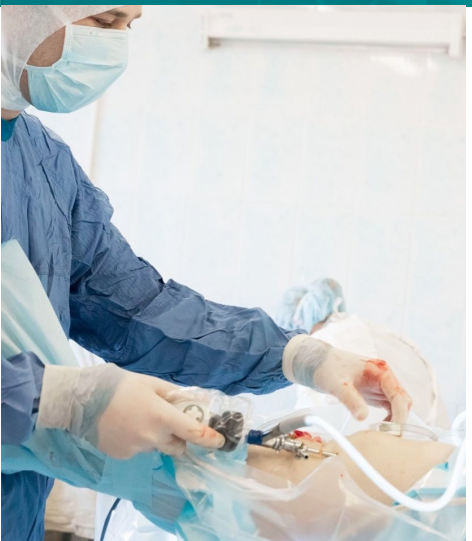
# Exponent®

Engineering & Scientific Consulting

Exponent®

# Medical Device Design and Infection Prevention: What Do Manufacturers Need to Know?



## Medmarc Insurance Group Webinar Series

## June 15, 2021

Howard Loree, Ph.D.

# Contents

- Background
  - Presenter
  - Exponent
- Medical Device Infections
  - Costs
  - Causes
- Design Strategies for Infection Prevention
  - Single Use Devices
  - Reusable Devices
- Device Use and Environment
- Design Verification & Validation for Infection Prevention
- Conclusions
- Q & A

# Background

# Howard Loree

## Education

- Ph.D. Medical Engineering Harvard – MIT HST
- M.S. Mechanical Engineering MIT
- B.S. Mechanical Engineering MIT

## Experience

- Complete product development life cycle for medical devices, especially cardiovascular
- Expert in mechanical circulatory support
- Technology assessment, product design optimization, and NIH grant strategy

## Positions

- Exponent, Manager (2020-Present)
- Flow Forward Medical, VP of R&D (2011-2020)
- Metactive Medical, VP of R&D (2013-2018)
- Avedro, VP of Research & Chief Scientist (2009-2010)
- ABIOMED, Principal Staff Scientist (2006-2009)
- Orthopeutics, VP (2005-2006)
- Thoratec, Manager of Research (2002-2005)
- Thermo Cardiosystems / Thoratec, Senior Scientist (1995-2002)
- Brigham and Women's Hospital, Harvard Medical School, Postdoctoral Research Fellow, Cardiovascular Biomechanics (1992-1995)

# Exponent

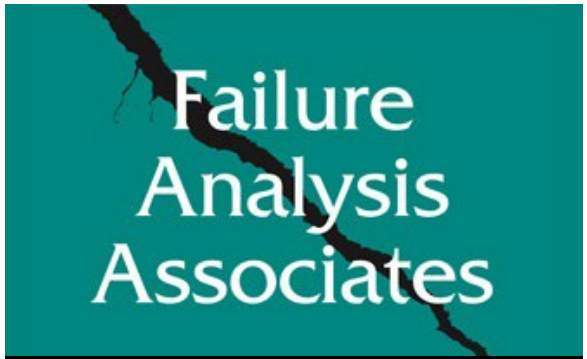
Exponent is a multi-disciplinary engineering and scientific consulting firm that brings together more than 90 different disciplines to solve important **technical, regulatory**, and **business** issues facing our clients.





# Then and Now

## Founded in 1967




5 PhDs | Palo Alto, CA

## Today

Exponent®

550+ PhDs | 900+ Consultants | 30 Offices

# Exponent Offices

# Organization & Teamwork

## Polymers & Biomedical

- Biomedical Engineering & Sciences
- Polymer Science & Materials Chemistry

## Environmental Sciences

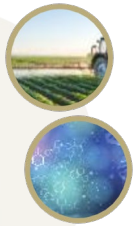
- Ecological & Biological Sciences
- Environmental & Earth Sciences

## Mechanical & Thermal

- Thermal Sciences
- Mechanical Engineering

## Health Sciences

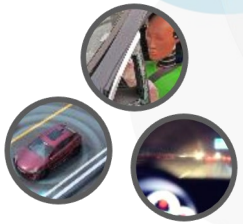
- Chemical Regulation & Food Safety
- Health Sciences



**PROJECTS**

## Transportation

- Biomechanics
- Human Factors
- Vehicle Engineering



## Infrastructure & Materials

- Buildings & Structures
- Civil Engineering
- Construction Consulting
- Materials & Corrosion Engineering

## Electrical & Data Sciences

- Electrical Engineering & Computer Science
- Statistical & Data Sciences

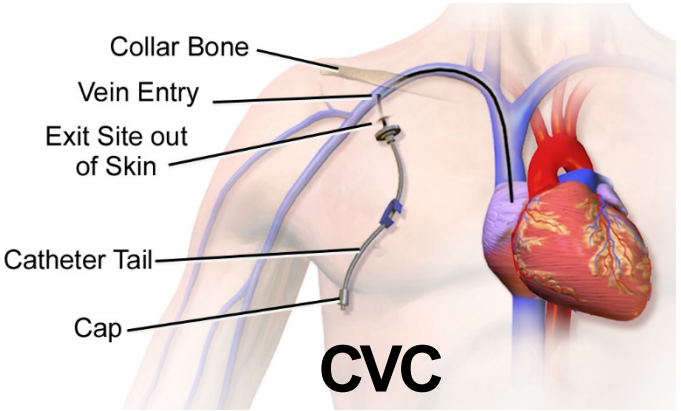
# Medical Device Infections

# Costs of Medical Device Infections

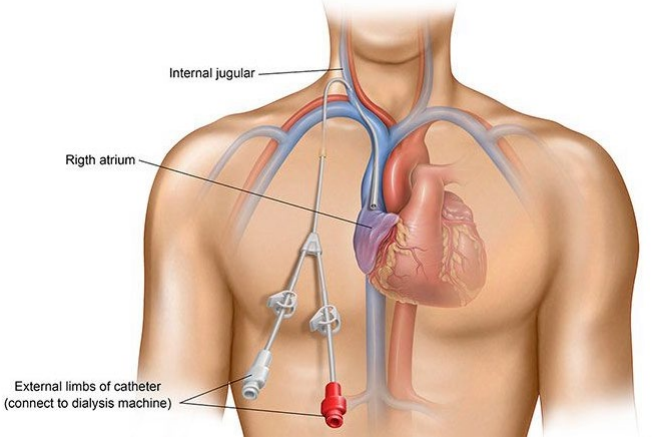
- Healthcare-associated infections (HAIs)
  - The overall annual direct medical costs of HAIs to US hospitals range from $37B to $58B.[1]
  - The benefits of prevention range from $32B to $41B, assuming that 70% of infections are preventable.[1]
- Medical device infections
  - Of the nearly 2 million HAIs reported by CDC, 50–70% can be attributed to indwelling medical devices.[2-4]
  - Based on the above estimates, costs range $18B to $29B, of which $16B to $20B could be saved through prevention.
  - Attributable mortality is highly device dependent but can range from < 5% for devices such as dental implants and foley catheters to > 25% for mechanical heart valves.[4]

# Catheter Infections

- There are over 15M patient days of exposure to central venous catheters (CVCs) in US ICUs annually.[5]
  - Incidence of non-dialysis catheter related bloodstream infection ranges 2.5 - 4 per 1000 catheter days.[6,7]
- Hemodialysis (HD) catheters have higher infection rates.
  - These range 3.8 - 5.5 per 1000 catheter days.[7,8]
  - In the ICU these infections can equate to financial costs as high as $30K per infection with the potential for increased duration of mechanical ventilation, 1 wk increased ICU stay, and 2–3 wks of additional hospital stay.[9,10]



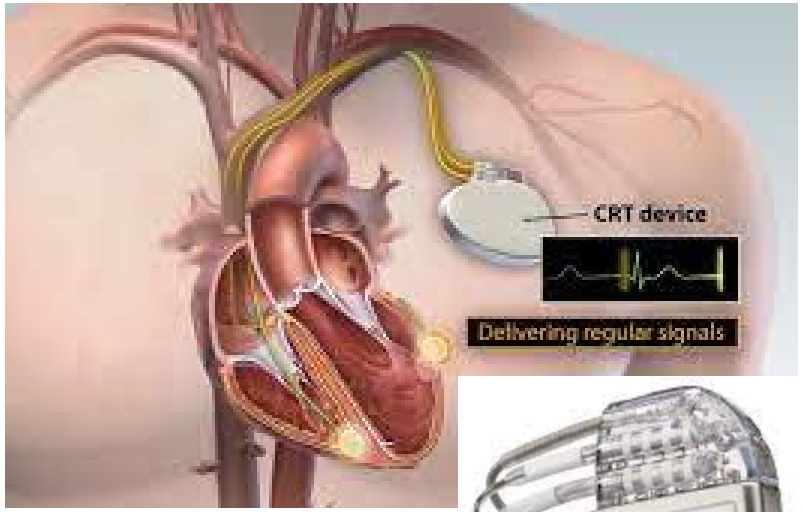
CVC



HD Catheter

# Cardiac Device Infections

- Cardiac implantable electronic devices (CIEDs) include pacemakers (IPGs), implantable cardioverter-defibrillators (ICDs), and cardiac resynchronization therapy (CRT) devices.
- The incidence of cardiac device infections (CDIs) averages 1.2 - 1.6%,[11] but can be > 4% for high-risk patients.[12]

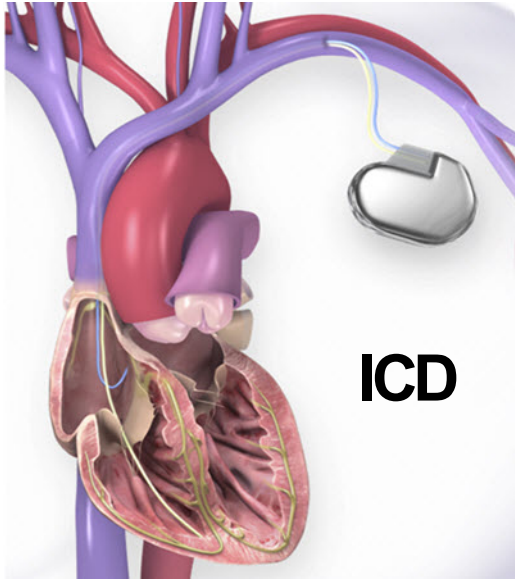




**CRT Device**

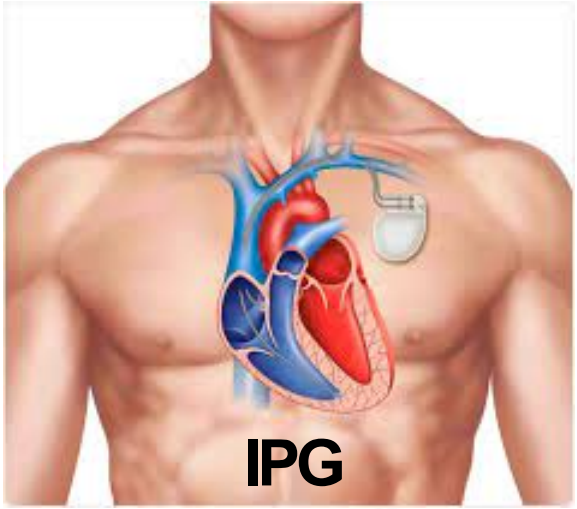
# Cardiac Device Infections (Cont.)

- CDI rates have not only increased over time, but several studies suggest the increase in CDI rate has outpaced the increase in device implantation rate.[13-15]
- CDIs are associated with substantial morbidity, mortality, prolonged hospital length of stay (LOS), as well as procedures for device & lead extraction and subsequent reimplantation.[13,16-19]



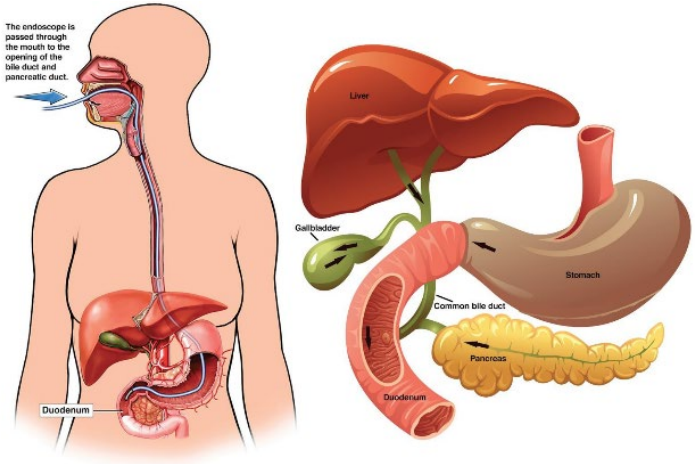
# Cardiac Device Infections (Cont.)

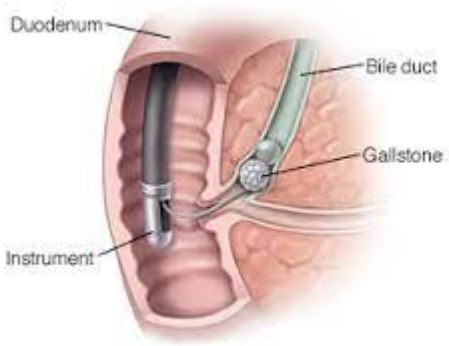
- CDIs are extremely costly to the healthcare system, with hospital charges ranging from $125K to $250K for inpatient admissions with a CDI-related extraction.[15]
- The total mortality in the case of CDIs is estimated at 9 - 35% during the first year after implantation.[17,21-24]




# Endoscope Infections

- Over 500,000 endoscopic retrograde cholangiopancreatographies (ERCP) are performed annually in the US.[25]
- Contaminated endoscopes cause more healthcare-associated infection outbreaks than any other medical device.[26,27]
- While some outbreaks have been associated with inadequate reprocessing of endoscopes, epidemics have occurred even without lapses in decontamination procedures. [28-36]




ERCP

# Endoscope Infections (Cont.)

- The duodenoscope is among the most complex medical instruments that undergo disinfection between patients.
- Transmission of infection by device contamination has remained a challenge since its inception.
- Risk factors include non-adherence to disinfection guidelines, biofilm deposition due to complex design and surface defects, and contaminated automated endoscope reprocessors (AERs).[37]

Duodenoscope

# Endoscope Infections (Cont.)

- From January 2010 to October 2015, more than 400 patients were infected at US hospitals during ERCP procedures.
- The infections often included antibiotic-resistant bacteria. The most notable was carbapenem-resistant Enterobacteriae (CRE), associated with a 50% mortality rate.


- Lawsuits were filed against duodenoscope manufacturers. A jury handed up an initial award of $6.6M in 2017.[38]
- In 2018, FDA issued warning letters to all 3 manufacturers for failure to provide sufficient data to address postmarket surveillance studies. [39]

# Root Causes of Medical Device Infection

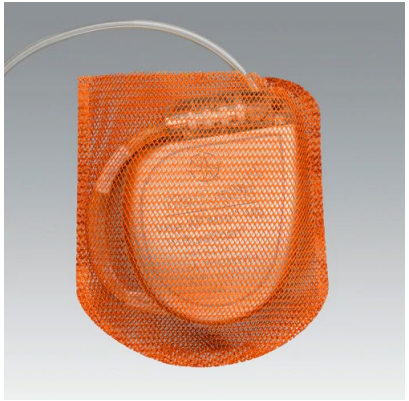
- Organisms originate from colonizing microbiota of patients or healthcare workers, or environmental sources.
- Antimicrobial resistance is expanding and evolving.
- Ineffective sterilization or poor sterile technique during implantation leads to device contamination.
- Inadequate cleaning of reusable instruments causes cross-contamination between patients.
- Poor aseptic technique in wound / exit site care allows pathogens to enter device, tunnel, or pocket.
- Bacteria form biofilms, which inhibit action of antibiotics and patient's immune system.

# Design Strategies for Infection Prevention

# Antimicrobial – Eluting Devices

## Example: Medtronic TYRX Envelope

- Large-pore mesh knitted from bioabsorbable filaments
- Coated with bioabsorbable polyarylate polymer formulated with antibiotics (*i.e.*, minocycline & rifampin)
- Elutes locally into tissue pocket
- Fully absorbs into body within ~ 9 wks[40]



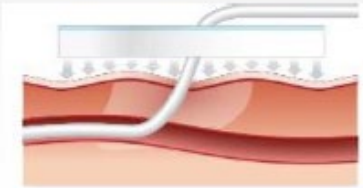
| WRAP-IT Trial[41] | | | | |
|---|---|---|---|---|
| **Number of Participants (n)** | **Study Population** | **Study Design** | **Follow-up Duration** | **Results** |
| 6,983 | High-risk CIED implantation (*e.g.*, replacement, upgrade, revision, or CRT procedures) | Antibiotic-impregnated mesh envelope vs. control | 12 mos | Decreased CIED infection rate with envelope (0.7%) vs. control (1.2%) (p = 0.04) |

# Antiseptic – Eluting Devices

## Example: Ethicon BIOPATCH

- Urethane disc adhered to skin around percutaneous devices (*e.g.*, catheters)
- Elutes chlorhexidine gluconate (CHG) over 7 days to maintain skin antisepsis[42]

**60%** reduction **in catheter-related bloodstream infections** as compared with standard care (P=.026)[1]



**44%** reduction **in local infections** as compared with standard care (P≤.0001)[1]

43

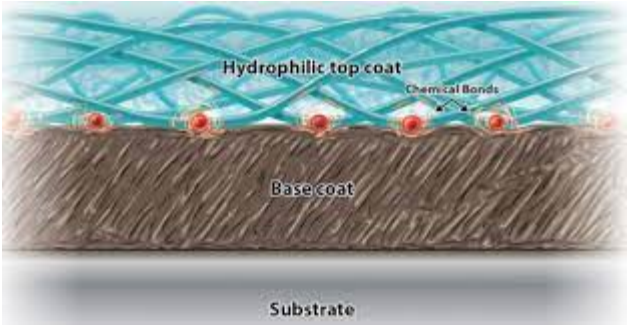
**Use with both vascular and nonvascular percutaneous devices**

# Hydrophilic Coatings

## Example: Surmodics Serene™ Coating

- Covalently bonded, UV cured
- Compatible with Pebax®, nylon, PEEK, HDPE, and a wide variety of other substrates
- Extremely thin coating with low friction and low particulates
- Reduces bacterial adherence
- Can be formulated with antimicrobial and antithrombotic agents[44]

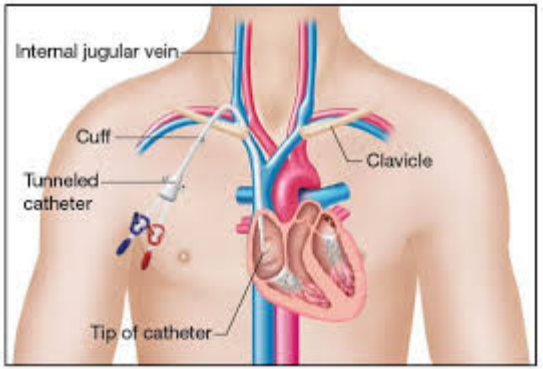
- Similar coatings shown to reduce infection rate by 50% for urologic implants[45,46]
- Widely used but not yet shown efficacy for urinary catheters[47]

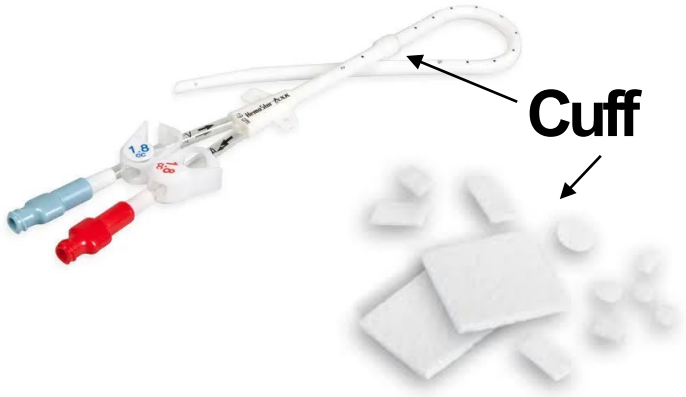



# Scaffolds for Tissue Ingrowth

## Example: Cuffed Tunneled HD Catheter

- Tunneled HD catheters are associated with lower rates of infectious complications compared with non-tunneled catheters.
- The catheter is generally placed so that the polyester felt cuff is positioned subcutaneously 1 - 2 cm from the skin exit site.
- Tissue ingrowth into the cuff seals off the catheter tunnel to reduce the risk of infection.
- Tunneled HD catheters are primarily used for intermediate or long-term vascular access.

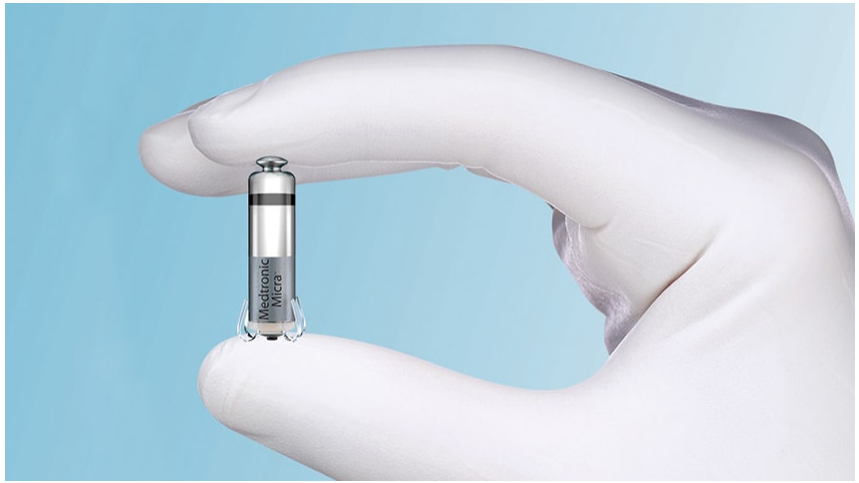


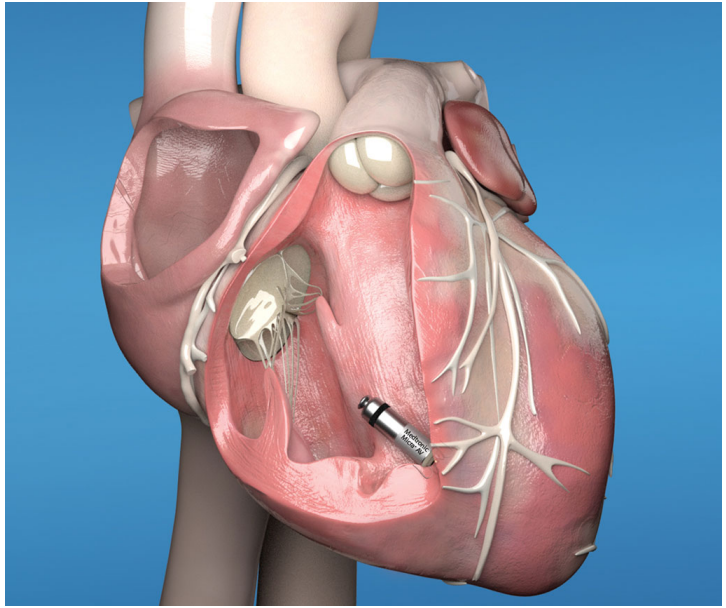



# Wireless Pacemaker

## Example: Medtronic Micra

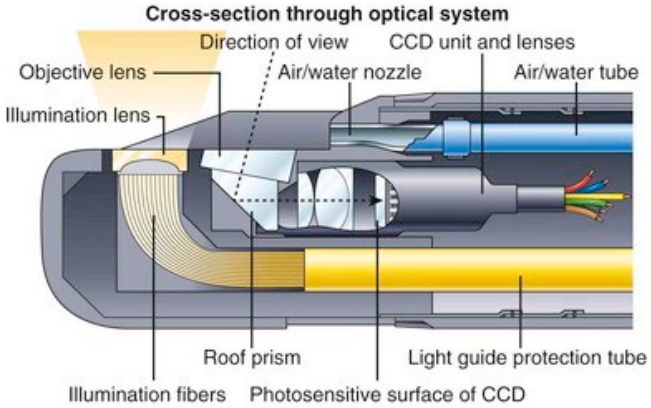
- 90% smaller than a transvenous pacemaker, placed directly into right ventricle
- Eliminates several complications associated with transvenous pacemakers and leads: pocket infections, hematoma, lead dislodgment, and lead fracture
- Currently limited to right ventricular pacing
- No long-term outcome data yet available[47,48]



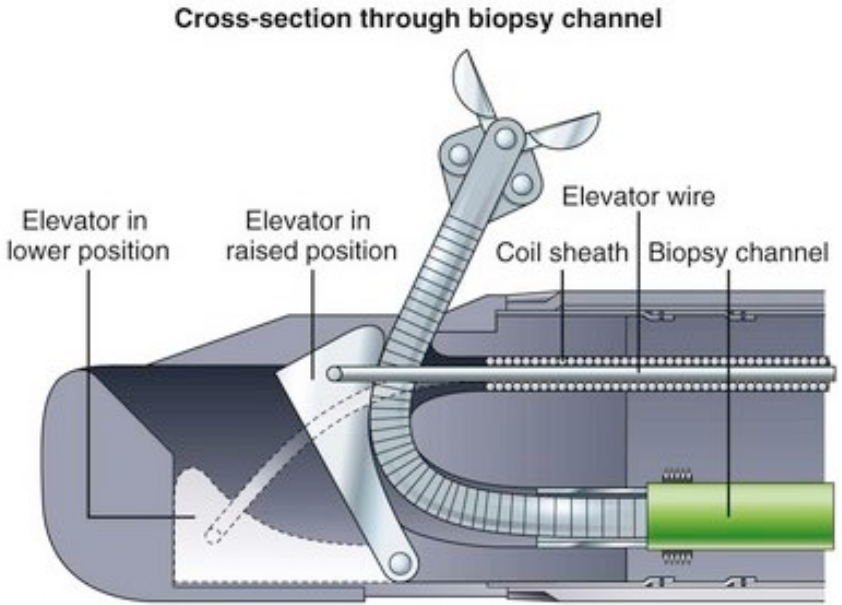
# Reusable Endoscope Design Guidelines

- FDA's evaluation of adverse event reports and other information identified design features that are prone to retaining debris and biological materials, including:[50]
  - Long, narrow interior channels (lumens), including those with internal surfaces that are not smooth, have ridges or sharp angles, or are too small to accept a brush
  - Hinges
  - Sleeves surrounding rods, blades, activators, inserters, etc.
  - Adjacent device surfaces between which debris can be forced or caught during use
  - O-rings
  - Valves that regulate the flow of fluid through a device (stopcocks)
  - Devices with these or other features that cannot be disassembled for reprocessing



# Reusable Endoscope Design Guidelines (Cont.)

- From the earliest stages of device design and engineering, manufacturers should consider alternative designs to facilitate effective reprocessing:[51]
  - Replace features that are challenging to reprocess with single-use parts
  - Include flush ports
  - Specify and/or provide dedicated cleaning accessories



# Single Use Endoscope

## Example: Ambu aScope Duodeno

- Packaged sterile
- No reprocessing / repair
- Familiar design[52]

# Sterilization of Single Use Devices

## Gas: Low temperature, but require permeable packaging & product design

- Ethylene oxide
  - Penetrates multiple layers of packaging and hard-to-reach places (*e.g.*, catheters)
  - Compatible with most materials
  - Cycle time: Days
  - Environmental hazard, so providers face increasing regulatory challenges
- Hydrogen peroxide
  - Limited penetration relative to ethylene oxide
  - Only residuals are water and oxygen
  - Cycle time: Hours
  - Devices must be free of moisture

# Sterilization of Single Use Devices (Cont.)

## Radiation & Heat: Limited material compatibility

- Gamma or X-rays
  - Precise control of dose and penetration
  - No chemical residuals
  - Cycle time: Hours
  - Incompatible with acetals, PTFE, or unstable polypropylene; causes color changes in some polymers (*e.g.*, PVC and polycarbonate) unless stabilized with additives
- Steam or dry heat
  - Low processing and capital cost, often done in-house
  - Cycle time: Minutes to hours
  - Suitable for glass and metal (*e.g.*, pharmaceutical vials and surgical tools)
  - Incompatible with electronics or complex assemblies

# Device Use and Environment

# Cause of Infections?

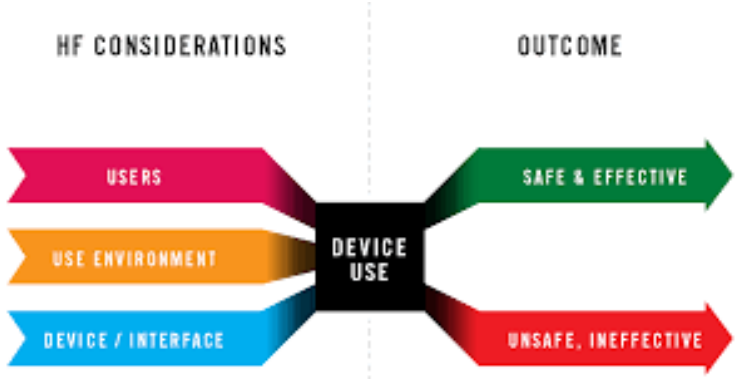
**THE NATURE OF ADVERSE EVENTS IN HOSPITALIZED PATIENTS**

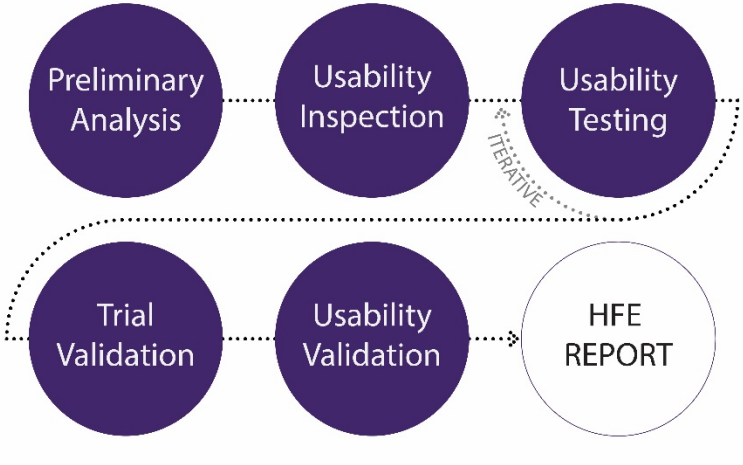
**Results of the Harvard Medical Practice Study II** [53]

- The most extensive study of adverse events: more than 30,000 randomly selected discharges from 51 randomly selected hospitals in NY in 1984.
- Adverse events, manifest by prolonged hospitalization or disability at the time of discharge or both, occurred in 3.7% of the hospitalizations.
- The proportion of adverse events attributable to errors (*i.e.*, preventable adverse events) was 58% and to negligence was 27.6%.
- Although most of these adverse events gave rise to disability lasting < 6 mos, 13.6% resulted in death and 2.6% caused permanently disabling injuries.
- Drug complications were the most common type of adverse event (19%), followed by wound infections (14%) and technical complications (13%)

# Human Factors

- Use errors can often be attributed to the design of devices or processes.
- For medical devices, human factors/usability engineering focuses on the interactions between users, the use environment, and the device itself.
- The goal is to minimize use-related hazards and risks and then confirm that users can use the device safely and effectively.



# Human Factors: Reusable Duodenoscopes

- In May, 2015, the FDA convened the Gastroenterology-Urology Devices Panel of the Medical Devices Advisory Committee Meeting to seek expert scientific and clinical opinion related to reprocessing of duodenoscopes based on available scientific information.[54]
- It is important to consider the device, end user, and use environment when developing reprocessing instructions.
- Human Factors testing plays an important role in ensuring that end users will be able to understand and correctly follow the reprocessing instructions in the labeling.
- Based on the panel's recommendation, the FDA is considering the role of Human Factors testing in the development of reprocessing instructions as part of premarket assessment and review.

# Design Verification & Validation for Infection Prevention

# Usability Study: Duodenoscope Reprocessing

- Q: How to ensure that user materials included in duodenoscope labeling and instructions for use are sufficient to ensure user adherence to reprocessing instructions?
- A: Put users into simulated-use studies and make sure they succeed in what the manufacturer intends for disinfection.
- Validation study participants should be representative of the professional staff that would perform these actual reprocessing procedures.


AER

# Sterilization Validation

- FDA has given guidance for sterilizing devices for over 30 years dating back to Blue Book Memorandum #G95-1.
- FDA recognizes various standards for sterilization validation:
  - ISO 11135 Ethylene Oxide
  - ISO 11137-1/2/3 Radiation
  - ISO 17665-1 Steam
- Practical aspects of sterilization validation:
  - Conducted after device and packaging design finalized
  - Often outsourced to specialized contract laboratory
  - Typically done along with related testing for bioburden and pyrogens

# Conclusions

# Conclusions

- Medical device infections lead to significant rates of patient morbidity & mortality, place an enormous cost burden on our health care system, and expose manufacturers to the risk of product liability litigation.
- These infections can be minimized by good design practices, including human factors and technologies that inhibit bacterial growth on implanted devices.
- Design verification & validation of infection prevention is necessary for single use devices (*i.e.,* sterilization validation) and reusable devices (*i.e.*, usability study of reprocessing).

# Q & A

Exponent®

# Thank You!


**Contact**

Howard M. Loree II, Ph.D.
Biomedical Engineering Manager
1075 Worcester St. | Natick, MA 01760
Office 508-903-4637 | Cell 617-780-6334
Email hloree@exponent.com | Website www.exponent.com

# Limitations

- At the request of Medmarc, Exponent accessed publicly available information regarding medical device infections and design approaches for prevention. The scope of services performed during this investigation may not adequately address the needs of all users, and any re-use of this report or its findings, conclusions, or recommendations presented herein are at the sole risk of the user.
- The opinions and comments formulated during this assessment are based on observations and information available at the time of the investigation. Exponent's role is advisory in nature and the opinions, analysis, conclusions, results, recommendations, and the like will be assessed by users with respect to their own products, processes, or services. As such, no guarantee or warranty as to the accuracy of this report is expressed or implied.
- Although Exponent has exercised usual and customary care in the conduct of this assessment, the responsibility for the specific design, construction, and quality of any product remains fully with the user.

# References


1. Scott RD. The Direct Medical Costs of Healthcare-Associated Infections in U.S. Hospitals and the Benefits of Prevention. *CDC*. 2009.
2. Darouiche RO. Treatment of infections associated with surgical implants. *N Engl J Med*. 2004; 350(14):1422–9. [PubMed: 15070792]
3. Bryers JD. Medical biofilms. *Biotechnology and Bioengineering*. 2008; 100(1):1–18. [PubMed: 18366134]
4. Weinstein RA, Darouiche RO. Device-associated infections: a macroproblem that starts with microadherence. *Clinical Infectious Diseases*. 2001;33(9):1567–72. [PubMed: 11577378]
5. O'Grady NP, *et al*. and the Healthcare Infection Control Practices Advisory, C. Summary of recommendations: Guidelines for the Prevention of Intravascular Catheter-related Infections. Clinical Infectious Diseases. *Infectious Diseases Society of America*. 2011; 52(9):1087–99. [PubMed: 21467014]

# References (Cont.)


6. Marik PE, *et al*. The risk of catheter-related bloodstream infection with femoral venous catheters as compared to subclavian and internal jugular venous catheters: a systematic review of the literature and meta-analysis. *Crit Care Med*. 2012;40(8):2479–85. [PubMed: 22809915]
7. Napalkov P, *et al*. Incidence of catheter-related complications in patients with central venous or hemodialysis catheters: a health care claims database analysis. *BMC Cardiovascular Disorders*. 2013;13:86. [PubMed: 24131509]
8. Fysaraki M, *et al*. Incidence, clinical, microbiological features and outcome of bloodstream infections in patients undergoing hemodialysis. *Int J Med Sci*. 2013; 10(12):1632–8. [PubMed: 24151435]
9. Blot SI, *et al*. Clinical and economic outcomes in critically ill patients with nosocomial catheter-related bloodstream infections. *Clinical Infectious Diseases*. 2005;41(11):1591–8. [PubMed: 16267731]

# References (Cont.)


10. Frasca D, *et al*. Prevention of central venous catheter-related infection in the intensive care unit. *Crit Care*. 2010;14(2):212. [PubMed: 20236456]
11. Kolek MJ, *et al*. Use of an antibacterial envelope is associated with reduced cardiac implantable electronic device infections in high-risk patients. *Pacing Clin Electrophysiol*. 2013;36(3):354–61. [PubMed: 23252988]
12. Polyzos KA, *et al*. Risk factors for cardiac implantable electronic device infection: a systematic review and meta-analysis. *Europace*. 2015;17(5):767–77. [PubMed: 25926473]
13. Greenspon AJ, *et al*. 16-year trends in the infection burden for pacemakers and implantable cardioverter-defibrillators in the United States 1993 to 2008. *J Am Coll Cardiol*. 2011;58(10):1001–16. [PubMed: 21867833]
14. Voigt A, *et al*. Continued rise in rates of cardiovascular implantable electronic device infections in the United States: temporal trends and causative insights. *Pacing Clin Electrophysiol*. 2010;33(4):414–9. [PubMed: 19793359]

# References (Cont.)


15. Joy PS, *et al*. Cardiac implantable electronic device infections: Who is at greatest risk? *Heart Rhythm*. 2017;14(6):839–45. [PubMed: 28315744]
16. Greenspon AJ, *et al*. Treatment patterns, costs, and mortality among Medicare beneficiaries with CIED infection. *Pacing Clin Electrophysiol*. 2018;41(5):495–503. [PubMed: 29411401]
17. Sohail MR, et al. Mortality and cost associated with cardiovascular implantable electronic device infections. *Arch Intern Med*. 2011;171(20):1821–8. [PubMed: 21911623]
18. de Bie MK, *et al*. Cardiac device infections are associated with a significant mortality risk. *Heart Rhythm*. 2012;9(4):494–8. [PubMed: 22056722]
19. Sridhar AR, *et al*. Cardiac implantable electronic device-related infection and extraction trends in the U.S. *Pacing Clin Electrophysiol*. 2017;40(3):286–93. [PubMed: 28084622]

# References (Cont.)


20. Sohail MR, *et al*. Incidence, treatment intensity, and incremental annual expenditures for patients experiencing a cardiac implantable electronic device infection: evidence from a large US Payer Database 1-year post implantation. *Circ Arrhythm Electrophysiol*. 2016;9(8):e003929. [PubMed: 27506820]
21. Chua JD, *et al*. Diagnosis and management of infections involving implantable electrophysiologic cardiac devices. *Ann Intern Med*. 2000;133:604–8. [PubMed: 27506820]
22. Le KY, *et al*. Impact of timing of device removal on mortality in patients with cardiovascular implantable electronic device infections. *Heart Rhythm*. 2011;8:1678–85. [PubMed: 21699855]
23. Tarakji KG, *et al*. Cardiac implantable electronic device infections: Presentation, management, and patient outcomes. *Heart Rhythm*. 2010;7:1043–7. [PubMed: 20470904]

# References (Cont.)


24. Athan E, *et al*. Clinical characteristics and outcome of infective endocarditis involving implantable cardiac devices. *JAMA*. 2012;307:1727–35. [PubMed: 22535857]
25. Andriulli A, *et al*. Incidence rates of post-ERCP complications: a systematic survey of prospective studies. *Am J Gastroenterol*. 2007;102:1781–8. [PubMed: 17509029]
26. Rutala WA, Weber DJ. Gastrointestinal endoscopes: a need to shift from disinfection to sterilization? *JAMA*. 2014;312:1405–6. [PubMed: 25291575]
27. Kovaleva J, *et al*. Transmission of infection by flexible gastrointestinal endoscopy and bronchoscopy. *Clin Microbiol Rev*. 2013;26:231–54. [PubMed: 23554415]
28. Epstein L, *et al*. New Delhi metallo-beta-lactamase-producing carbapenem-resistant Escherichia coli associated with exposure to duodenoscopes. *JAMA*. 2014;312:1447–55. [PubMed: 25291580]

# References (Cont.)


29. Alrabaa SF, *et al*. Early identification and control of carbapenemase-producing Klebsiella pneumoniae, originating from contaminated endoscopic equipment. *Am J Infect Control*. 2013; 41:562–4. [PubMed: 23171594]
30. Gastmeier P, Vonberg RP. Klebsiella spp. in endoscopy-associated infections: we may only be seeing the tip of the iceberg. *Infection*. 2014; 42:15–21. [PubMed: 24166131]
31. Alfa MJ. Monitoring and improving the effectiveness of cleaning medical and surgical devices. *Am J Infect Control*. 2013; 41:S56–9. [PubMed: 23622750]
32. Aumeran C, *et al*. Multidrug-resistant Klebsiella pneumoniae outbreak after endoscopic retrograde cholangiopancreatography. *Endoscopy*. 2010; 42:895–9. [PubMed: 20725887]

# References (Cont.)


33. Doherty DE, *et al*. Pseudomonas aeruginosa sepsis following retrograde cholangiopancreatography (ERCP). *Dig Dis Sci*. 1982;27:169–70. [PubMed: 7075412]
34. Muscarella LF. Investigation and prevention of infectious outbreaks during endoscopic retrograde cholangiopancreatography. *Endoscopy*. 2010; 42:957–9. [PubMed: 21072715]
35. Wendorf KA, *et al*. Endoscopic retrograde cholangiopancreatography-associated AmpC Escherichia coli outbreak. *Infect Control Hosp Epidemiol*. 2015:1–9. [PubMed: 25817743]
36. Smith ZL, *et al*. Transmission of carbapenem-resistant Enterobacteriaceae during ERCP: time to revisit the current reprocessing guidelines. *Gastrointest Endosc*. 2015. [PubMed: 25638508]

# References (Cont.)


37. Rahman MR, *et al*. Duodenoscope-Associated Infections: Update on an Emerging Problem. *Dig Dis Sci*. 2019;64(6):1409-18. [PMID: 30569333]
38. https://www.drugwatch.com/duodenoscope/lawsuits
39. https://www.fda.gov/medical-devices/safety-communications/fda-provides-interim-results-duodenoscope-reprocessing-studies-conducted-real-world-settings-fda
40. https:// europe.medtronic.com/xd-en/healthcare-professionals/products/cardiac-rhythm/infection-control/tyrx-antibacterial-envelope.html
41. Tarakji KG, *et al*. Antibacterial envelope to prevent cardiac implantable device infection. *N Engl J Med*. 2019;380(20):1895–1905. [PMID: 30883056]
42. https://www.jnjmedicaldevices.com/sites/default/files/2021-05/BIOPATCH-Value-Proposition-Overview-097336-180821.pdf

# References (Cont.)


43. Maki DG, *et a*l. An evaluation of BIOPATCH® Antimicrobial Dressing compared to routine standard of care in the prevention of catheter-related blood stream infection. Ethicon. 2000.
44. https://www.surmodics.com/performance-coatings
45. Wolter CE, *et al*. The hydrophilic-coated inflatable penile prosthesis: 1-year experience. *J Sex Med*. 2004;1(2):221-4. [PMID: 16429621]
46. Mandava SH, *et al*. Infection retardant coated inflatable penile prostheses decrease the incidence of infection: a systematic review and meta-analysis. *J Urol*. 2012;188(5):1855-60. [PMID: 22999690]
47. Tjong FVY and Reddy VY. Permanent leadless cardiac pacemaker therapy: a comprehensive review. *Circulation*. 2017;135(15):1458-70. [PMID: 2839638]
48. Groner A, Grippe K. The leadless pacemaker: An innovative design to enhance pacemaking capabilities. *JAAPA.* 2019;32:48-50. [PMID: 31136402]

# References (Cont.)


49. Hydrophilic catheters: an evidence-based analysis. *Ont Health Technol Assess Ser*. 2006;6(9):1-31. [PMID: 23074500]
50. https://www.fda.gov/medical-devices/reprocessing-reusable-medical-devices/factors-affecting-quality-reprocessing#design
51. Reprocessing Medical Devices in Health Care Settings: Validation Methods and Labeling Guidance for Industry and Food and Drug Administration Staff. FDA. March 17, 2015.
52. https://www.ambuusa.com/endoscopy/gastroenterology/duodenoscopes/product/ambu-ascope-duodeno
53. Leape L, *et al.*, The nature of adverse events in hospitalized patients, results of the Harvard Medical Practice Study II. *N Engl J Med*. 1991;324(6):377–84. [PMID: 1824793]
54. https://www.fda.gov/media/80265/download