



Mycobacterium chimaera infections in post-operative patients exposed to heater-cooler devices: An overview

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Abstract

A multi-country outbreak of *Mycobacterium chimaera* infection associated with contaminated heater-cooler devices (HCDs) has been reported, with more than 70 cases in Europe and the United States and two cases in Canada to date. The epidemiological and microbiological characteristics of this outbreak provide evidence for common-source transmission of *M. chimaera* from the exhaust air of intrinsically contaminated HCDs to patients during cardiac surgery. To date, all reported cases have been associated with Stöckert 3T HCDs manufactured at one plant by LivaNova prior to September 2014. Implantation of prosthetic material increases the risk of infection. Infections usually present as prosthetic valve endocarditis, vascular graft infection or disseminated infection. Reported mortality rates have varied, but were often over 40%.

Several measures are recommended to facilitate case-finding and mitigate risk of exposure. The feasibility of some risk mitigation measures and their effectiveness in reducing the risk of exposure are yet to be determined. Until HCDs are redesigned in a manner that prevents water contamination and aerosolization, separating the HCD exhaust air from the operating room air during surgery may be the most effective risk mitigation strategy. However, possible unintended consequences of this approach should be considered. This overview summarizes findings from peer-reviewed and other relevant national documents on key features of the outbreak, including the source, identified risk factors for infection, signs and symptoms of infection, burden of disease, risk mitigation measures, management challenges and knowledge gaps.

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Introduction

Health care-associated infections related to medical device contamination and biofilm formation have been documented in the literature (1). Recently, heater-cooler devices (HCDs) used during cardiopulmonary bypass (CPB) for cardiac surgeries and during extracorporeal membrane oxygenation (ECMO) have come under scrutiny due to infections linked to contaminated devices (2,3).

Heater-cooler devices have water tanks that pump temperature-controlled water through closed circuits to external heat exchangers that regulate patient body temperature by convection (4). The device is equipped with a radiator and fan to facilitate constant dissipation of excess heat through grid openings and the stirring of water in the tank results in aerosolization via the exhaust air (4,5). HCDs are subject to

biofilm formation. A biofilm is an aggregate of microorganisms embedded within an extracellular matrix that adhere to each other and to internal surfaces, such as the interior of HCDs.

Several types of microorganisms have been isolated from contaminated HCDs, including nontuberculous mycobacteria (NTM), which are ubiquitous in soil and water and have been linked to health care-associated infections (6-9). Investigations of NTM infection clusters following cardiac surgery detected *Mycobacterium chimaera* as the causative microorganism. *M. chimaera* is a slow-growing NTM included in the *Mycobacterium avium* complex (3,9-12). It is less susceptible to disinfection procedures due to its cell wall constituents and its ability to form biofilms. Isolation and identification of *M. chimaera* from clinical specimens requires specialized microbiological techniques

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(3). Transmission was associated with a single model of HCD manufactured by Sorin (now LivaNova) (3,13). Cultures from HCD water tanks, water circuits and air samples taken while HCDs were in use have grown *M. chimaera* (5,8,9,11).

Although *M. chimaera* contamination of ECMO devices has been reported, contamination did not spread to the air in the room while the devices were running and no ECMO-associated *M. chimaera* infections were reported (2,14). Nonetheless, the need to assess potential patient exposure from ECMO has been recognized since patients treated with ECMO, who are often critically ill and highly immunocompromised, may be exposed to the device for an extended period of time (2). National guidance documents and safety communications describing risk mitigation measures and testing recommendations in Canada, United Kingdom (UK), United States (US) and Australia have been published (13,15-20).

The objective of this overview is to summarize relevant literature on the current multi-country outbreak of *M. chimaera* infection. The source of exposure, risk factors for infection, signs and symptoms of infection, disease burden, risk mitigation measures, challenges and gaps are summarized. This overview may be a helpful resource for Canadian health care facilities and providers who use HCDs. It may also support informed decision-making by authorities responsible for implementing infection prevention and control measures.

Scope

A worldwide literature search was undertaken by the Health Library (Health Canada) using Ovid MEDLINE, EMBASE and Global Health databases for studies published from January 1, 2007 to March 8, 2017. The search strategy was developed using database-specific thesauri for "*Mycobacterium chimaera*", "heater-cooler devices", and "cardiac surgery". The search was limited to studies in English and French with no filters applied to limit retrieval by study design. A grey literature search was also conducted by the Health Library to identify relevant national guidance documents and safety communications. The reference lists of relevant guidance documents were hand searched for additional relevant studies.

Full texts of all relevant studies were screened to identify those reporting on HCD-associated *M. chimaera* infection in postoperative cardiac surgery patients and any risk mitigation measures described. A narrative synthesis of the relevant peer-reviewed publications, national guidance documents and/or safety communications was done.

Findings

A total of 95 articles were retrieved from peer-reviewed and grey literature searches, including a reference list search of identified documents. Information from 38 relevant documents was included in this overview. Fifty-seven articles were excluded for one of several reasons including studies that reported on case(s) already described in detail elsewhere; studies that focused on NTM in general (not specifically *M. chimaera*); studies that did not discuss patient exposure or transmission; and national guidance documents or safety communications that did not provide additional information to that obtained from similar documents from Canada, the US, Australia and Europe.

Source of exposure

To date, all cases of *M. chimaera* infection reported internationally have been associated with Stöckert 3T HCDs manufactured in Germany by LivaNova before September 2014 (3,9,13,15,21-23). Phylogenetic analysis by whole genome sequencing and other means showed that isolates from infected patients and from water and exhaust air of used and new Stöckert 3T HCDs were closely related, suggesting global distribution of contaminated HCDs and a hospital-independent, common source for the current outbreak (5,9,12,22,24-26). LivaNova implemented changes to their disinfection processes in an attempt to reduce the risk of *M. chimaera* contamination of 3T HCDs manufactured after September 2014 (13,15,27,28). Tests conducted on HCDs manufactured by a different company detected *M. chimaera* in the water but not in air samples, and the isolate obtained was genetically distinct from isolates obtained from Stöckert 3T HCDs (12,25,29).

During surgeries, the HCD is often positioned adjacent to the cardiopulmonary bypass machine and the patient. Recently, one of the considerations related to minimizing patient exposure to exhaust air from the HCD has to do with the feasibility of positioning the HCD immediately beside the floor-level exhaust in the operating room.

Risk factors for infection

Cases of *M. chimaera* infection following exposure to HCDs during cardiopulmonary bypass have been reported in patients who had undergone surgery in Europe (UK, France, Switzerland, Netherlands, Germany, Ireland and Spain) as well as in the US, Australia, Canada and Hong Kong Special Administrative Region (18). Patients undergoing cardiac surgery involving cardiopulmonary bypass where body temperature is regulated by HCDs are at risk of exposure and infection (8). Patients undergoing cardiopulmonary bypass for over two hours had higher odds of NTM infection (odds ratio: 16.5; 95% CI: 3.2–84) (8). In hospitals where at least one HCD-associated *M. chimaera* infection was identified, the risk of a patient getting an infection was approximately 0.1–1% (11,30,31). Of 115,664 surgical procedures in England involving repair or replacement of cardiac valves (between 2007 and 2014), the risk of NTM infections increased from less than 0.2/10,000 person-years before 2010 to 1.65/10,000 person-years in 2013 (29).

Implantation of prosthetic material (e.g., heart valve, vascular graft, left ventricular assist device) increased the risk of infection (3,11,13,29). Limited data suggest that heart transplants may also increase the risk of infection (3,32).

No case has occurred in operating room personnel exposed to aerosolization from HCDs.

Signs and symptoms of infection

Signs and/or symptoms of invasive *M. chimaera* infection following exposure to aerosols from an HCD may not occur for months or years after exposure, with a mean time between exposure and diagnosis of 1.6 years (range: 0.1–6.3 years) (3,10,14,23,32). The infection usually presents as prosthetic valve endocarditis, vascular graft infection or disseminated infection although a variety of extracardiac sites may also be infected (Table 1) (9-11,13,18,29,33). Clinical manifestations of infection are diverse and symptoms may be nonspecific (12,23). In some cases, extracardiac manifestations preceded cardiovascular disease (11). A description of a compatible syndrome for NTM infection published by the Canadian Public Health Laboratory Network (CPHLN) is shown in Table 1 (16).

**Table 1: Clinical symptoms of patients with *Mycobacterium chimaera* infection**

Type of symptoms	Clinical symptoms
Constitutional	Recurrent or prolonged fever, fatigue, shortness of breath, weight loss, night sweats
Cardiac	Prosthetic valve endocarditis and/or prosthetic vascular graft infection
Extracardiac	Bone infection, sternotomy surgical wound infection, mediastinitis, hepatitis, bloodstream infection, ocular infection (panuveitis, multifocal choroiditis, chorioretinitis)
Immunologic/embolic	Splenomegaly, cytopenia
Infants	Febrile episodes and failure to thrive

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Disease burden

M. chimaera infection requires aggressive medical treatment with combination antimycobacterial therapy and sometimes repeat surgical intervention. The infection generally results in substantial morbidity with prolonged hospitalization, adverse effects of medical and surgical treatment, and/or treatment failure (3,11,18,29). In Europe, at least 52 cases have been reported as of January 2017 (12,18). Three cases have been identified in Australia, 24 in the US and two in Canada (20,23,32,34). Individual patient information was not always reported. From the data available, most cases were in older adults although patient age ranged from one to 81 years old, including two pediatric patients. Approximately 83% of the patients were male. Most studies reported a mortality rate over 40% (see Table 2) (3,11,12,29,32) and mortality was high when significant delays in diagnosis occurred and patients were severely ill when appropriate antimycobacterial treatment was implemented. It remains unclear whether increased awareness and earlier diagnosis will reduce the mortality associated with *M. chimaera* infection.

Table 2: Reported mortality from *Mycobacterium chimaera* infection associated with heater-cooler devices

Reference (country / region)	Number of patients diagnosed	Number of deaths (mortality) %
Kohler et al., 2015 (Europe) (11)	10 ¹	4 (40%) ²
Chand et al., 2016 (Europe) (29)	18 ³	9 (50%)
Appenheimer et al., 2016 (US) (32)	24	NR (46%) ⁴
European Centre for Disease Prevention and Control, 2016 (Europe) (18)	52 ⁵	10 (<19%) ⁶
Haller et al., 2016 (Germany) (9)	5	1 (20%) ⁷
Tan et al., 2016 (US) (33)	3	2 (67%) ^{6,7}
Public Health England, 2017 (Europe) (12)	26	15 (58%)
Australian Commission on Safety and Quality in Health Care, 2017 (Australia) (20)	3	0 (0%)

Table 2 Abbreviations: NR, not reported; US, United States; %, percentage

¹ Nine cases were confirmed and one was probable

² An additional death was not linked to *M. chimaera* infection

³ All cases were probable

⁴ Number of deaths were not reported

⁵ Some of these cases have been reported in other publications

⁶ Cause of death not described or not all deaths attributed to the infection

⁷ Percent mortality not reported in the study, was calculated for inclusion in this table

Risk mitigation measures

Key measures identified to facilitate case-finding and mitigate future exposure to *M. chimaera* are summarized in Table 3.

Table 3: Recommended measures to facilitate case-finding and mitigate future risk of *Mycobacterium chimaera* exposure

Risk mitigation measure	Additional context and/or limitation
Health care provider notification and education (11,12,28,32)	<ul style="list-style-type: none"> Cases have been detected via provider notification. Earliest implicated surgery was performed in 2007. Maintain high clinical suspicion for <i>M. chimaera</i> or other NTM infection in patients (who underwent surgery involving CPB with use of HCDs from 2007 to implementation of risk mitigation measures).
Patient notification (8,12,28,32)	<ul style="list-style-type: none"> To date, no cases have been identified via patient notification. Testing is not recommended for asymptomatic exposed individuals. Until effective risk mitigation measures are implemented, information regarding potential exposure should be provided to patients prior to surgery.
Enhanced prospective NTM surveillance (9,21)	<ul style="list-style-type: none"> The ECDC has published a protocol for case detection.
Ensure traceability of HCDs in use (12)	<ul style="list-style-type: none"> Individual units used in each surgery should be recorded in the event of a later infection.
Remove potentially contaminated HCDs from service (12,15,27)	<ul style="list-style-type: none"> Where possible, all Stöckert 3T HCDs manufactured by LivaNova prior to September 2014 should be removed from service. In some settings, risk of deferring surgery exceeds risk of surgery with use of proven or suspect contaminated HCD.
Replace contaminated HCDs, plus accessories, tubing and connectors, to prevent recontamination (13,15,27,35)	<ul style="list-style-type: none"> LivaNova implemented a program to, in some circumstances, provide users with a loaner device to continue surgical procedures while their devices are undergoing deep disinfection. International demands for replacement of HCDs may result in a backlog in supply.
Use manufacturer's operation protocol including updated cleaning and disinfection procedures (3,9,12,15,27,28,35)	<ul style="list-style-type: none"> Maintain log of cleaning and disinfection of HCDs. Regularly check manufacturer's website for relevant updates. Current decontamination protocols are yet to be validated. Studies have challenged the effectiveness of these protocols, suggesting a systematic decontamination failure. Biofilm removal is essential for effective decontamination of HCDs.
Routine microbiological testing of HCDs in use (12,15,17,25,27,36)	<ul style="list-style-type: none"> This is not widely adopted because of the high rate of false negative results and the lack of standardized and validated methods for sample collection, processing and detection of <i>M. chimaera</i>. The Canadian Public Health Laboratory Network and the US FDA advise against obtaining routine environmental cultures from HCDs for <i>M. chimaera</i>.
Apply engineering solutions to enable reliable separation of HCD exhaust air from operating room air (4,5,12,13,15,18,25,26,37)	<p>Options include:</p> <ul style="list-style-type: none"> Place the HCD outside the operating room with tubing connected through an opening



Table 3: Recommended measures to facilitate case-finding and mitigate future risk of *Mycobacterium chimaera* exposure (continued)

Risk mitigation measure	Additional context and/or limitation
Apply engineering solutions to enable reliable separation of HCD exhaust air from operating room air (4,5,12,13,15,18,25,26,37) (Continued)	<p>in the wall (ensuring operating room positive air pressure is maintained). Although this is the most reliable solution, the unintended consequences of this solution (e.g., possibly altered airflow in operating rooms and a longer distance between the HCD and surgical field) are unknown.</p> <ul style="list-style-type: none"> Encase the HCD in custom-made housing with separate ventilation (e.g., connected to the operating room exhaust conduit). Attachments to the HCD may need to be approved by the manufacturer. The unintended consequences of this solution (e.g., effects of custom-made housing on how well the device functions) are unknown. If unable to reliably separate HCD exhaust air from operating room air, move the HCD as far as possible (preferably more than five metres) from the surgical field with the vent exhaust directed away from both the patient and the exposed instruments, and if possible, place the HCD close to the room air exhaust. Smoke dispersal experiments demonstrated that exhaust air from HCDs was propelled to merge with ultraclean airflow near the ceiling of the operating room. As a result, it is unclear whether this approach is useful in separating HCD exhaust air from operating room air (4).

Abbreviations: CPB, cardiopulmonary bypass; ECDC, European Centre for Disease Prevention and Control; HCD, heater-cooler device; NTM, nontuberculous mycobacteria; US FDA, United States Food and Drug Administration

Challenges and gaps

Table 4 summarizes the challenges and gaps in evidence informing the clinical management of *M. chimaera* infection.

Table 4: Challenges and gaps in evidence informing the management of *Mycobacterium chimaera* infection

Challenge / gap	Additional context
The magnitude of the risk of <i>M. chimaera</i> infection and the extent of the outbreak is unknown (12,14,29)	<ul style="list-style-type: none"> High prevalence of <i>M. chimaera</i> in HCDs has been reported (up to 80% in Denmark). The risk of patient infection currently appears to be low; however, if infection occurs, the impact on the patient could be severe. The risk of infection and clinical presentation among the pediatric patient population is unknown.
Delay in symptom onset and diagnosis of infection (3,10,14,23,32)	<ul style="list-style-type: none"> Documented time from exposure to diagnosis was between 0.1–6.3 years (mean of 1.6 years). Few laboratories are equipped to culture and identify <i>M. chimaera</i>, which could contribute to delay in diagnosis. Slow growth of <i>M. chimaera</i> culture contributes to delayed diagnosis. Early collection of dedicated mycobacterial culture can result in diagnosis within a shorter timeframe than is commonly reported.
Effectiveness and adverse effects of therapy (3,11,29,32)	<ul style="list-style-type: none"> <i>M. chimaera</i> infection can be very difficult to treat due to the microorganism’s intrinsic resistance to many antimicrobial agents; its propensity for biofilm formation on implanted devices; and deep-seated infection sites that are challenging for antimicrobial penetration (e.g., endocarditis, graft infection and bone). Therapy is prolonged and requires a combination of antimicrobial agents. Disseminated infection has often required repeat surgical interventions with high mortality rates reported.

Table 4: Challenges and gaps in evidence informing the management of *Mycobacterium chimaera* infection (continued)

Challenge / gap	Additional context
Development of new HCD designs is pending (5,15)	<ul style="list-style-type: none"> Construction of custom-built containers with HEPA filters to house HCDs that cannot be placed outside the operating room is underway, but their effectiveness is currently unknown. HCD manufacturers are modifying HCD designs to limit aerosolization and prevent transmission.
Extent of HCD-associated infections caused by other microorganisms such as <i>Legionella</i> species is unknown (12,29)	<ul style="list-style-type: none"> National surveillance in the UK (2007–2016) did not identify any cases of Legionnaire’s disease in health care workers with potential occupational exposure to HCDs. Postoperative cardiac surgery endocarditis due to <i>Legionella</i> species has not been reported during this outbreak.

Abbreviations: HCD, heater-cooler device; HEPA, high-efficiency particulate air; UK, United Kingdom

Discussion

Findings from this overview indicate a low but increased risk of *M. chimaera* infection with use of common source-contaminated HCDs during CPB (29). Given the long latency period, additional cases are expected. The true magnitude of risk following exposure is uncertain; current estimates are based on very limited data. Nonetheless, the risk of delaying cardiac surgery is generally considered far greater than the risk posed by this infection, even when the infection risk has not been entirely mitigated (28).

Future patient exposure may be prevented by implementing risk mitigation measures, including the use of uncontaminated HCDs or replacement of contaminated HCDs as soon as possible. Case finding may be expedited by the development of polymerase chain reaction (PCR)-based assays for rapid and reliable detection of *M. chimaera* in clinical or environmental samples.

Improved HCD designs that facilitate reliable decontamination and prevent aerosols from reaching the operative field are urgently needed (5,11). These developments may require collaborative discussions between medical device manufacturers, engineers and infection prevention and control experts.

This overview is limited by insufficient data to estimate the true magnitude of risk of infection and absence of data on efficacy and feasibility of risk mitigation measures.

Conclusion

The epidemiological and microbiological characteristics of this outbreak provide evidence for transmission of *M. chimaera* from the exhaust air of contaminated Stöckert 3T HCDs to patients during CPB, resulting in endocarditis, surgical site infections and/or disseminated infections. The true magnitude of risk following exposure is uncertain; it is currently estimated based on very limited data.

Strategies that separate the HCD exhaust air from the operating room air during surgery may be the most effective risk mitigation measures. The feasibility of implementing currently recommended risk mitigation measures is yet to be determined and studies are needed to determine if there are any unintended



consequences from implementation of these measures. Development of HCDs with new designs that are airtight and/or not susceptible to biofilm formation may help address this problem.

Authors' statement

TO – project administration, conceptualization, methodology, research, data abstracting and writing (original draft, review and editing); GT, LJ, MM – clinical expertise, intellectual content, review, editing and writing; KA - clinical expertise, intellectual content, review and editing; AC, K Defalco – review of abstracted data, research, review and editing; K Dunn – conceptualization, supervision, review and editing; JJ, SS, JE, BH, JS – clinical expertise, intellectual content, review and editing.

Conflict of interest

None.

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