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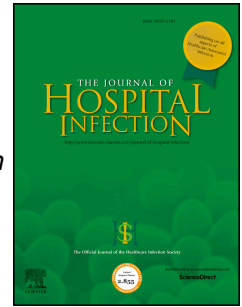
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A review of the microbiological problems and biofilms associated with *Mycobacterium chimaera* in heater cooler units used for cardiopulmonary bypass

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Title: A review of the microbiological problems and biofilms associated with *Mycobacterium chimaera* in heater cooler units used for cardiopulmonary bypass

Authors: Jimmy Walker, Ginny Moore, Samuel Collins, Simon Parks, Mark I Garvey, Theresa Lamagni, Grace Smith, Lincoln Dawkin, Simon Goldenberg and Meera Chand

Summary:

The role of heater cooler units (HCUs) in the transmission of *Mycobacterium chimaera* during open heart surgery has been recognised since 2013. Subsequent investigations uncovered a remarkable global outbreak reflecting the wide distribution of implicated devices. HCUs are an essential component of cardiopulmonary bypass operations and their withdrawal would severely affect capacity for life-saving cardiac surgery. However, studies have demonstrated that many HCUs are contaminated with a wide range of microorganisms, including *M. chimaera* and complex biofilms. Whole genome sequencing of *M. chimaera* isolates recovered from one manufacturer's HCUs, worldwide, has demonstrated a high level of genetic similarity, for which the most plausible hypothesis is a point source contamination of the devices. Dissemination of bioaerosols through breaches in the HCU water tanks is the most likely route of transmission and airborne bacteria have been shown to have reached the surgical field even with the use of ultraclean theatre ventilation. Controlling the microbiological quality of the water circulating in HCUs and reducing biofilm formation has been a major challenge for many hospitals. However, enhanced decontamination strategies have been recommended by manufacturers and while not always effective in eradicating *M. chimaera* from HCUs, UK hospitals have not reported any new cases of *M. chimaera* infection, since implementing these mitigation strategies. Water safety groups in hospitals should be aware that water in medical devices such as HCUs can act as a vector in the transmission of potentially fatal water-borne infections.

Key words

Mycobacterium chimaera, heater-cooler, cardiac-surgery, non-tuberculous mycobacterium, biofilm, aerosol

Introduction and Background

Mycobacterium chimaera infections following cardiac surgery have been attributed to the use of heater-cooler units (HCUs) which form part of the cardiopulmonary bypass equipment. Cases have been reported worldwide reflecting the global problem of microbial colonisation and the need for effective management of HCUs¹⁻⁴. This review summarises the knowledge to date as well as the challenges faced by those who have to prevent and control infection.

Burden and history of Non-tuberculous mycobacteria (NTM)

Water-borne opportunistic pathogens are responsible for a range of infections in immunocompromised and vulnerable patients particularly in health-care facilities. Organisms including *Legionella* spp., *Pseudomonas aeruginosa* and non-tuberculous mycobacteria (NTM) have been recovered from water systems⁵⁻⁹ and can cause persistent problems in hospitals¹⁰⁻¹².

NTM as water-borne pathogens

NTM are ubiquitous within the environment, particularly in natural waters and building water distribution systems where they appear to inhabit a similar niche as *Legionella* spp.¹³⁻¹⁷. However, unlike *Legionella*, the control of NTM is not covered by any specific legislation or guidance¹⁸.

Infections caused by rapidly growing NTM have been reported following cardiac bypass surgery¹⁹⁻²³, peritoneal dialysis²⁴ and middle ear cleaning²⁵. Individuals tend to be predisposed to NTM infection e.g. have comorbidities and/or are immunosuppressed but infections are increasingly being seen in otherwise healthy individuals²⁶.

In the majority of countries, the most common manifestation of NTM infection is sporadic pulmonary disease caused by members of the *Mycobacterium avium complex* (MAC) - a group of organisms that includes *M. avium*, *M. intracellulare* and *M. chimaera*²⁶⁻³¹.

Members of the MAC are relatively slow growing and can take upwards of 6 weeks to culture from patient and environmental samples. Delays in identification and diagnosis, coupled with the fact that MAC infections do not require notification to public health teams, means that the true burden of these organisms within healthcare facilities in the UK, is difficult to quantify.

NTM and cardiac surgery

Exposure to water droplets aerosolised from contaminated hospital water systems has been linked to pulmonary MAC infection^{10, 32-34} but other routes of infection are possible. In 1976, NTM infections following cardiac surgery were attributed to porcine heart valves contaminated with *M. fortuitum* and *M. chelonae*³⁵⁻³⁷. Inadequate sterilisation had allowed NTM to survive on the surface of porcine valves³⁷. The valves were recalled and, following changes in procurement and sterilisation, contamination rates reduced from approximately 4% to <0.0001%.

In 1992, Hector *et al.* described four nosocomial outbreaks of *M. fortuitum*. All cases followed cardiac surgery and two were attributed to the hospital potable water supplies³⁸. To determine the source of a *M. wolinskyi* bacteraemia and aortic prosthesis colonisation

(only 16 days after surgery), Dupont *et al.*, sampled a range of environmental surfaces and water sources³⁹. Although *M. wolinskyi* was not recovered, *M. chelonae*, *M. mucogenicum*, and *M. llaterense* were detected in potable water sources.

HCU as reservoirs of NTM

The first report of *M. chimaera* infections following cardiac surgery was published in 2013⁴⁰. A follow-up investigation by Sax *et al.*, described a total of 6 *M. chimaera* prosthetic valve endocarditis or vascular graft infections and an epidemiological link to HCUs utilised during surgery¹. Since then, additional reports of *M. chimaera* infections associated with the use of HCUs have emerged from Australia^{2, 41}, Canada⁴², France⁴³, Germany⁴⁴, Hong-Kong⁴⁵, Ireland⁴³, Netherlands⁴⁴, Spain⁴³, Switzerland⁴⁴, UK⁴ and United States^{46, 47}, reflecting the global use of these devices.

Interestingly, the potential significance of HCUs in infection control was determined as early as 2002 in a publication that highlighted HCU microbial contamination, malfunctions, possible patient exposure routes, incompatibility of biocides with HCU components and problems regarding effective decontamination⁴⁸. These are all issues that are again discussed in light of recent investigations^{4, 49}.

What is a heater cooler and how do they operate?

HCUs are integral for cardiopulmonary bypass operations and can be used for extracorporeal membrane oxygenation (ECMO) or extracorporeal life support (ECLS)⁵⁰. They have two or three interconnected cold and warm water tanks which function in combination, to deliver temperature-controlled water to external heat exchangers associated with cardioplegia and oxygenation equipment as well as the patient heating blanket (Figure 1). The temperature difference between the water circulated by the HCU and the blood determines heat transfer and regulates the temperature of the blood perfusing the patient. Heat exchangers should prevent any contact between the HCU water and the patient, although rare leaks causing infection have been described^{51, 52}. The sealed water tanks contain a number of different materials such as plastic tubing, insulation material, stainless steel and copper. Some models have two overflow pipes which can be used to vary the volume of water contained within (Figure 2). However, as only one of these overflow pipes is used at any one time, the other becomes a dead-leg, resulting in stagnation of water, debris accumulation and formation of biofilm. The overflow bottle and the dead-leg which are usually filled with tank water must also be included in the decontamination regimen.

Determining the source of infections related to HCUs

The water circulating in an HCU can contain a wide range of microorganisms. Extremely high heterotrophic plate counts ($> 10^8$ cfu/L) comprising a range of environmental Gram-negative organisms including *P. aeruginosa*, *Sphingomonas paucimobilis*, *Stenotrophomonas maltophilia* and *Brevundimonas vesicularis* have been reported^{4, 49}. Other opportunistic pathogens including *M. chelonae*, *Aspergillus flavus* and non-aspergillus moulds (*Paecilomyces* spp) have also been identified. The presence of *L. pneumophila* has also been detected^{4, 39, 49, 53}. The aerosolisation of *L. pneumophila* could represent a risk to users and surrounding staff⁴⁸. However, in the UK, no cases of Legionnaires' disease associated with HCUs have been identified⁴. The presence of high numbers and a diverse range of

microorganisms within an HCU is likely to facilitate the formation of extensive biofilms on tubing associated with the water tanks (Figure 5)^{4, 49}.

During their outbreak investigations, Sax *et al.*, recovered *M. chimaera* from water taken from 5 different HCUs¹. Similar randomly amplified polymorphic DNA polymerase chain reaction (RAPD-PCR) patterns were observed in isolates recovered from one of these HCUs and an associated air sample implying the aerosolisation of *M. chimaera* from within the unit. However, no isolate recovered from any of the HCUs was an exact match to that from an infected patient and it was hypothesised that this was due to the long time lag between patient exposure and the sampling of the HCU¹. Samples taken from drinking water fountains were also positive for *M. chimaera* but it was concluded that drinking water was unlikely to be responsible for the invasive infections. Chand *et al.*, sampled 45 HCUs across 12 different UK hospitals and nineteen (42%) were positive for *M. chimaera*. The results of these and other studies suggest that *M. chimaera* is a common contaminant of HCUs and that contaminated water within a HCU could be the source of *M. chimaera* infections^{2, 3, 49, 54}.

To date, all *M. chimaera* infections have been attributed to a specific make/model of HCU (Sorin 3T, LivaNova PLC, formerly Sorin Group Deutschland GmbH). *M. chimaera* has been recovered from in-use 3T HCUs within hospitals worldwide^{1, 2, 4, 43, 44, 55, 56}, from new unused 3T HCUs, and from water samples obtained at the manufacturing site of LivaNova PLC⁵³. However, microbial contamination of HCUs is widespread and is not specific to particular manufacturers or models^{4, 57}. Such contamination implies a systemic failure of the decontamination regimen resulting in the formation of biofilms. The environmental conditions and usage of the HCU favours the growth of a wide range of microorganisms^{4, 49, 54}. In operating theatres, the HCU is set up and connected to allow water to circulate through the unit, tubing, cardioplegia equipment and oxygenator some hours prior to the entry of the patient. This gives time to ensure that all the equipment is operating appropriately but also for the temperatures to stabilise. The temperature of the water circulating in the HCU can be as high as 40°C; this temperature encourages bacterial growth and formation of biofilm^{4, 49}. When not in use the 3T HCUs are stored at ambient temperatures allowing bacterial survival and proliferation of the biofilm in the stagnant water particularly on pipe materials and inside the water tanks (Figure 2 and 5). Biofilms produce extensive extracellular polysaccharides (EPS) which presents a physicochemical barrier to the penetration of disinfectants⁵⁸. As such the tolerance of biofilms is thought to be associated with the quenching of disinfectants as they pass through the EPS and due to the presence of slow growing or persister cells that have reduced susceptibility to many disinfectants and other antimicrobials⁵⁹⁻⁶¹. Resistance to disinfectants may also be due to a genetic characteristics acquired either by mutation or by gene exchange⁶².

In terms of mycobacteria, the presence of a high cell surface hydrophobicity may result in their preferential attachment to surfaces at air-water interfaces and may contribute to disinfectant tolerance of NTM within the HCU⁶³. Hydrophobicity varies between MAC species⁶⁴. Both *M. avium* and *M. intracellulare* are recovered more frequently from pipe surfaces in biofilms, than in the planktonic phase^{65, 66}. However, *M. intracellulare* forms biofilms more readily than the less hydrophobic *M. avium*, which is more commonly found in the bulk water^{65, 67}. The presence of NTM biofilms in HCUs makes their decontamination

extremely challenging and hospitals are still reporting intermittent positives of heater-cooler units despite complying with the recommended disinfection procedure(s) (J Walker personal communication).

Despite the global distribution and use of 3T HCUs, whole genome analysis has demonstrated a lack of genetic diversity between isolates^{2,4}. In Australia, *M. chimaera* was recovered from 10 HCUs across four different hospitals². Representative isolates clustered into two groups which differed by 28 single nucleotide polymorphisms (SNPs), with 2–17 SNP differences between isolates within a single group². Recent evidence also suggests that a high level of DNA sequence conservation (equivalent to 6 SNPs) exists between isolates recovered from the southern and northern hemispheres⁵⁵. During an outbreak investigation in the US, genomic analysis identified a maximum of 38 SNPs between any two isolates in the outbreak. Of the 261 isolates examined by Chand *et al*, 94%, including all those from probable cases and 86% of isolates from 3T HCUs clustered very closely (mean pairwise distance of 10 SNPs)⁴. In comparison, a minimum of 2,900 SNPs were detected between any single outbreak isolate and an epidemiologically unlinked isolate³. Such data strongly indicate a point source for the contamination of HCUs i.e. that the LivaNova 3T units were contaminated within the manufacturing site^{2,4}. Preliminary data from Haller *et al* supports this hypothesis⁵⁴. However, Svensson *et al.*, 2017 provided evidence that HCUs from other manufacturers (e.g. Maquet) have cultured *M. chimaera*⁵⁷. However, these *M. chimaera* isolates were genetically distinct (47-49 SNP differences) compared with isolates from the Sorin 3T HCUs and have not been linked with any clinical cases. In addition, other manufacturer units have been shown to be positive for *M. chimaera* which indicates that there may be alternative routes to contaminating the HCU, to that of a manufacturing, point source⁵⁷. Indeed, the water supplies within hospitals used to fill HCUs cannot be excluded as a source of *M. chimaera* contamination^{1,2} and reinforces the need for implementing a water safety plan and decontamination strategies by the water safety group¹⁸.

Airborne transmission of *M. chimaera* from HCUs to the surgical site

Robinson *et al.*, identified a genetic relatedness between 10 HCU *M. chimaera* isolates from four hospitals, but a patient *M. chimaera* isolate was not genetically related to the HCU *M. chimaera* isolates from that hospital, nor to the other HCU isolates; indicating that the HCUs were not the source of the infection in that patient². However, a high genetic similarity between *M. chimaera* isolates recovered from HCUs and patients in other studies is consistent with a role for HCUs in transmission⁵⁷.

Sax *et al.*, hypothesized that contaminated water leaking from the circulation tubing or connectors can reach the turbulent airflow produced by fans in the lower body of the HCU¹. Gotting *et al.*, also attributed the aerosolisation of water droplets to the operating fans; specifically a fan located in the upper rear part of the HCU⁶⁸. Public Health England, Porton Down, carried out a controlled laboratory study to investigate the microbial aerosols generated by a naturally contaminated (decommissioned) 3T HCU that had been in service since 2002⁴. A high volume cyclone air sampler was used to confirm that the HCU released a bioaerosol.

As was also demonstrated by Sax *et al.* this aerosol significantly increased with circulation of water and the highest level of aerosol was detected at the rear of the HCU ¹. An aerodynamic particle sizer was used to carry out a more detailed examination of the HCU. A series of holes close to the flow and return pipes of both water circuits and a gap between the tank sealing plates were identified as areas of significant aerosol release (Figure 3). Flow visualisation demonstrated the movement of smoke particles from these areas to the outside environment via the operation of a small cooling fan at the rear of the HCU (Figure 4a and 4b). To date, these holes have only been observed in 3T HCUs manufactured before 2004 and may be due to the sealing plates shifting over years of operation. When the holes were sealed with mouldable putty the production of aerosols was greatly diminished ⁴.

Sommerstein *et al.*, investigated the dispersal of *M. chimera* from a 3T HCU in a fully functional cardiac theatre fitted with an ultraclean air ventilation system validated to ISO EN 14644-3:2005. The vertical flow of laminar air from the ceiling should prevent aerosols from entering the operating field ⁶⁹. The authors investigated aerosol transmission using a particle counter, a thermic anemometer, smoke dispersal and microbial monitoring when the HCU was switched off and when it was operating. When the HCU was operating and orientated such that its exhaust airflow (at the rear of the unit) was directed towards the surgical field, smoke from a source 20 cm from the HCU penetrated the ultraclean ventilation system and reached the operating field. This correlated with increased particle counts and the detection of *M. chimera* (settle plates) up to 5m from the HCU. By combining these results with previous work using active air samplers, Sommerstein *et al.*, concluded that the concentration of mycobacteria in the air was high enough to contaminate implant devices in the surgical field ^{1, 69}.

Clinical features and diagnosis

A number of investigations have demonstrated an increased risk of invasive *M. chimaera* infection in patients who have undergone cardiothoracic surgery, particularly valve replacement or repair ^{1, 4, 44}. Although infections following coronary artery bypass grafts (CABG), vascular grafts, heart transplant, and left ventricular assist devices have been identified, risk assessment suggests heart valve repair and replacement carry the highest risk ⁷⁰. A number of disseminated infections and secondary focal infections such as discitis have been reported ^{4, 44, 70}. Patients affected have been primarily but not exclusively adults ^{4, 44} with a median age of 61 (range 36-76 years) which may reflect the age of those likely to require valve replacement surgery ⁴⁴. The interval from surgery to diagnosis has ranged from 3 months to 6 years with a median interval of 17-18 months ^{1, 4, 70}.

Estimated risk of infection varies, in part a likely reflection of under-ascertainment of cases ⁴. Estimates from affected centres in Switzerland and the USA range from 1 per 100 to 1 per 1000 ^{1, 56, 71}. In England, national risk assessment was possible through access to national health datasets. This identified an overall risk per patient undergoing heart valve surgery of 1 in 5,000 between 2007-2015, although rising over time to reach 1 in 2,000 in 2014 ⁷².

Patient outcome has been described as poor, which is probably multifactorial from late diagnosis and treatment, intrinsic drug resistance of *M. chimera* biofilm which may hinder the penetration and action of antimicrobials in the cardiac and pulmonary tissue ^{44, 73}.

M. chimaera may also be misidentified which could result in an underestimation of the number of cases. *M. chimaera* and *M. intracellulare* are genetically similar and most commercially available laboratory assays cannot differentiate *M. chimaera* from *M. intracellulare*. When 149 *M. intracellulare* isolates were reanalysed using 16S rRNA sequencing, 63 % of them were found to be *M. chimaera*,⁷⁴. Reanalysis of *M. intracellulare* isolates from relevant sites in cardiothoracic patients may result in an increase in *M. chimaera* cases.

How to prevent and control contamination of HCUs

Compatibility of manufacturer's equipment

To compound the issue of decontamination, hospitals using 3T HCUs with oxygenators manufactured by a different manufacturer (Maquet) have been informed that H₂O₂ should not be used as a disinfectant^{75, 76}. Tests had shown that the diffusion rate of H₂O₂ through the Maquet oxygenator heat exchangers (polyurethane hollow fibres) can result in amounts of diffused H₂O₂ that exceed the daily allowable limits⁷⁵. Alternative chemicals recommended for the disinfection of HCUs by LivaNova include peracetic acid, however, a number of hospitals have concerns regarding the occupational exposure of staff to peracetic acid and are using clorina (active ingredient sodium p-toluenesulfonchloramide, recommended for Maquet oxygenators) for both the Maquet oxygenators and HCUs. However, hospitals should be aware that the advice from the regulator in the UK (MHRA) is to follow the manufacturer's instructions for cleaning and disinfecting these devices and the associated components at all times, as the impact on the safety and performance of the devices are unknown and such activities may invalidate the manufacturers' warranty⁷⁷.

Decontamination recommendations

To date, all *M. chimaera* infections have been attributed to the 3T HCUs. However, microbial contamination of HCUs is widespread and is not specific to particular manufacturers or models^{4, 57}. Such contamination implies a systemic failure of the decontamination regimen resulting in the formation of biofilms. The environmental conditions and usage of the HCU favours the growth of a wide range of microorganisms^{4, 49, 54}. All manufacturers provide advice for sampling and decontamination of heater coolers on their websites.

In terms of the 3T HCU, in 2015 LivaNova advised the following: decant HCUs of water every two weeks, refill with filtered (0.2 µm) tap water and add 100 mL of medical grade 3% hydrogen peroxide (H₂O₂) to the HCU tanks. 50 mL of 3% H₂O₂ should then be added every five days. A full system HCU decontamination using Maranon (>30% sodium hypochlorite) was advised every three months⁷⁸. There was also a change in the cleaning and disinfection guidance in 2015 to require more frequent disinfection of the water circuit (i.e. disinfection every two weeks rather than every 3 months) with specified disinfectant solutions including peracetic acid; weekly water changes; and the addition of hydrogen peroxide solution to the water to act as a preservative and to further prevent biofilm formation^{49, 79}. In terms of microbiological sampling LivaNova advised users to sample the water prior to disinfection for heterotrophic bacteria, coliforms, *P. aeruginosa* and NTM. During usage in the operating theatre, users were also advised to carry out biweekly microbiological water and air sampling.

Efficacy of decontamination assessed by microbiological testing

Studies have indicated that the decontamination procedures provided by the manufacturer do not sufficiently inhibit the growth of microorganisms in HCUs^{49, 79}. Garvey *et al.*, found that using the initial decontamination advice provided by the manufacturer, environmental Gram-negative bacteria, *Pseudomonas* spp., fungi and *M. chimaera* were recoverable from the HCU⁴⁹. Working with the manufacturers, Garvey *et al.*, carried out two consecutive full system HCU decontamination cycles with Maranon (420 mL, >30% sodium hypochlorite). In addition the HCUs were subjected to weekly water changes (with filtered tap water), daily addition of medical grade 3% H₂O₂ (100 mL) and a weekly full system decontamination using Maranon. However, based on the manufacturer's guidance, water samples from the HCU remained microbiologically unacceptable⁴⁹.

It was only after complete refurbishment and replacement of the internal tubing by the manufacturer, followed by the application of the disinfection regimen; that the weekly HCU microbiological sampling counts reduced to a satisfactory level⁵². The addition of an effective disinfectant to a HCU with minimal biofilm (either because it is new or refurbished) would be expected to control the survival and growth of water-borne microorganisms which may explain the lack of detection of *M. chimaera* from HCUs after refurbishment by LivaNova⁴⁹. In addition, the daily water changes and subsequent dilution of slow growing NTM may have resulted in the bacterial numbers being below the level of detection in water and air sampling⁴⁹. Replacement of the internal tubing and renovation of the HCUs is a service that is offered by the manufacturer as a way of eradicating *M. chimaera* from the units. However, this service is only available for units that were manufactured after 2008 and there is an associated cost. More recently a number of perfusionists in the UK have been trained by the manufacturer to undertake this refurbishment (J Walker – personal communication).

Whilst enhanced disinfection may fail to eradicate NTM in water or biofilm phase, Schreiber *et al.*, found that aerosolised *M. chimaera* were not detectable in brand new HCUs that were undergoing the manufacturer recommended enhanced disinfection regime,⁶⁰ suggesting that the infection risk via this route may have been reduced. To date there has been no detailed investigation of risk to patients in terms of the number of *M. chimaera* in the water phase compared to the number present in aerosols which would have assisted in the establishment of a risk assessment based on quantifiable results.

It is clear that the increased disinfection and sampling regimens recommended by the manufacturer have added a considerable burden of duties and costs for perfusionists, cardiology and theatre staff. The microbiological analysis, air sampling, air filters and disinfectants have been estimated at £34,391.54 per year for one UK hospital operating eight LivaNova 3T HCUs (Table 1) (J Walker - personal communication). In addition, conversion of an existing space to be used for decontamination has also been estimated by that hospital to cost an additional £28,444.

Whilst disinfection has not completely removed the presence of *M. chimaera* in the water tanks, there has so far, been no new cases of *M. chimaera* infections identified originating from surgery since the introduction of the enhanced decontamination strategies. However,

it may still be too early to speculate as we remain well within the recognised incubation period for the infection. Indeed other NTM strains, notably *M. abscessus* linked to hospital tap water, have also been associated with cardiac surgery patient infections⁸⁰.

HCU containment and relocation strategies

Reliable, effective decontamination of HCUs and maintaining the microbiological quality of the water is difficult and many hospitals have adopted alternative control strategies. In line with guidance, hospitals have been positioning the HCU as far from the patient area as is feasible, as well as directing the rear fan away from the operating field and where possible close to an air extraction port in the theatre⁸¹. An alternative approach involves enclosing the water reservoirs and tubing of the HCU within an air tight 'biosafety box' and extracting the air from within the box to the outside of the theatre⁸². Another is to place the HCU outside of the operating theatre. Gotting *et al.*⁶⁸ positioned the HCU through a doorway, however, the positioning of the tubing connecting the cardiopulmonary bypass machine to the HCU prevented the theatre door from closing. This may have been the reason why the air samples from the operating room were positive and underlines the importance of controlling air flow in the whole operating area.

In Bern University Hospital, four new cardiac operating theatres have been built with ante-rooms specifically designed for housing the HCUs in 2009 prior to the current *M. chimaera* outbreaks⁸². The tubing passes into each operating room via cavities in the walls removing the risk of exhaust air from the HCU entering the operating room⁸². A UK hospital has recently taken a similar approach by building modular plates into the walls that seal the tubing passing through the wall (Figures 6 & 7). The costs of this intervention, including revalidation of the theatre air flows, have been estimated at £15,000. Figures 6 & 7 also show the newly recommended polyethylene tubing (blue) for use with the HCUs to try to reduce biofilm formation. Perfusionist's comments are that the tubing is less flexible and being opaque the perfusionists are unable to see if there has been a blood/water breach in the system (J Walker – personal communication).

Assessment and revalidation of the operating theatre airflows is essential to ensure that they are not disrupted by any changes. The use of longer lengths of tubing can cause further complications such as the requirement for larger volumes of water, inefficient heat transfer and the inability to maintain temperature control with the additional possibility of increased trips and falls. Any containment and relocation strategy should involve the manufacturer.

In due course the manufacturers may be able to i) implement an engineering solution to upgrade existing devices to prevent dissemination of aerosols from the HCUs and or ii) design new HCUs to prevent the growth of NTM in the water and to ensure that aerosolisation is minimalised during the operation of the HCU. However, these units should be fully tested and validated for microbial control and aerosol containment by independent and objective scientists.

Implications for other thermoregulatory equipment

The concern surrounding post-surgical *M. chimaera* infections had until recently, been limited to HCUs. However, heater cooler units are also used for extracorporeal membrane

oxygenation (ECMO) and similar thermoregulatory devices are also required for circulating-water mattress to maintain body temperature^{50, 83}. *M. chimaera* was detected in 9 of 18 water samples taken from 10 different heater cooler units used for ECMO devices⁵⁰. Of 76 ECMO patients who had bronchial specimens analysed for mycobacteria, *M. chimaera* was found in three individuals without signs of mycobacterial infection at the time of sampling. It would be prudent for water safety groups to ensure that HCUs used in ECMO are assessed as part of the water safety plans to ensure that the risk is reduced for those who may be exposed via this route.

In summary

There is an ongoing international outbreak of *M. chimaera* infection following cardiac surgery. Whilst a transmission risk has been identified, it is essential to recognise that many cardiac procedures, which can be life saving, are dependent on these devices. The low risk of infection must be balanced with usually much higher risks from delaying surgery.

The genetic similarity between case (patient) and environmental isolates supports the hypothesis that *M. chimaera* is transmitted to the surgical site via the aerosolisation of contaminated water from within HCUs. The water tanks of HCUs have been shown to contain a wide variety of microorganisms including extensive biofilms on a number of different components which likely contributes to the survival of *M. chimaera*.

The evidence from whole genome sequencing of *M. chimaera* in the UK, USA, Australia/New Zealand and Europe has demonstrated close relatedness between patient and device isolates, supporting the hypothesis of transmission from the HCUs and suggestive of a point source outbreak from the manufacturer's factory; within a wider potential risk of microbial transmission from this type of device. Rigorous disinfection regimens have been recommended by the different manufacturers, but these protocols and microbiological tests can be time consuming and resource intensive for hospitals, both in terms of personnel and cost.

Whilst disinfection has not completely removed the presence of *M. chimaera* in the water tanks, there has so far, been no new cases of *M. chimaera* infections identified originating from surgery after the introduction of the enhanced decontamination strategies. However, it may still be too early to speculate and indeed other NTM strains, notably *M. abscessus* linked to hospital tap water, have been associated with cardiac surgery patient infections. Therefore, in order to reduce the risk of future infection, it is critical that hospitals are aware of the risk and follow strict decontamination procedures of HCUs. Water safety groups should work with users to ensure control of microbiological risks from heater cooler units, and that water system management is embedded in routine infection control practice.

It is not clear why *M. chimaera* is currently the dominant clinical infection, when other species of NTM are found regularly within the HCUs. It may be an artefact of methods used for surveillance, may relate to *M. chimaera* being more widespread rather than being only from a point source, or perhaps may relate to as yet an undescribed biological characteristic of the species facilitating survival either in the HCU or the patient.

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ACCEPTED MANUSCRIPT

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Table 1 Estimated costs for one hospital to undertake testing of eight LivaNova 3T heater-cooler units.

Microbiological analysis / Air sampling	Estimated cost per month or every 3 months	Annual Costs
Legionella (water)	£18 x 8 samples (every 3 months)	£576.00
<i>Pseudomonas aeruginosa</i> (water)	£7.65 x 8 samples (every month)	£734.00
Environmental Mycobacteria (water)	£50.40 x 8 samples (every month)	£4838.00
Total air analysis costs for 8 machines	£150 x 8 machines (every month)	£14,400.00
Water filters	Box of 2 for 2 outlets per year	£903.00
Peracetic acid	For 8 units over one year	£1326.00
Staff time	For 8 units over one year	£11,614.50
Total		£34,391.50 (excl VAT)

Figure 1. Schematic of a typical heater cooler unit, oxygenator and cardioplegia equipment

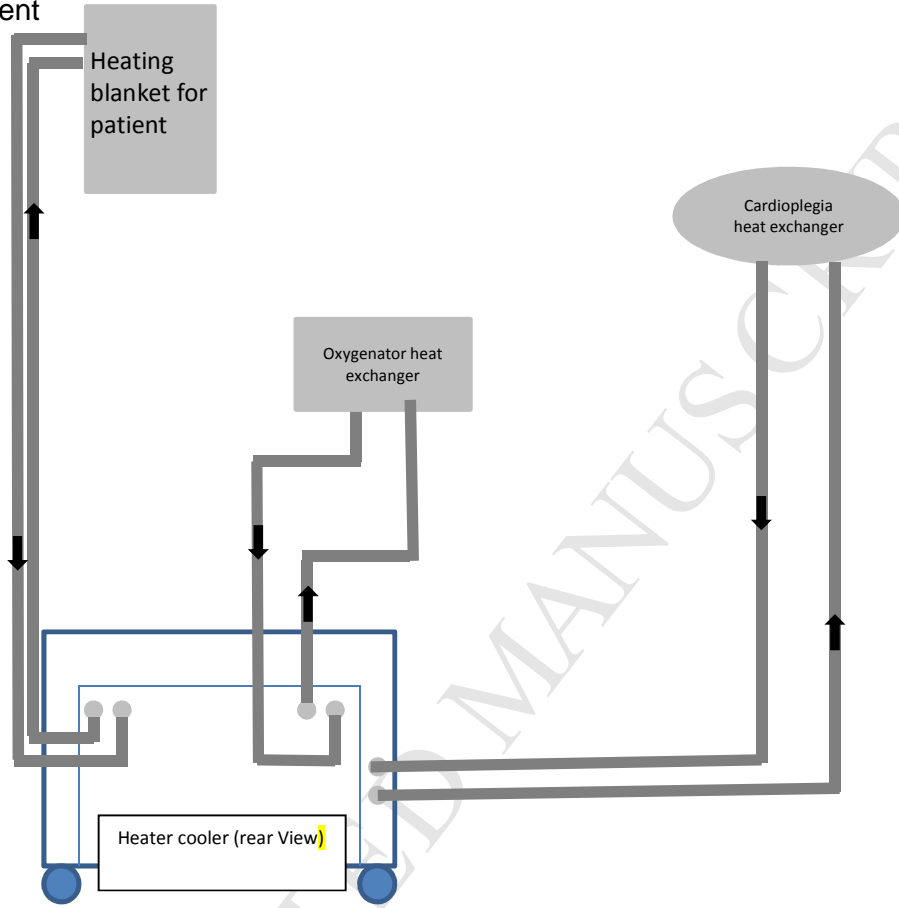


Figure 2. Two overflow pipes which can be used to vary the volume of water in LivaNova 3T HCU tanks. The lower pipe takes the overflow (and visible debris) from the tank to the overflow bottle that is attached to the rear of the HCU. The upper pipe is blocked at the top and contains stagnant water, biofilm and debris.

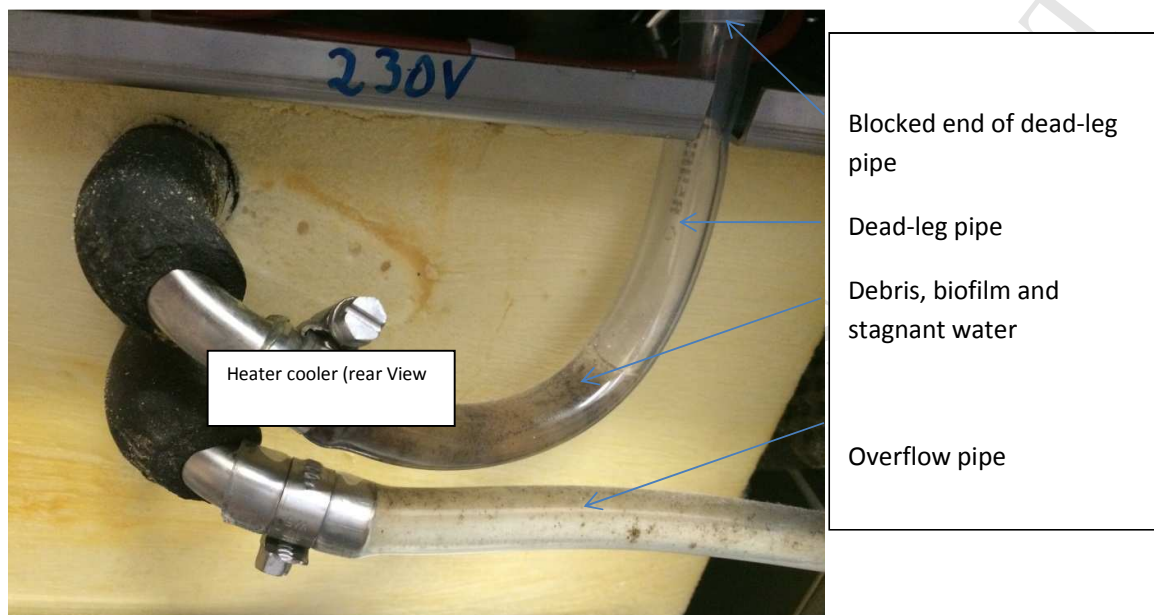


Figure 3. Location of the gaps in the water tank top plates that contributed to the release of aerosols from the heater-cooler unit studied by Public Health England, Porton Down.

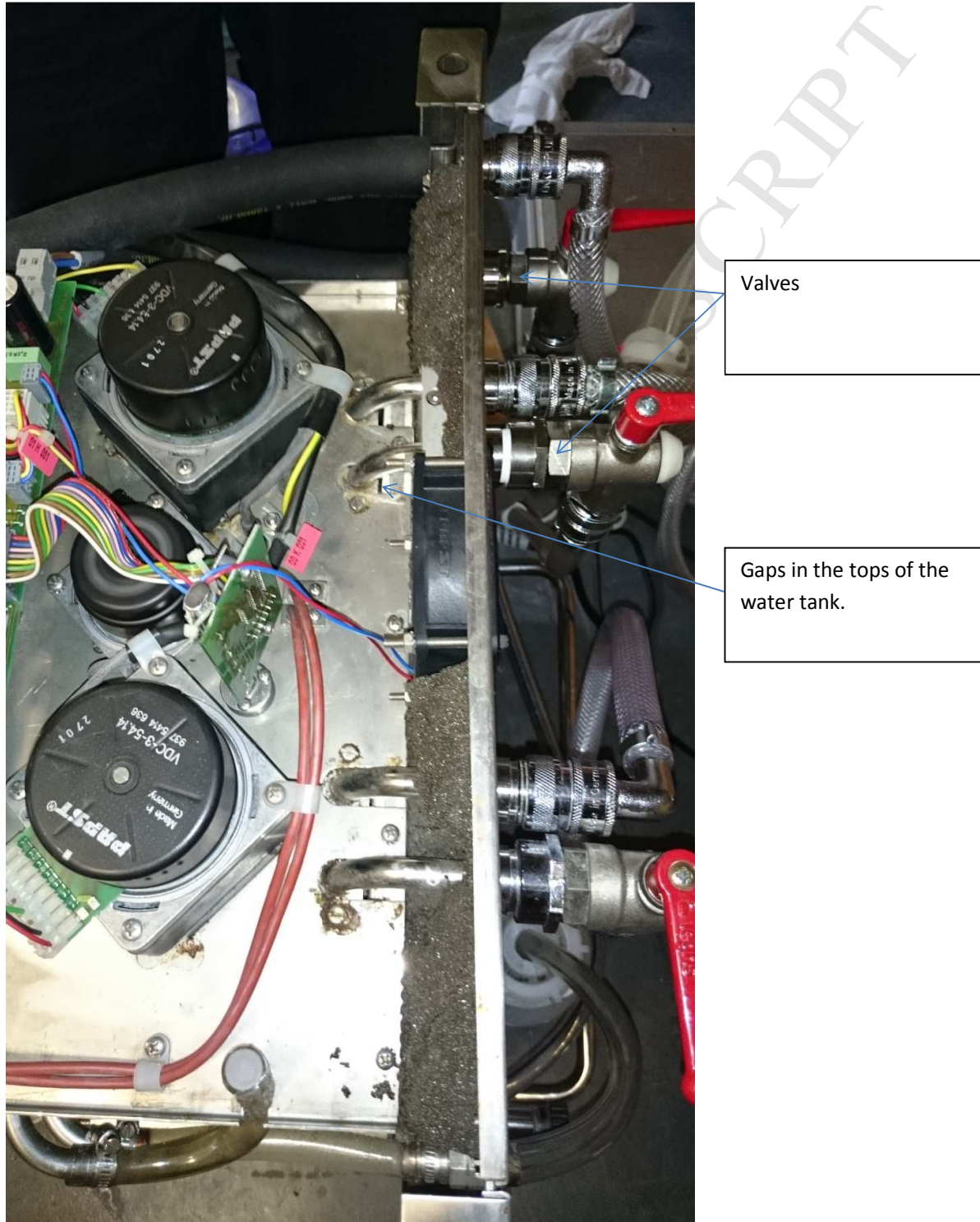


Figure 4a. Use of a smoke pen to visualise air flow path as it is extracted from the pumps/gaps associated with the water tanks and exiting the heater-cooler unit via the rear fan.

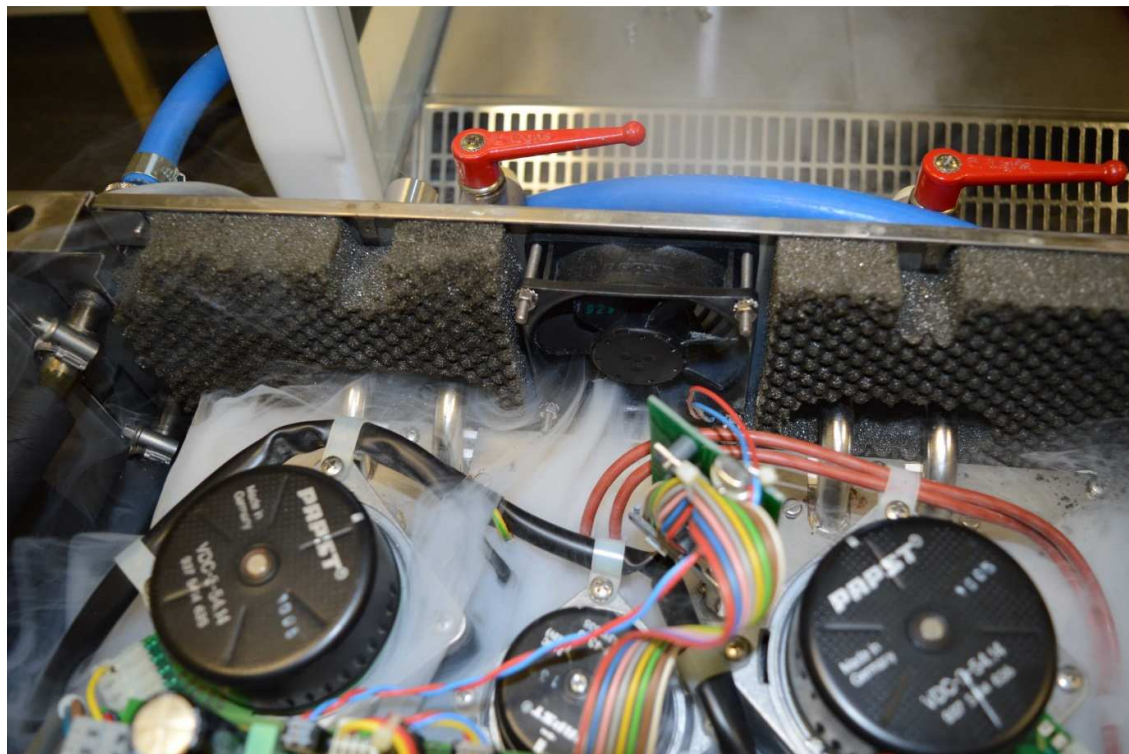


Figure 4b. Video of smoke pen to visualise air flow path as it is pulled away from the pumps and gaps associated with the water tanks to the rear fan and as it is excited from the HCU.



mycobacteria hcu review Figure 4b air path video.avi

Figure 5. Presence of extensive biofilm on materials in the water tanks of the LivaNova PLC, Sorin 3T heater-cooler unit, studied at Public Health England, Porton Down.



Biofilm present on insulation material and steel piping in the hot water tank.

Figure 6. Positioning of the heater-cooler unit outside the operating theatre with tubing passing through modular plates in the wall.

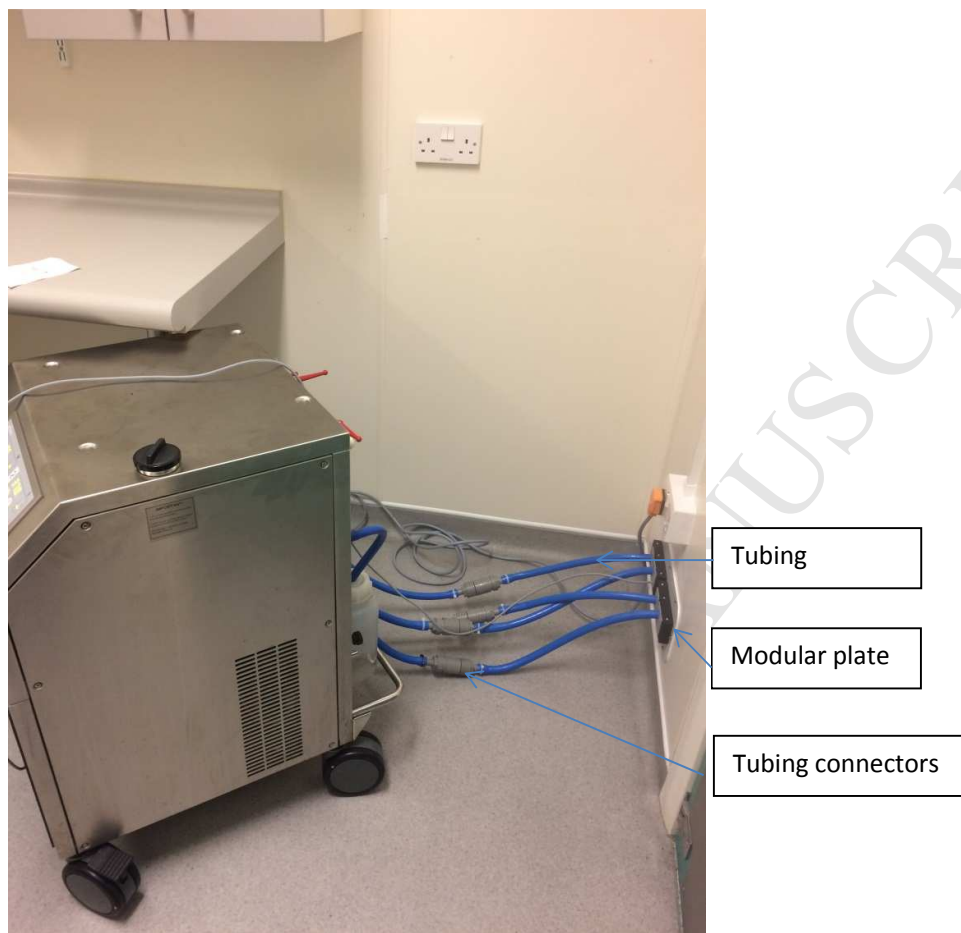


Figure 7. Position of the tubing through the wall into the operating theatre, using anti-slip matt housing and connection to the cardiopulmonary bypass equipment.

