Information for all clinicians to support patient discussions

Purpose

This information has been prepared in order to support clinicians with the provision of information as part of routine clinical follow up of patients who have undergone heart/lung transplant and patients who have had non-valve related congenital heart disease repair. The information provided below is not intended to replace the materials prepared as part of the primary and secondary care guidance materials and should be viewed as complementary. The existing guidance materials can be accessed through the following links:

- **Information for healthcare providers**

The document details the responsibilities of healthcare providers in assessing and mitigating the infection risks posed by the use of heater cooler units (HCUs) as part of cardiopulmonary bypass.
Available here: website

- **Scottish specific appendix**

This document has been prepared for use in Scotland and details how the information for healthcare providers mentioned above translates across for use in a Scottish context. Guidance on the provision of information to patients as part of the consent process is also included. http://www.hps.scot.nhs.uk/pubs/detail.aspx?id=3169

- **Clinical guidance for secondary care**

The document provides guidance on the recognition of *M.chimaera* infections associated with cardiopulmonary bypass, the investigation and clinical management of suspected and confirmed cases, sources of expert advice and the relevant reporting requirements.
Available here: website

- **Information for general practice**

The document provides guidance on the assessment and referral of patients in whom infection is considered a possibility in addition to supporting information in relation to patients who may have been exposed but who are currently well.
http://www.hps.scot.nhs.uk/pubs/detail.aspx?id=3169

- **Patient support materials**

The patient support materials include a video of a clinician talking through the issues and also a Question & Answer (Q&A) document.
Available at NHS Inform

Situation

During 2014-15, PHE were made aware of cases of *Mycobacterium chimaera* endocarditis or deep infection following cardiac surgery in Switzerland, Germany and The Netherlands.[i,ii] *M. chimaera* is a recently described species within the *Mycobacterium avium* complex, a

group of environmental organisms usually associated with lung infections, or systemic infections in the immunocompromised host.

A Swiss investigation implicated the Sorin (now LivaNova) 3T heater cooler unit (HCU) of the cardiopulmonary bypass equipment, with the transmission of bacteria to the surgical site by aerosolisation of contaminated water from within the unit[i]. The LivaNova device is widely used in the UK and internationally. Maquet, another manufacturer of devices used in the UK, has also indicated that *M. chimaera* has been identified in its HCU water tanks and issued advice to manage any associated risk. The risk associated with HCUs from other manufacturers is currently unknown.

A national investigation was undertaken in 2015 indicating a low risk in patients undergoing valve replacement and repair and widespread contamination of devices in use in the UK.[iii] Surveillance and microbiological investigations have been continuing since that time. A number of findings triggered review of the UK response leading to the recommendation to undertake a patient notification exercise.

Notification of very large numbers of patients who are at extremely low risk has the potential to cause harm through anxiety and distress with minimal benefit. Given the overall low level of risks it was felt necessary to balance the potential harms of notification against the likelihood of acquiring the infection and thus a risk stratification process has been employed to identify patients for inclusion in the exercise:

Patient Notification Exercise (PNE) group
The patient group deemed at highest risk are those patients who have undergone valve replacement or repair in centres using Sorin (Liva Nova) heater cooler units since January 2013 and it is therefore this group of individuals who will receive letters as part of the main Patient Notification Exercise (PNE).

Clinician follow up group
Even though the overall risk for all groups is low, investigations undertaken to date indicate that patients who have undergone heart/lung transplant, and patients who have had non valve related congenital heart disease repair appear to be at lower risk of infection with *M. chimaera*. Therefore these patient groups will not be included in the main patient notification exercise. These groups will usually have remained under routine follow up and therefore they will be followed up by their clinical team and receive information as part of their hospital clinical follow up at their next appointment.

Background

M. chimaera
M. chimaera is a non-tuberculous mycobacterium which is a member of the *Mycobacterium avium* complex, most similar to *Mycobacterium intracellulare*. It was relatively recently described and would have been identified previously as *M. intracellulare*. This type of mycobacterium is widespread in the environment, including tapwater, and is usually associated clinically with respiratory disease or with disseminated disease in the immunocompromised patient. *M. chimaera* infection has an insidious and non-specific presentation, is not always identified through conventional microbiology, and requires specific treatment. It has a high mortality.

In early 2015, following an international alert, Public Health England (PHE) convened a team, including MHRA, NHS England, the Department of Health, Society for Cardiothoracic Surgery (SCTS), Association of Cardiothoracic Anaesthetists (ACTA), Society of Clinical Perfusion Scientists and volunteer NHS Trusts, to investigate and assess the risk in the UK

of severe non-tuberculous mycobacterial infections associated with essential medical devices used in cardiothoracic surgery and ECMO. These devices are heater-cooler units (HCUs), used to cool or warm patients on cardiopulmonary bypass to allow lifesaving surgery to be performed safely. PHE identified 18 patients in the UK with *M. chimaera* endocarditis, deep surgical site infection or disseminated infection following cardiothoracic surgery. All cases were associated with valve replacement or repair. No cases were detected in ECMO patients.

M. chimaera and other potential pathogens were detected in water from a number of LivaNova (previously Sorin) HCUs and in the air around them when running at NHS Providers across the country. Aerobiological investigation showed aerosol generation in one of two 3T HCUs tested, indicating that variation between devices due to age, maintenance or other factors is likely. A small number of devices from another manufacturer were also tested; some of these also contained *M. chimaera*, but aerobiological investigations were negative.

LivaNova (Sorin) issued a Field Safety Notice (FSN) in June 2015, updating the cleaning and disinfection regime for HCUs and recommending microbiological monitoring and removal of some contaminated devices from service in order to reduce the likelihood of transmission of infection. These measures were rapidly introduced during 2015 to reduce risk, whilst preserving NHS capacity to provide essential cardiothoracic surgery. A PHE risk assessment published at this time indicated that the risk of acquiring infection was likely to be much lower than the risk of delaying cardiothoracic surgery. Providers were alerted to the risk and the possibility of further cases. MHRA commenced work with a European Taskforce to ensure lessons being learned were shared globally. A further FSN was issued in November 2016.

Investigations during 2016 in the UK and internationally have substantiated the risk of transmission, identified further cases, and highlighted difficulties and delays in diagnosing and treating this very uncommon infection. In the last year, seven cases have been reported as a result of surgery undertaken before the problem was recognised. Whilst this does not exceed projected case numbers, it is of concern that there continue to be delays in diagnosis. The clinical presentations are diverse and non-specific. One of the most recent cases was diagnosed post mortem. The cases originate from surgery performed before the introduction of mitigation measures in 2015, suggesting a reduction in risk may have already occurred. Monitoring is required to confirm this as the incubation period still continues. However, one of the aims of the patient notification exercise and the associated guidance materials is to increase awareness which should improve timeliness of appropriate diagnosis.

Assessment

Case numbers and estimated risk

Between 2007 and 2 November 2016, 26 probable cases of *M. chimaera* infection associated with cardiopulmonary bypass (15 of whom have died) have been identified in the UK. Twenty-five of the cases identified are thought to have acquired their infection during surgery involving cardiac valve replacement or repair, sometimes as part of more complex surgery, the remaining single case having had coronary artery bypass graft surgery.
From retrospective and prospective case finding beginning in 2007, the earliest cases identified were diagnosed in 2008 and the earliest implicated surgery was performed in 2007. One of the cases had their cardiac surgery in the private sector with 13 of 41 NHS cardiothoracic centres identifying at least one case to date; numbers of *M. chimaera* infection by cardiothoracic centres varied considerably. The median interval between surgery and diagnosis was 18 months but has been up to 5 years.

Based on the numbers of cases diagnosed in England where surgery was performed in NHS hospitals (n=23), the risk to patients was estimated as follows:

- *Cardiac valve repair/replacement*
  Between 2007 and 2015 approximately 130,000 patients underwent valve repair or replacement surgery in the NHS in England according to Hospital Episode Statistics, which means an estimated risk of **two cases of *M. chimaera* infection per 10,000 patients (or 1 in 5,000**). In 2014, the year with the highest number of cases reported to date, this risk increases to approximately 1 in 2,000.
- *Coronary artery bypass graft (CABG)*
  Between 2007 and 2015 approximately 186,000 patients underwent CABG surgery in the NHS in England, translating to an estimated risk of **<1 case of *M. chimaera* per 100,000 patients**, substantially lower than for cardiac valve patients.
- *Heart/lung transplant*
  Between 2007 and 2015 approximately 2,800 patients underwent heart or lung transplants in the NHS in England. No cases associated with these procedures have been identified to date in the UK. However the number of procedures is relatively small and there is less certainty around risk assessment in this group.
- *Congenital heart disease*
  Between 2007 and 2015 approximately 28,000 patients underwent surgical procedures other than valve replacement or repair on cardiopulmonary bypass as a result of congenital heart disease in the NHS in England. No cases associated with these procedures in the absence of heart valve surgery have been identified to date in the UK suggesting a very low risk of *M. chimaera* infection.

Risk stratification for inclusion within the PNE

Notification of very large numbers of patients who are at extremely low risk has the potential to cause harm through anxiety and distress with minimal benefit. Given the overall low level of risks it was felt necessary to balance the potential harms of notification against the likelihood of acquiring the infection and thus a risk stratification process has been employed to identify patients for inclusion in the exercise. As described above, the patient group deemed at highest risk are those patients who have undergone valve replacement or repair in centres using Sorin (Liva Nova) heater cooler units since January 2013 and it is therefore this group of individuals who will receive letters as part of the main Patient Notification Exercise (PNE).

Even though the overall risk for all groups is low, investigations undertaken to date indicate that patients who have undergone heart/lung transplant, and patients who have had non valve related congenital heart disease repair appear to be at even lower risk of infection with *M. chimaera*. Therefore, these patient groups will not be included in the main patient notification exercise. These groups will usually have remained under routine follow up and therefore they will be followed up by their clinical team and receive information as part of their hospital clinical follow up at their next appointment. It should be noted that in the event of a case outside the highest risk group, the clinical guidance and improved awareness generated should still improve timeliness of appropriate diagnosis.

The rationale for these decisions is detailed below and reflects the risk estimates provided above:

1. Selection of surgical procedures

Recommendations:

- Patients undergoing cardiac valve repair/replacement surgery, including those where bypass equipment on standby, should receive letters as part of the main PNE.

- Patients who have undergone heart/lung transplant, and patients who have had non valve related congenital heart disease repair appear to be at lower risk of infection with *M. chimaera*. Therefore these patient groups will not be included in the main patient notification exercise. These groups will usually have remained under routine follow up and therefore they will be followed up by their clinical team and receive information as part of their hospital clinical follow up at their next appointment.

Supporting information:

- 25 of 26 cases of *M. chimaera* infection identified to date in the UK were in patients who underwent cardiac valve surgery. Risk estimates calculated on NHS patients in England (which excludes 2 Welsh and 1 private patient) indicate a significantly higher risk in cardiac valve surgery patients than CABG patients. Whilst 1 of the cases identified to date had congenital heart disease, this patient underwent heart valve surgery placing them within this risk group; no cases have been identified to date amongst patients undergoing such procedures in the absence of surgery on their heart valves.
- retrospective case finding included all types of cardiopulmonary surgery including CABG, congenital heart repair, heart/lung transplant, and ECMO
- no methodological artefact can explain uneven risk in CABG and congenital repair vs. cardiac valve surgery
- the small number of heart/lung transplants means there is less certainty around the relative risk in this group of patients

2. Selection of time period

Recommendation:

- Include patients who underwent surgery from January 1st 2013 onwards to ensure capture of patients undergoing surgery during the years of highest risk and to identify all those within their 2 year post-surgical window.

Supporting information:

- There is a rising incidence rate from <0.2 before 2011 to 2 in 2014 per 10,000 person years of post-operative follow-up (assuming 5 years at risk after surgery). However, only one case operated on in 2015 has been diagnosed, and no case has been diagnosed who had had surgery since the introduction of the enhanced cleaning and disinfection regime. These patients may still develop symptoms at a later date, but this may provide an early indication that risk has already been reduced.
- More cases were diagnosed in 2015 than in other years, consistent with the retrospective case finding exercise and efforts to raise clinical awareness.
- Number of cases, risk and incidence increased by year of surgery between 2010 and 2014 suggesting a real increasing risk and/or improved case finding.

- Most cases were diagnosed within 2 years of surgery.
- It is acknowledged that this recommendation is potentially inconsistent with the duty of candour and the known incubation period for the infection given the longest known interval time from operation to overt infection is a little over 6 years. However, the risk stratified approach was suggested following review of the distribution of cases from year of operation and the fact that notification of very large numbers of patients who are at extremely low risk has the potential to cause harm through anxiety and distress with minimal benefit. Given the overall low level of risks it was felt necessary to balance the potential harms of notification against the likelihood of acquiring the infection and thus a risk stratification process has been employed to identify patients for inclusion in the exercise.

3. Selection of cardiothoracic centres for inclusion

Recommendation:

- Notify all patients who underwent relevant surgery in NHS and independent sector treatment facilities.

Supporting information:

- The numbers and risk estimates based on cardiac valve surgery are very heterogeneous between centres.
- The differences in risk estimates may reflect differences in microbial contamination, possibly as a result of the age of heater coolers in use, but likely to be significantly affected by local diagnostic practices. Other factors such as greater awareness of the potential diagnosis and a different case mix of patients could also be contributory.

4. Type of Heater Cooler Unit (HCU) used

Recommendation:

- Exclude patients whose surgery was solely performed in centres that have only ever used Maquet HCUs at the time of surgery.

Supporting information:

- All heater cooler units irrespective of the manufacturer have a risk of contamination with *M. chimaera* amongst other pathogens. However aerosol generation has only been demonstrated from Sorin devices, and this is the leading hypothesis for the route of transmission.
- There have been no recorded cases of patient infection associated with Maquet machines. Data from the USA has been reviewed and is in accord with assessments made in the UK.

Other possible areas for discussion/FAQs

What does this mean for patients who are due to undergo surgery on cardiopulmonary bypass?

Patients who are considering surgery which will or may involve cardiopulmonary bypass must be informed of this small but known risk of *M.chimaera* infection. All consent should be informed by an understanding of the risks and benefits of any proposed intervention. The risk of not intervening should always be part of that process.

Over time, the onus on deciding how much information to consider and who should decide on whether or not to proceed with the intervention has shifted from the doctor or health care provider to the patient. This cultural shift in society has been matched by regulation and legislation, Montgomery being the most recent high profile case.

It is now recognised that it is the patient taking the risk and who is the one therefore to decide how much information to receive and consider. Importantly, the impact of any specific risk and the associated weight a person places on it when making decisions about treatment will depend on the individual patient.

Consent is therefore an individualised process. This makes it challenging when designing consent documents and mandates supplementation of any generic form with:

a) separate guidance for the surgeon and
b) information sheets for the patient.

The benefit of such an approach is that it enables the supplementary guidance to change as understanding of the issue changes while keeping the generic consent form relatively constant, requiring less frequent updating.

In this specific instance, the consideration is the bio-burden associated with cardiothoracic surgery. This includes, but is not limited to, transfusion transmissible disease, early prosthetic valve endocarditis due to endogenous or exogenous transmission of commensal flora and mycobacterial infection from contaminated water in HCUs.

While the overall risk of being affected by *M. chimaera* is low, the potential impact is high and a small number of deaths have resulted from this infection. Furthermore there is much that is unknown in relation to this organism and the means of contamination of the HCU. For these reasons the decision has been made that all patients being consented for surgery must be made aware of the risk.

Although the Patient Notification Exercise was a targeted exercise towards the patients at highest risk, all patients who are considering surgery which may involve cardiopulmonary bypass should be consented with respect to the risks of *M.chimaera* infection.
It has been agreed that a standard consent process should be implemented across Scotland.

Cardiothoracic surgical teams must therefore:

- advise patients of the contemporaneous knowledge of the risks associated with *M. chimaera*. The risk assessment will be regularly reviewed and updated by PHE in conjunction with health protection leads from each of the devolved nations.

This should include information regarding any known cases at that specific provider and where available a risk ratio. At the current time, there have been no cases of *M.chimaera* infection associated with the use of heater cooler units during cardiothoracic surgery in Scotland.

As such, the risk estimates provided earlier in this document should be used to support discussions. This must be done with the provision of information sheets about their surgery.

An example of such an information sheet is provided in the Scottish appendix document

At the time of discharge patients must also be provided with information regarding the symptoms of infection with *M. chimaera* and how to seek help, even if this is many years after the surgery. A suggested information leaflet for use at discharge is found in the Scottish appendix document.

Should surgical procedures be delayed?
Decisions regarding continuing or delaying cardiothoracic surgery must be made by the provider. In most cases the risk from delaying cardiothoracic surgery is likely to outweigh the infection risk. The highest risk is associated with valve replacement or repair.

The Society for Cardiothoracic Surgery (SCTS) advises that the risk of dying or suffering other adverse events due to delay in valve replacement is likely to be significantly greater than the risk of acquiring mycobacterial infection in this context. If mitigating measures are currently being implemented, SCTS advises that surgeons may wish to consider on an individual case basis whether there are any planned procedures that would not be affected by delay.

What is being done to reduce the infection risks in order to prevent future infections?
The cleaning and disinfection regime for HCUs has been updated and recommendations have been implemented regarding microbiological monitoring and removal of some contaminated devices from service in order to reduce the likelihood of transmission of infection. MHRA will continue to work with manufacturers on design and engineering solutions to provide longer term elimination of risk.

There is an early indication that enhanced cleaning and disinfection may have reduced risk of infection, since no cases have been diagnosed who were operated on since the introduction of these measures. However these patients are still in the potential incubation period and continued surveillance is required.

Why are the recommendations different in other countries?
In addition to valve surgery, cases have been described in the UK and US after Coronary Artery Bypass Graft (CABG), and in the US also after other vascular grafts, left ventricular assist device implantation and cardiac transplant. The maximum period from surgery to overt infection described is 6.3 years.

The Centers for Disease Control and Prevention has published a Health Advisory notice (13/10/2016). Whilst generally consistent with UK guidance, it also advises hospitals to retrospectively notify patients who underwent other types of open heart surgery involving a Sorin 3T heater cooler. As detailed previously, in light of the overall very low risk, the UK approach has involved a risk stratification process in that only the highest risk patients have been directly notified as part of the exercise. This decision was recommended by the Core Incident Group and tested with patients and patient groups in England. There has also been agreement across the Devolved Administrations with respect to this approach.

Why are these machines still being used?
The FDA now recommends only using 3T devices manufactured before 2014 in emergency/life threatening situations. This response has been replicated across Europe and Australia. However, having completed a data collection exercise to understand the profile of machines in use, it would be impossible to safeguard operational delivery of cardiac surgery if this approach were to be taken in the UK and therefore this cannot be replicated in

England or the Devolved Administrations. Work is being undertaken to progress a coordinated approach to the prioritisation of procurement for new equipment.

How does the UK risk compare to other countries?
The UK risk estimate has a high degree of uncertainty since it is not standard practice in the UK to look for mycobacteria in cardiac or post-surgical infections. Risk estimates from The University Hospital of Zurich are around 1 per 500 cases and estimates from hospitals in the US where cases have been identified range from 1 per 100 to 1 per 1000.[i,iv] National data from these countries is not published. Their individual centre risks are similar to the risks seen in our centres with cases in the years with the highest risk (from 1 per 1000 to 1 per 100).

Patient recall exercises have been conducted at some US centres and press reports indicate that these are also underway in Canada. At least 30 cases have been reported in the US.

Why are patients not being recalled for testing alongside notification?
It is understood that other countries have initiated a patient recall for testing alongside notification. However, there is no evidence to date that testing asymptomatic patients will reliably identify incubating infection and therefore patient recall has not been suggested for the UK.

References

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[ii] 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(40):2745-2753. doi:10.1093/eurheartj/ehv342.

[iii] Chand M, Lamagni T, Kranzer K, et al. Insidious risk of severe Mycobacterium chimaera infection in cardiac surgery patients. *Clin Infect Dis*. 2016. doi:10.1093/cid/ciw754.

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