PHLN guidance regarding Mycobacterium chimaera & heater-cooler units

Background

The development of laboratory guidelines for addressing the colonisation of HCUs by M*ycobacterium chimaera* must balance divergent considerations. On the one hand, infection of prostheses by *M. chimaera* represents a significant preventable nosocomial disease that should be avoided.[1] Furthermore, HCUs represent large ventilated reservoirs of warmed stagnant water, which are inherently unsafe in the healthcare setting. A recent review catalogues a litany of water-related nosocomial infections by Gram-negative bacteria, legionella, non-tuberculous mycobacteria (NTM) and fungi.[2]

Conversely, the incidence of *M. chimaera* disease among all potentially-exposed cardiac-bypass patients is difficult to quantify but is probably extremely low - estimated at 0.16%[1] - in a seriously-ill patient population often requiring life-saving surgery, which of itself carries much-higher rates of other complications. For example, the rate of prosthetic valve endocarditis from all causes is 1-3% in the first year after surgery and 3-6% after five years,[3] dwarfing the apparent risk of *M. chimaera*-related infections. Increasing evidence also suggests that *M. chimaera* colonisation of HCUs results from a point source, possibly at the manufacturing site.[4] If true, remedial measures at the factory should curtail the cluster of HCU-related *M. chimaera* infections. Testing of HCU waters could then downgrade from frequent intense investigations to regular periodic surveillance.

Finally, the overarching principle should be that the correct maintenance, cleaning & disinfection of HCUs are the most important interventions in controlling and preventing colonisation of HCUs by *M. chimaera* and other organisms. Accurate maintenance records “documenting the process” are therefore more important than “testing the outcome” by bacteriological surveillance.

Guidance for laboratory testing of HCU waters

In view of the above considerations, the following guidance document aims to present a rational and pragmatic approach for laboratory investigations in the prevention and control of HCU-related infections. The guidance is based largely on the protocol published by Public Health England (PHE) supplemented with laboratory experiences documented in a PHLN survey of Australian laboratories handling HCU specimens.[5,6] PHLN will update this guidance document as experience accrues with testing HCUs, and as this *M. chimaera* event unfolds nationally and internationally.

Laboratories and healthcare professionals are also referred to any directives from the HCU manufacturers and to three other Australian publications on this topic. The Therapeutic Goods Administration (TGA) has provided two advisories and the Australian Commission for Safety and Quality in Health Care (ACSQHC) has produced an infection control guidance document.[7-9] This PHLN laboratory guidance provides more detail relating to laboratory testing methodology and is intended to complement the ACSQHC publication.

Specimen collection

a) The HCU should be connected and running for at least five minutes before water samples are collected.
b) Sampling should occur before the HCU's disinfection cycle.
c) The addition of sodium thiosulphate may not be necessary to inactivate chlorine-based disinfectants at the levels in (filtered) tapwater for the isolation of mycobacteria.[10] The requirement for and type of neutralising agent required to inactivate other disinfectants (eg. hydrogen peroxide) now used by HCU manufacturers is being investigated.
d) In HCUs with two tanks, a sample should be collected from each tank (ie. from the patient "arm" and the cardioplegia "arm" of the circuit).
e) Each sample should be of at least 100 ml.
f) Sample labelling & the specimen request form should include: date of collection, hospital name, HCU serial number, sample site (i.e., which circuit) and details of a designated point of contact for results.
g) Samples should be stored at 2-8°C and for no longer than 24 hours before processing.

Heterotrophic plate counts

Heterotrophic plate counts (HPCs) can be used to monitor the integrity, cleanliness and maintenance of water systems.[11] These HPCs might be performed monthly. Laboratories appear to use a range of HPC methodologies and the Australian Drinking Water Guidelines cite a number of HPC methodologies.[6,11] In the absence of a standard HPC methodology and while experience accumulates with testing HCU waters, trends rather than absolute numbers of organisms should be followed for this monitoring.

The survey of mycobacteriology laboratories highlighted that no relationship existed between HPCs and the isolation of *M. chimaera* from HCU waters (ie. *M. chimaera* was isolated from HCU water with low HPCs). Monitoring by HPCs therefore does not obviate the need for surveillance by mycobacteriology cultures.

Mycobacteriology culture methodology

a) At least 100 ml of water from each sample should be centrifuged in 50-ml universal tubes at 3,000*g* for 15-30 minutes
b) After discarding the supernatants, the concentrated aliquot should be pooled in one 50-ml universal tube
c) The standard decontamination method employed in the local mycobacteriology laboratory can then be employed.
d) The concentrate should be inoculated into an automated broth-based system (eg. MGIT, BD Bioscience, Sparks, MD, USA) and incubated for 6-8 weeks at 35-37 C.
e) The concentrate should also be inoculated onto a solid medium (eg. LJ slopes) and incubated at 35-37 C for 8-12 weeks.
f) Any mycobacterial isolate should be referred to the relevant MRL for identification and the isolate stored.
g) Accurate speciation of *M. chimaera* requires sequencing of genes in addition to/instead of 16S rDNA, such as *hsp65*, *rpoB* and/or ITS.

h) Isolates should be stored should future WGS analysis be required to assess genetic relatedness of *M. chimaera* from HCUs to: (i) epidemiologically-associated patient isolates, and (ii) the HCU-associated *M. chimaera* clone in Australia and NZ.

The sensitivity of the detection of mycobacteria in HCU waters using the above specimen collection, processing and culture methodology is uncertain. While these methods are being quantified and optimised, laboratories and end-users should recognise the risk of false-negative culture results.

PHLN has corresponded with the National Association for Testing Authorities (NATA) about an accreditation dilemma. Environmental laboratories accredited for water testing generally do not perform mycobacterial cultures while mycobacteriology laboratories are usually not accredited to perform HCU water testing. Until this impasse is resolved, mycobacteriology laboratories are advised to perform the testing following the above guidelines and to add a rider to their reports that this testing is outside the scope of their NATA accreditation.

Other tests

Based on the survey of Australian & NZ laboratories that found that air sampling had been unrewarding,[6] air sampling in the cardiothoracic theatre is not mandated. Air sampling may be performed at the discretion of the responsible institution or jurisdiction based on local considerations. If performed, an air sampling device, selective Middlebrook 7H11 plates and the methodology described in the PHE guidelines should be used.

The PHLN laboratory survey also found that legionella testing of HCU waters had been unproductive. However, there have been reports from Dutch microbiologists and internet forums of *Legionella pneumophila* isolation from HCU waters.[12] These reports have implications for occupational health and safety as well as patient care. A prudent approach would be to test HCU waters monthly as required by various state guidelines for the maintenance of non-domestic water systems. The on-going need for legionella testing of HCU waters will be reviewed as experience accumulates.

Surveillance for patients with M. chimaera infections

All relevant health professionals must be alert for patients with possible prosthetic infections (eg. prosthetic valves or vascular grafts) that may be caused by *M. chimaera* and related to HCUs. Kohler *et* al have provided a useful case definition for prospective detection of patients with HCU-related *M. chimaera* infections.[1] Laboratory investigations for these patients should include:

a) at least two mycobacterial blood cultures (collected on separate days) done in Myco/F lytic or similar bottles incubated for 6 weeks;
b) mycobacterial culture of urine and, if collected, bone marrow aspirate;
c) investigations of explanted prosthetic valves or grafts should include mycobacterial cultures
d) if available, PCR targeting the 16S or other genes able to detect mycobacteria should also be performed on these explanted specimens.

References

1. Kohler P, Kuster SP, Bloemberg G,*et al*. Healthcare-associated prosthetic heart valve, aortic vascular graft, and disseminated *Mycobacterium chimaera* infections subsequent to open heart surgery. *Eur Heart J* 2015: 36: 2745-53.
2. Kanamori H, Weber DJ, Rutala WA. Healthcare outbreaks associated with a water reservoir and infection prevention strategies. *Clin Infect Dis* 2016; 62: 1423-35.
3. Karchmer AW. Infections of prosthetic valves and intravascular devices. In: Principles and Practice of Infectious Diseases, 5th ed, Mandell GL, et al (Eds), Churchill Livingstone, Philadelphia 1999. p. 903.
4. Haller S, Höller C, Jacobshagen A, *et al*. Contamination during production of heater-cooler units by *Mycobacterium chimaera* potential cause for invasive cardiovascular infections: results of an outbreak investigation in Germany, April 2015 to February 2016. *Euro Surveill* 2016 Apr 28; 21(17).
5. Public Health England. Protocol for environmental sampling, processing and culturing of water and air samples for the isolation of slow-growing mycobacteria: standard operating procedures, July 2016. Available at: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/540325/Air_water_environmental_sampling_SOP_V2.pdf
6. Public Health Laboratory Network. PHLN survey regarding Mycobacterium chimaera & heater-cooler units - Available at: http://www.health.gov.au/phln.
7. Therapeutic Goods Administration. Non-tuberculous mycobacterium infections associated with heater-cooler devices. Available at: https://www.tga.gov.au/publication-issue/medical-devices-safety-update-volume-4-number-3-may-2016#a2.
8. Therapeutic Goods Administration. Non-tuberculous mycobacterium infections associated with heater-cooler devices. Alert - updated advice for health professionals and facilities following report of patient infection, 2 August 2016. Available from: https://www.tga.gov.au/alert/non-tuberculous-mycobacterium-infections-associated-heater-cooler-devices
9. Australian Commission on Safety and Quality in Health Care. National infection control guidance. Non-tuberculous mycobacterium associated with heater-cooler devices, 2 September 2016. Available at: https://www.safetyandquality.gov.au/wp-content/uploads/2016/09/National-Infection-Control-Guidance-for-Non-tuberculous-Mycobacterium-Heater-Cooler-Devices-PDF.pdf
10. Thomson R, Carter R, Gilpin C, Coulter C, Hargreaves M. Comparison of methods for processing drinking water samples for the isolation of *Mycobacterium avium* and *Mycobacterium intracellulare*. *Appl Environ Microbiol* 2008; 74: 3094-8.
11. Australian Drinking Water Guidelines Paper 6 National Water Quality Management Strategy, Version 3.2 Updated February 2016. National Health and Medical Research Council, National Resource Management Ministerial Council, Commonwealth of Australia, Canberra. Available at: https://www.nhmrc.gov.au/guidelines-publications/eh52
12. Australian College for Infection Prevention and Control. Non-tuberculous mycobacterium and heater-cooler devices webinar. Available at: http://www.acipc.org.au/Professional-Development/Webinars/Nontuberculous-Mycobacterium-Infection-and-Heater-Cooler-Devices