig gebruik zal afhangen van de kosteneffectiviteit. De vraag die hierbij nog onbeantwoord is, is hoe vaak transmissie van micro-organismen voorkomt en hoe vaak het leidt tot een klinisch relevante infectie of kolonisatie van de patiënt. Een eerste retrospectieve revisie door Kwakman et al. laat een risico van duodenoscoop-geassocieerde infecties zien van 0.01%, wat ten minste 180 keer hoger is dan eerdere schattingen. Met een

prospectieve geblindeerde studie in meerdere ziekenhuizen waarbij patiënten pre- en postendoscopie worden bemonsterd, zou de werkelijke omvang en belasting het beste beoordeeld kunnen worden.

De nieuw ontworpen endoscopen (voor eenmalig gebruik) zijn niet de voor iedereen beschikbare oplossing om het transmissie risico te beëindigen. Daarom moet het decontaminatieproces van de huidige herbruikbare endoscopen, die nog vele jaren zullen worden gebruikt, verbeterd worden om het aantal gecontamineerde endoscopen te verlagen.

List of abbreviations

AER	Automated endoscope reprocessor
AM20	Any microorganism with ≥20 CFU/20mL
ASGE	American Society for Gastrointestinal Endoscopy
CFU	Colony forming units
CRC	Colorectal cancer
DLE	Duodenoscope and linear echoendoscope
EtO	ethylene oxide
Contam.	Contaminated
ERCP	Endoscopic retrograde cholangiopancreatography
ESBL	Extended-Spectrum Beta-lactamase
ESGE	European Society of Gastrointestinal Endoscopy
EUS	Endoscopic ultrasound
FDA	Food and Drug Administration
GA	glutaraldehyde
HLD	High-Level Disinfection
IFU	Instructions for use
ISO	Independent service organization
MDRO	Multidrug-resistant organisms
MGO	Presence of microorganisms with gastrointestinal or oral origin, independent of CFU count
MR-K. pneumoniae	Multidrug-resistant K. pneumoniae
PAA	peracetic acid
PD	Pancreatic duct
PROCESS study	Prevalence of contamination of complex endoscopes in the Netherlands
SFERD	Dutch Steering Group for Flexible Endoscope Cleaning and Disinfection
TU Delft	University of Technology, Delft
UMCU	University Medical Center Utrecht

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1. PhD Training	Year	Workload (hours)	ECTS
Courses and workshops			
Weekly Journal club, Dept. Gastroenterology and Hepatology, Erasmus MC Rotterdam	2015 – 2018	60	2.14
Endnote workshop, Erasmus MC library, Rotterdam	2015	6	0.2
Systematic literature retrieval in Pubmed workshop, Erasmus MC library, Rotterdam	2015	6	0.2
Systematic literature retrieval in other databases workshop, Erasmus MC, Rotterdam	2015	6	0.2
Basis introduction on SPSS, Molecular medicine postgraduate school, Rotterdam	2016	28	1
Biomedical English Writing Course, Molecular medicine postgraduate school, Rotterdam	2016	56	2
Biomedical English Writing and Communication (NIHES)	2017	56	2
Basiscursus Regelgeving en Organisatie van Klinisch Onderzoek (BROK, NFU)	2017	42	1.5
Integrity in scientific research, Dept. of Medical ethics and Philosophy, Erasmus MC, Rotterdam	2017	8.4	0.3
Open clinica	2018	28	1
Oral presentations			
Verpleegkundige Endoscopie Congres, Boston Scientific, Utrecht	2016	28	1
Nederlandse Vereniging voor Gastro-enterologie (NVGE), Veldhoven	2016	42	1,5
26th European Congress of Clinical Microbiology and Infectious Diseases (ECCMID), Amsterdam	2016	28	1
Digestive Disease Week, San Diego, USA	2016	28	1
Pentax Meeting, San Diego, USA	2016	6	1
Nederlandse Vereniging voor Gastro-enterologie (NVGE), Veldhoven	2017	28	1
Stuurgroep Flexibele Endoscopen Reiniging en Desinfectie (SFERD) Symposium	2018	28	1
Poster presentations			
United European Gastroenterology (UEG) Week, Barcelona, Spain	2017	28	1
Digestive Disease Week, Washington D.C., USA	2018	28	1
Attended (inter)national conferences			
Nederlandse Vereniging voor Gastro-enterologie (NVGE), Veldhoven	Fall, 2015	12	0.5
Nederlandse Vereniging voor Gastro-enterologie (NVGE), Veldhoven	Spring, 2016	12	0.5
26th European Congress of Clinical Microbiology and Infectious Diseases (ECCMID), Amsterdam	2016	28	1

Digestive Disease Week, San Diego, USA	2016	28	1
Nederlandse Vereniging voor Gastro-enterologie (NVGE), Veldhoven	Fall, 2016	12	0.5
Nederlandse Vereniging voor Gastro-enterologie (NVGE), Veldhoven	Fall, 2017	12	0.5
United European Gastroenterology Week, Barcelona, Spain	2017	28	1
Nederlandse Vereniging voor Gastro-enterologie (NVGE), Veldhoven	Spring, 2018	12	0.5
Digestive Disease Week, Washington D.C., USA	2018	28	1
Platform Deskundigen Endoscopie	2018	12	0.5
Stuurgroep Flexibele Endoscopen Reiniging en Desinfectie (SFERD) Symposium	2018	12	0.5
Awards			
Best abstract, Nederlandse Vereniging voor Gastro-enterologie (NVGE), Veldhoven	Spring, 2016		
NVMM abstract award, 26th European Congress of Clinical Microbiology and Infectious Diseases (ECCMID), Amsterdam	2016		
Grants			
Ministerie van Volksgezondheid, Welzijn en Sport – Project: 'Prevalence of contamination of complex endoscopes in the Netherlands'	2016	56	2
3M – Project: 'The effect of ATP tests on the incidence of contamination of complex endoscopes'	2017	56	2
Pentax Medical - Project: 'In vitro comparison of cleaning and disinfection efficacy of three duodenoscope types'	2018	56	2
Guidelines			
Working group Infection Prevention - Addendum to the Guideline heat sensitive flexible endoscopes	2015	56	2
Werkgroep Hygiëne en Infectiepreventie, Nederlandse Vereniging voor Medische Microbiologie – Guideline control on microbiological safety of heat sensitive flexible gastrointestinal endsocopes	2018	56	2
Attended seminars and workshops			
Diner pensant	2015 2018	24	0.5
Lagerhuisdebat, Utrecht	2015	7	0.25
30th Erasmus Liver Day, Rotterdam	2015	7	0.25
11th Yearly Gastroenterology symposium, Amsterdam	2016	7	0.25
31st Erasmus Liver Day, Rotterdam	2016	7	0.25
32nd Erasmus Liver Day, Rotterdam	2017	7	0.25
Symposium Nederlandse vereniging voor Hepatologie, Amsterdam	2017	7	0.25
33rd Erasmus Liver Day, Rotterdam	2018	7	0.25
Peer reviews			
Peer review Endoscopy	2016		
Peer review Antimicrobial Agents and Chemotherapy	2017		
Peer review Endoscopy	2017		
Peer review Clinical Microbiology and Infection	2017		
Peer review Gastrointestinal Endoscopy	2018		

Supervision			
Detect Study Students Team	2017 - 2018		
Other activities			
PhD committee, Erasmus MC, Rotterdam	2016 – 2017		
Multidisciplinary guideline committee – Microbiological surveillance of gastrointestinal complex flexible endoscopes	2016 - 2017	56	2
Update of the booklets - Introduction for PhD-students at the department of Gastroenterology and Hepatology - Scientific Integrity for Dummies Data management and storage	2017	56	2
Extracurricular			
Board member Promeras, representing board of all PhD students, Erasmus MC, Rotterdam	2016 - 2018		
Board member Young Medical Delta, connecting students and young professional in Medical technology	2016 – 2017		

List of publications

1. Arjan W. Rauwers, Anne F. Voor in 't holt, Jolanda G. Buijs, Woutrinus de Groot, Nicole S. Erler, Margreet C. Vos*, Marco. J. Bruno×. × both authors contributed equally. Assessment of post-manual cleaning adenosine triphosphate tests to prevent the use of contaminated duodenoscopes and linear echoendoscopes: the DETECT study. *Gastrointestinal Endoscopy 2022;96(2):282-290.e5*.
2. Judith A. Kwakman, Arjan W. Rauwers, Jolanda G. Buijs, Woutrinus de Groot, Margreet C. Vos**×**, Marco J. Bruno×. × both authors contributed equally. No relation between adenosine triphosphate after manual cleaning and presence of microorganisms on endoscopes after automated high-level disinfection. *Endoscopy International Open 2022; 10(09): E1275-E1281*
3. Judith A. Kwakman, Arjan W. Rauwers, Corné H. W. Klaassen, Marco. J. Bruno×, Margreet C. Vos×. × both authors contributed equally. Investigation of possible transmission of a susceptible microorganism through a contaminated duodenoscope; a case report. *Antimicrobial Resistance & Infection Control (2021) 10:127*
4. Arjan W. Rauwers, Anne F. Voor in 't holt, Jolanda G. Buijs, Woutrinus de Groot, Nicole S. Erler, Marco. J. Bruno×, Margreet C. Vos×. × both authors contributed equally. Nationwide risk analysis of bacterial contamination of duodenoscopes and linear echoendoscopes. *Gastrointestinal Endoscopy 2020;92(3):681-91 e1*.
5. Arjan W. Rauwers, Annet Troelstra, Ad C. Fluit, Camiel Wissink, Arjo J. Loeve, Frank P. Vleggaar, Marco J. Bruno, Margreet C. Vos, Lonneke G.M. Bode, Jan F. Monkelbaan. Independent root cause analysis of contributing factors, including dismantling of 2 duodenoscopes, to an outbreak of multidrug-resistant *Klebsiella pneumoniae*. *Gastrointestinal Endoscopy 2019;90(5):793-804*.
6. Arjan W. Rauwers, Judith A. Kwakman, Margreet C. Vos×, Marco. J. Bruno×. ×both authors contributed equally. Endoscope-associated infections: A brief summary of the current state and views toward the future. *Techniques in Gastrointestinal Endoscopy. 2019;21(4)*
7. Arjan W. Rauwers, Anne F. Voor in 't holt, Jolanda G. Buijs, Woutrinus de Groot, Bettina E. Hansen, Marco. J. Bruno×, Margreet C. Vos×. ×both authors contributed equally. High prevalence rate of digestive tract bacteria in duodenoscopes: a nationwide study. *Gut. 2018;67(9):1637-45*.
8. Arjan W. Rauwers, Margreet C. Vos, Jan-Werner Poley, Jolanda G. Buijs-Hegeman, Marco J. Bruno. Outbreaks related to contaminated duodenoscopes: causes and solutions / Uitbraken door gecontamineerde duodenoscopen: Oorzaken en oplossingen. *Nederlands Tijdschrift voor de Geneeskunde. 2016;160:D458*.
9. Arjan W. Rauwers, J. de Nooij. Intranasale fentanylspray als analgeticum in de prehospitale setting. *Ambulancezorg 2012; 18-20*

Dankwoord

About the author

Arjan Wouter Rauwers was born on June 1st, 1989 in Malden, the Netherlands. He is the youngest son of Wim and Alida Rauwers, and has a sister Lisette (1982) and a brother Vincent (1987). After graduating Cum Laude from the Stedelijk Gymnasium Nijmegen, Arjan moved to Utrecht to study Medicine at the University of Utrecht. At that time he joined the rowing fraternity and competed as a lightweight rower. As a medical student, he traveled to South America and the Indian subcontinent while participating in an internship ophthalmology at the Himalaya Eye Hospital in Pokhara, Nepal. During his graduation year, he performed a research internship on ischemic colitis supervised by dr. L.M.G. Moons at the department of Gastroenterology and Hepatology (G&H) at the UMCU. After obtaining his medical degree in 2014, Arjan started working as a resident not in training (ANIOS) in Amsterdam at the Onze Lieve Vrouwe Gasthuis. He worked at both the departments of Internal Medicine under the supervision of dr. Y.F.C. Smets and G&H under the supervision of dr. L.C. Baak. In September 2015, he started his PhD trajectory as described in this thesis under supervision of prof. dr. M.J. Bruno and prof. dr. M.C. Vos at the Departments of G&H and Medical Microbiology & Infectious Diseases of the Erasmus Medical Center in Rotterdam. During his PhD trajectory, he served on the board of Promeras, the representing body of all PhD students in the Erasmus Medical Center. As part of the training in G&H with dr. R. de Knegt as program director, he started as a resident Internal Medicine at the Franciscus Gasthuis & Vlietland under supervision of dr. Y.C. Schrama and dr. S.A. Eskes in 2020. After working as a resident G&H in Deventer Hospital under supervision of dr. F. ter Borg, he currently works at Erasmus University Medical Center in Rotterdam. Arjan lives together with Valérie in The Hague.