

This Medicines Information Leaflet is produced locally to optimise the use of medicines by encouraging prescribing that is safe, clinically appropriate and cost-effective to the NHS.

Antimicrobial Use In Bone Cements

Bone cements are medical devices implanted alongside bone and/or metal work during orthopaedic operations. There are a range of cements and the choice depends on the type of procedure being undertaken along with other patient factors.

Polymethyl Methacrylate (PMMA) is a type of bone cement often used in surgical procedures for prosthesis fixation. It is often used to fashion spacers to preserve limb length during staged revision arthroplasty.

Some types of PMMA are antibiotic loaded (ABL) with antibiotics including gentamicin and vancomycin pre-mixed into the cement so that these can diffuse within the operated site over a period, with an initial high release of antibiotic to reduce the risk of bacterial colonization of any prosthesis. There are certain scenarios in which, on advice of microbiology, other specific antimicrobials may also be mixed into these cements in order to provide greater /more specific antimicrobial effects and to help keep newly revised joints clear from microbial colonization to help improve outcomes.

The purpose of this MIL is to set out a standard procedure to be followed when the addition of further antimicrobial agents are to be made to PMMA based cements

in order to standardise the antimicrobials used and the procedure that should be followed.

All cases in which additional antimicrobials are to be added to PMMA need to be approved by Micro/ID to ensure the antimicrobial choice is appropriate. This must be approved by the BIU registrar, contacted via bleep 7186 or the on call ID registrar via switchboard if out of hours.

Materials used

PMMA Cements

PMMA cements used vary based on procedure, availability and antibiotic that they are pre-loaded with but include Copal®, CMW®, Palacos® and Refobacin®, and are available in theatres. There are other types of cements used in orthopaedic surgeries including fixation cements and beads but the further addition of antimicrobials to these is not covered by the scope of this MIL.

Calcium Sulphate Cements

Stimulan® the main calcium sulphate cement used in trust doesn't have CE approval for use in combination with antimicrobial agents, recently confirmed by MHRA. Thus any additions to this are outside the product use licence and only the addition of 280mg of gentamicin and 1g vancomycin per 10ml Stimulan® are

covered in the product literature. So any requests to add antibiotics to calcium sulphate cements must be specifically discussed on an individual patient basis and are not covered by this MIL.

Antimicrobials

Though some types of PMMA contain antibiotics, there are scenarios in which further additions may be of specific patient benefit, particularly in relation to prosthetic joint infection (PJI). The main antimicrobial agents for which efficacy and safety is known and thus covered by this MIL are daptomycin, amikacin, liposomal amphotericin B (Ambisome®) and colistimethate sodium. [Table 1](#) shows the agreed quantities of antimicrobial agents to be incorporated into PMMA mixes but as a general rule the total concentration of antimicrobials should be no more than 10% w/w of the PMMA cement mix to ensure ongoing cement strength.

Factors to consider for choice of antimicrobials

Systemic absorption of antimicrobials in drug-eluting cement is possible though theoretically limited. However, if there are concerns regarding renal impairment, allergy/hypersensitivity risk, therapeutic drug monitoring or potential toxicity then a discussion may be needed with the relevant teams. Patients must also be counselled on the unlicensed use, the procedure and any risks from the surgery overall. [Unlicensed Medicines PIL](#)

Certain factors have been considered when assessing the antimicrobials which are to be incorporated into PMMA

cements. These are evidently considered within a number of case reports. These include:

- The antimicrobial agent's thermal and chemical stability in situ
- The formulation of the antimicrobials – liquid/powder. Affects the setting of the cement.
- The elution profile of the antimicrobial agent once formulated into the PMMA.
- The risk of hypersensitivity reactions associated with the antimicrobial agent.
- The effects of the antimicrobial on the PMMA's porosity and compressive strength.

Prescribing Guidance

All additional antimicrobial agents for PMMA must be prescribed via EPR. When prescribing prior to admission, the antimicrobial agent should be prescribed as a TTO under a NOC outpatient encounter. If prescribing for an inpatient, the antibiotic is to be prescribed and charted as a 'Once Only' item but future dated to the proposed operation date.

Antibiotics must be requested AT LEAST 48 hours prior to the procedure.

In both cases, the antimicrobial should have the drug form as 'powder' with the indication listed as 'bone cement' with special instructions stating 'FOR THEATRE USE ONLY' **AND** the ratio of antimicrobial to cement must be included (see Figure 1 as an example). Upon prescribing, the BIU pharmacist must be notified (bleep 7166) so the antimicrobial agent can be clinically screened and ordered.

Amikacin	Processing	Dose: 4 g - topical - powder - once ONLY - GP to Continue. No - Dose Change Reason: N/A - FOR THEATRE USE ONLY (2g amikacin per 40g of PMMA) - Indication: Bone Cement		
Time View	08/Jul/2020 0000 - 2359	09/Jul/2020 0000 - 2359	10/Jul/2020 0000 - 2359	11/Jul/2020 0000 - 2359
Scheduled				
Amikacin				
Dose: 4 g - topical - powder				
Amikacin				
Dose: 4 g - topical - powder - once ONLY - FOR THEATRE USE ONLY. (2g of amikacin per 40g PMMA) - Indication: Bone Cement - Start On: 06/Jul/20 16:00:00 - Stop On: 06/Jul/20 10:00:00				

Figure 1: Special Instructions to include 'THEATRE USE ONLY'. Must also have ratio of drug: cement. E.g. for Amikacin x2 mixtures (2g each), therefore, must be prescribed as 4g (total quantity required).

Prior to the operation, the antimicrobial must be collected from the designated area in the BIU ward treatment room by a member of the theatre team.

Preparation of Bone Cement

The antimicrobial can then be used as designated and mixed into the PMMA cement in the ratios outlined in Table 1, as per the surgeon's requirements and discretion. The antimicrobial powder and PMMA powder are first mixed in the mixing chamber and then the liquid is added and mixed to form the PMMA cement. As for antimicrobial agents formulated as liquids (such as amikacin), the antimicrobial liquid and PMMA liquid are added at the same time to the PMMA powder and mixed to form the PMMA cement.

References

European Medicines Agency Completes Review of Polymyxin-based Medicines: Recommendations Issued for Safe Use in Patients with Serious Infections Resistant to Standard Antibiotics. Available online: https://www.ema.europa.eu/documents/press-release/european-medicines-agency-completes-review-polymyxin-based-medicines_en.pdf (accessed on 10/7/2020).

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Pocket Guide to Diagnosis and Treatment of implant-associated infections after fracture fixation. Pro-Implant Foundation. Version 2 October 2017. cs.pro-implant-foundation.org

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Table 1: Unlicensed local antibiotic additions, according to infecting organisms

Reported combinations of antimicrobial agent and PMMA cement described in clinical use amended from the Pocket Guide to Diagnosis and Treatment of implant-associated infections after fracture fixation (2017).

Pathogen	Antimicrobial(s)	Concentration recommended (per 40g PMMA bone cement) [Not more than 4g antimicrobial/40g PMMA bone cement , to ensure compressive strength]
Unlicensed addition of antimicrobial agents		
MRSA or Enterococcus (not VRE)	Gentamicin AND Vancomycin OR Daptomycin	0.5-1g 2-4g 2g*
VRE Other resistant Gram positive	Gentamicin AND Daptomycin	0.5g 2g*
Resistant Gram negative organisms (Klebsiella, Pseudomonas, Acinetobacter)	(Gentamicin AND) Amikacin OR Gentamicin AND Colistimethate sodium	(0.5g) 2g* 0.5g 60 million IU* (this equates to 4.8g of the sodium salt or 2g of Colistimethate base)
Candida spp. Other fungi	(Gentamicin AND) AmBisome Liposomal (liposomal Amphotericin B)	(0.5g) 200 mg for non-load bearing *

** These agents and/or doses are not available as a premixed commercial product. The combinations are described on the basis of reported specialist clinical use in patients, outside the license of the carrier and antimicrobial agent. Informed consent sought from patients as unlicensed preparations and no data regarding mechanical stability of cement following these additions, and patients must be informed as per ULM procedure. These recommendations are based on limited evidence and may change with time as the evidence base increases.*

Any proposed cement mixes outside the parameters outlined in this MIL will still need to be discussed with Microbiology, MMTC chair and pharmacy for approval