

Brief Summary of the Circulatory System Devices Panel Meeting – Heater-Cooler Devices June 2-3, 2016

Introduction:

Heater-cooler devices (HCDs) are non-sterile devices utilized in the operating room (OR) alongside the heart lung machine and outside the sterile field. They serve a critical role in life-supporting/life-sustaining cardiothoracic procedures that require extracorporeal circulation by providing temperature controlled water to 1) oxygenator heat exchangers, 2) cardioplegia heat exchangers, and/or 3) warming/cooling blankets thus effecting thermal exchange to control a patient's core body temperature. These HCDs include water tanks, pumps and tubing that provide the temperature-controlled water through closed water circuits (i.e., not intended to come into contact with the patient, circulating blood or body fluids).

Recently in Europe and the US, nontuberculous mycobacteria (NTM) infections have been identified in patients that have previously undergone open chest cardiothoracic surgeries and were exposed to heater-cooler devices during surgery. The Circulatory System Devices Panel of the Medical Devices Advisory Committee to the Food and Drug Administration (FDA) met on June 2-3, 2016, to discuss and make recommendations regarding aerosolized transmission of NTM from contaminated water inside HCDs, into the operating room environment and sterile field, and ultimately into patients undergoing open chest surgical procedures. While FDA believes that these invasive, non-pulmonary infections are currently uncommon and that the benefits of open chest cardiac surgery with cardiopulmonary bypass outweigh the risks in appropriately selected patients, the NTM infections that have been reported in the US and Europe linked to prior cardiothoracic procedures have caused serious illness and in some cases have resulted in death. One of the NTM organisms identified among these patient infections associated with HCDs – *Mycobacterium chimaera* - is emerging as particularly pathogenic.

This public health concern is multi-faceted, involving an entire class of devices and a complex array of issues. Design and engineering considerations, infection control measures, the environment of use (the OR) and the labor-intensive instructions for use which must be followed in order to maintain routine cleaning and decontamination of these devices are but some of the factors. Difficulties associated with case finding and patient identification pose additional challenges. Therefore, the composition of this FDA Medical Device Advisory Committee meeting reflected the cross-cutting nature of this issue. Participants included panel members and invited speakers from different disciplines, representing expertise in: aerosolization science and industrial hygiene; microbiology and in particular NTM; hospital infection control; cardiothoracic surgery and perfusionist responsibilities; clinical and molecular epidemiology; and ethics. The panel heard directly from healthcare facilities that have been impacted by this public health concern; manufacturers of these medical devices; as

well as state and federal public health agencies who play a critical role in this investigation and response.

To aid in the mitigation of these NTM infections associated with HCDs, the Advisory Committee was asked to make recommendations regarding both short-term and long-term mitigations including: (1) mitigating water contamination and biofilm formation in heater-cooler devices and the water circuit, (2) case definition and patient and provider notifications, and (3) present and future device design considerations for reducing the risk of NTM infections.

Important Panel Discussion Topics:

- *Clinicians, and in particular cardiothoracic surgeons and infectious disease specialists, have had minimal, if any, awareness of these invasive, non-pulmonary NTM infections and their potential association with HCDs.*
- *Latency in development of clinical, often nonspecific, symptoms along with difficulty and delay in obtaining accurate diagnosis of an NTM infection can lead to worse patient outcomes.*
- *While invasive NTM infections associated with HCDs are currently uncommon, the actual prevalence of the problem is unknown. Increased provider awareness across the continuum of care for patients who received cardiopulmonary bypass, prompting additional investigation, is critical to case finding.*
- *Staffing and time required for cleaning and disinfection can have an impact on a facility's operations.*
- *Lack of standardization of device design raises additional unanswered questions regarding the potential for a HCD to generate and disperse aerosols, the ability to effectively clean the device and minimize biofilm formation, as well as how to disinfect and maintain adequate water quality. The panel recommended that research should be conducted to address these questions.*
- *Existing water quality standards may or may not be useful in mitigating NTM proliferation; however, they can be used to verify that the device is being maintained in accordance with the instructions for use.*
- *Patient/provider notification –Awareness across healthcare providers needs to be escalated. It is important, however, to consider the consequences of patient notification that is too broad in potentially creating alarm.*

FDA Questions/Panel Recommendations

Mitigating Water Contamination in Heater-Cooler Devices (HCDs)

- Should existing standards or limits for microbial water quality (e.g., EPA drinking water standard – 500 cfu/ml Heterotrophic Plate Count (HPC) or water for hemodialysis – 50 cfu/ml) be used as a surrogate when determining acceptable levels of NTM in the circulating water in the HCD water pathways to minimize/mitigate patient infection?

Panel: *Manufacturers stated that with newly manufactured machines, it is possible to attain and maintain water quality standards. However, the panel suggested that HPC can really only be used as a marker for good maintenance of the system. Use cleanest water possible i.e., using 0.22 filter or smaller. Changing water daily was determined to be impractical. Disinfecting and draining frequently, however, is necessary and should be documented. There was no consensus from the*

panel about whether older machines can meet and maintain water quality standards. A “deep cleaning” service performed by the manufacturer may be necessary to bring water quality back to standard/acceptable levels if counts are persistently elevated in spite of adherence to manufacturer’s IFU. When asked what water standard should be utilized for HCDs, the informal vote was split between 100 cfu/ml and 500 cfu/ml.

- Upon release of a new or serviced heater-cooler device from the manufacturer for shipping to a clinical facility, what is an acceptable level of bacterial contamination in the water pathways of the device?

Panel: *The devices should be shipped dry (as any residual water could initiate a biofilm), and HPC level should be < 50 cfu/ml.*

- In the clinical environment, should monitoring (i.e. surveillance) of the HCD water for NTM or bacterial contamination be performed?

Panel: *Routine surveillance of the HCD water for NTM was not recommended unless there is initiation of an investigation because of a patient infection. Monitoring the HPC counts before and after disinfection is recommended. HPC testing should be performed at a frequency as per the manufacturer’s instructions for use (IFU) for cleaning and disinfection of device. FDA should consider developing a standardized procedure and interval for this testing so that perfusionists can follow one procedure for all HCDs.*

Mitigating Biofilm Formation in HCDs

- Given a consistent low-level of water contamination in the water pathways, device labeling indicates that regular preventative maintenance is necessary to mitigate / minimize risk of patient infections. What factors would have the most impact on minimization of biofilm formation?

Panel: *Once biofilm has taken up residence in a device, it is impossible to eradicate through routine cleaning and disinfection alone. Diligent adherence to the device manufacturer’s IFU is therefore paramount as the best measure to prevent biofilm buildup. Vigilance with respect to routine visual inspections should also be performed. In the future, HCD devices should be designed so that the water pathways, tubing and interior of tanks can easily and routinely be inspected. Routine disinfection per IFU is essential. Manufacturers should utilize or develop materials that help slow down biofilm formation and are compatible with cleaning detergents and disinfecting agents.*

- Should cleaning/disinfection servicing performed by the manufacturer be part of routine maintenance to demonstrate an acceptable level of contamination (as discussed in question 1a)? If so, at what frequency?

Panel: *Panel recommends that if the HPC is too high (e.g. cannot stay below a pre-determined maximum HPC limit) or if there is a visual cue (e.g. discolored tubing, visible biofilm), the HCD should be removed from service and deep cleaning should be performed by the manufacturer.*

Case Definition and Patient and Provider Notifications

- What case definition should be used for patient identification and stratification for communication with patients?

Panel: *Even with FDA outreach, awareness of this issue is low, especially among cardiothoracic surgeons. FDA should consider also reaching out to high impact journals and societies to increase awareness. Once a patient with disseminated NTM (non-pulmonary) and prior exposure to HCD is identified, this should be the index case and the hospital that performed the surgery should be notified of this index case. Further investigation is warranted after an index case is identified, including notification of the local health authority. Patients with diagnosis of sarcoidosis and previous CT surgery should be re-evaluated for possibility of NTM infection.*

- Please discuss what methods could be implemented for identification and tracking of potentially infected patients (e.g. registries, electronic health record, etc.)?

Panel: *Panel recommends provider notification before patient notification. If a facility discovers one patient infection, the panel does not recommend notifying all patients. Instead, if one patient is identified with an infection, the panel recommends that an investigation be initiated at the facility where the surgery occurred, and local authorities should be informed (i.e. Department of Health). The panel was more receptive to recommending notification of all patients at a facility, if more than one patient infection has been identified. Moreover, if the specific HCD can be tracked, the panel suggested notifying only those patients that were exposed to the contaminated HCD. At this time, there is insufficient data to recommend stratifying and prioritizing notification for patients with prosthetic materials, heart transplant, LVAD or ECMO.*

- Understanding the latency period for the onset of symptomology of NTM infection, what would be the best approach and appropriate time periods (for healthcare providers to communicate with their potentially infected patients)?

Panel: *The panel recommended that facilities look back 5 years from the date of discovering a patient infection for patients that should receive notification. The panel suggested making atypical NTM (non-pulmonary) a reportable infection to local and/or state health authorities. A best practice recommended for perfusionists includes the identification of the specific HCD used during the surgery be included in the patient's electronic health record.*

Present and Future Device Considerations for Reducing Risk of NTM Infections

- In addition to the recommendations in the FDA HCD safety communication and FDA's HCD webpage, what other suggestions do you have for devices already on the market that may help mitigate/minimize patient infections from aerosolized NTM?

Panel: *Re-directing the exhaust from the HCDs out of the OR through the facility's infrastructure should be considered if cost effective. There is a need to standardize the way aerosols are evaluated. In addition, panel members suggested reviewing the current IFU with respect to human factors to ensure that the disinfection/cleaning protocol can be adequately followed.*

- For devices in development, what design features, instructions for use and/or environmental/use-related considerations might you suggest to mitigate aerosolization and minimize patient infection?

Panel: *Ideas that the Panel suggested include: Improved device/water pathway material to slow growth of biofilm; disposable tanks/tank liners; re-configure OR to minimize aerosolization of the HCD; evacuating gas mechanism; ultraviolet light (UV) light to kill bacteria when the device is not in use; make water pathways visual; automatic indicator of cleaning (e.g., litmus test); exposure of water pathways and tank to heat that will kill off the bacteria; include aerosolization testing as part of marketing clearance; can a fluid other than water be used?*

- In order to develop a validated disinfection process both currently in use and for future devices, how should manufacturers properly challenge the device in a lab environment that would replicate real-world use (i.e., test organism, mixture vs individual organisms, simulated use, parts of the device to test, microbicidal threshold (6- log, intermediate, high-level disinfection), etc.)?

Panel: *Ideas that the Panel suggested include: Use fluorescent microspheres for cleaning and aerosolization testing ; use gram negative bacteria; use bacteria that can be aerosolized for aerosolization testing; regular examination of the tubing; Use hard water during testing as this would represent worst case and probably need 6-log reduction; intermediate level of disinfection recommended; and process needs to be as simple as possible to assure adherence to the IFU's – Human factors should be used to make the disinfection process as simple as possible.*