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The microbiology of chronic osteomyelitis: Changes over ten years

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SUMMARY

Aim: This study quantified changes in the microbiology of osteomyelitis over a ten year period from a single centre within the UK with regard to infection with multi-drug resistant (MDR) bacteria and susceptibility of antimicrobial regimens.

Method: Patients with chronic osteomyelitis undergoing definitive surgery from 2013–2017 were inluded ($n = 223$). Microbiology was compared to patients in a cohort from 2001–2004, using the same diagnostic criteria, and same deep tissue sampling technique ($n = 157$). Clinical features associated with MDR bacterial infection were analysed using logistic regression.

Results: Both cohorts had similar baseline characteristics. Despite a similar proportion of *Staphylococcus aureus* in both cohorts, the rate of methicillin resistant *Staphylococcus aureus* (MRSA) infection was lower in 2013–2017 compared to 2001–2004 (11.4% vs 30.8% of *Staphylococcus aureus*, $p = 0.007$). However, the proportion of MDR infections was similar in both cohorts (15.2% versus 17.2%). Metalwork was associated with MDR infection (unadjusted OR 5.0; 95% CI: 1.15 to 22.0). There was no change in resistance to glycopeptide / meropenem combination treatment (2.2% vs 2.5%, $p > 0.9$).

Conclusions: In this centre, rates of MRSA osteomyelitis have fallen by two thirds, over the past 10 years, in line with the reducing rate of MRSA bacteraemia nationally. A history of metalwork may predict MDR infection. A glycopeptide with an anti-pseudomonal carbapenem remains the post-operative empiric systemic regimen of choice. Resistance patterns support the use of a glycopeptide with an aminoglycoside in local antibiotic therapy.

Introduction

Osteomyelitis is a frequent and feared complication of trauma, affecting up to one third of patients who present with severe limb injury or open fracture during their recovery.[1–3] In addition, haematogenous seeding and soft tissue infections, especially in patients with diabetes mellitus and pressure ulceration, can result in osteomyelitis.[4,5]

A number of previous studies have demonstrated a variety of microorganisms isolated in osteomyelitis.[1,6] However, few have focused on the prevalence of multi-drug resistant (MDR) bacteria and how they can influence the choice of empiric local and systemic antimicrobial therapy. Some concern has been voiced regarding the rising frequency of MDR pathogens in orthopaedic infections, in the UK and worldwide.[7,8]

Here, we compare two prospectively identified cohorts of patients with osteomyelitis from the same specialist bone infection centre treated ten years apart. The aims of this study were to (i) investigate whether clinical features of osteomyelitis correlate with microbiology, (ii) quantify the change in the incidence of osteomyelitis caused by MDR organisms over a 10-year time period and (iii) ascertain changes in resistance patterns to local and systemic empirical antibiotic regimens.

Patients and methods

All patients with surgically treated osteomyelitis during a four year period (March 2013 – May 2017) in one specialist unit were included (see Fig. 1).[9,10] Some patients had given informed consent for participation in cohort studies. Further analysis of anonymised, unidentifiable data for the purpose of service evaluation and

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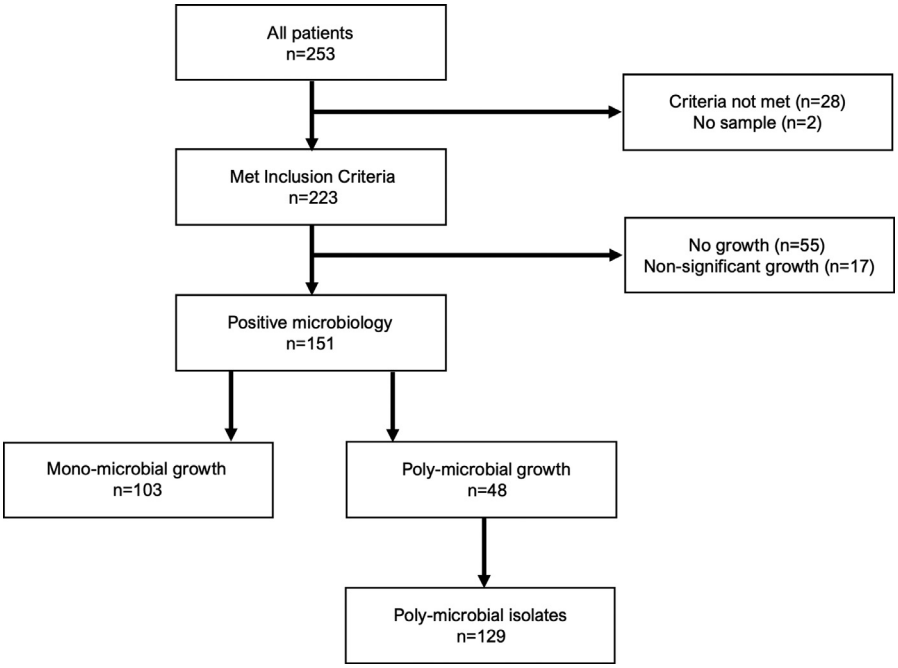


Fig. 1. Flow diagram of patient inclusion and isolate analysis for the 2013–2017 cohort.

quality improvement (selection of empiric antimicrobial regimens) was supported by institutional review (#5071).

Cessation of all antimicrobial therapy at least two weeks before surgery and sampling was recommended for patients without systemic sepsis. In the cases where multiple operations were performed on the same patient, only the first intervention was included for analysis.

For comparison of resistance patterns, a cohort taken from the same centre, who received surgery for osteomyelitis between 2001 and 2004, was used.[6] Pre-operative microbiological investigation was not considered and inclusion was thus independent of prior microbiological test results.

Definition and diagnosis of osteomyelitis

Chronic osteomyelitis was defined by symptoms of at least six months duration or radiological appearances suggestive of bone infection.[4] In addition, the presence of at least one of the following operative findings were required: (i) two or more sterile site specimens culture positive with an indistinguishable organism, (ii) histology suggestive of chronic osteomyelitis (a mean of >5 neutrophils per high power field, averaged over at least 10 fields)[11] or (iii) sinus, abscess or purulence present at time of surgery. These criteria align with established methods of confirming the diagnosis of osteomyelitis.[6]

Clinical information

Information was collected prospectively from case notes which included the site of osteomyelitis, aetiology and history of metalwork. Throughout, the term 'metalwork' refers to any internal fixation, external fixation or stabilisation device. The Cierny and Mader classification and the likely aetiology (endogenous: haematogenous; exogenous: contiguous infection, following elective orthopaedic surgery, or complicating fracture)[12] was applied at the time of surgery by the operating surgeon.[13]

The Cierny and Mader classification is used in chronic osteomyelitis and consists of both an anatomic and host classification. The anatomic part divides long bone osteomyelitis into four stages: medullary (Stage I), superficial (Stage II), localised cortical and medullary osteomyelitis (Stage III), and diffuse or segmental osteomyelitis (Stage IV). Host status is divided into A (healthy), B (compromised by local or systemic factors that impede healing) or C (treatment is worse than living with the disease, or when the patient is not a surgical candidate).[13]

Surgical sampling technique

Deep bone samples were taken according to a validated protocol designed to minimise cross contamination during surgery. This consisted of a separate set of sterile instruments to obtain each specimen, and avoidance of instrument contact with the skin.[14] Each patient had up to 10 specimens retrieved from abnormal tissues, including dead bone, granulation tissue and medullary pus; none were taken from cutaneous ulcers or sinuses. These underwent microbial culture (described below) and histological examination. Infected metalwork was removed and in some cases subject to sonication. The results of sonication were interpreted as an additional surgical specimen. Patients were advised to stop all antibiotics two weeks prior to surgical sampling.

Microbiological sample processing

Samples were processed in a Class 2 microbiological safety cabinet within 4 h of collection. They were agitated with sterile glass (Ballotini) balls in 10 mL of Peptone water. 200 mL of sample was plated onto each of blood agar (incubated aerobically and anaerobically), lysed blood agar (incubated in air with 5% CO_2) and blood culture bottles (BACTEC Plus Aerobic/F bottle and BACTEC Lytic/10 Anaerobic/F bottle). If no growth occurred from primary plates, blood bottle culture broths were routinely sub-cultured at 10 days onto blood agar (cultured aerobically and anaerobically) and lysed blood agars (cultured in air with 5% CO_2) and incubated for an additional five days.

All colonial phenotypes received further work up. Standard microbial phenotyping methods, including Matrix Assisted Laser Desorption / Ionisation - Time of Flight mass spectrometry, were

used for identification. Antimicrobial susceptibility testing was performed using BD Phoenix (BD Diagnostics, Oxford, UK) or the modified Stokes method, with confirmatory testing using Etest (BioMerieux, Basingstoke, UK).

Antimicrobial susceptibility testing was determined for each isolate and the minimum inhibitory concentration (MIC) to define resistance for each isolate were based on the EUCAST guidelines.[15,16]

Interpretation of microbiological culture

Results of microbial culture were retrospectively sought from case records with the reviewer blinded to detailed clinical information. Significant microbial growth was defined as two or more specimens per patient yielding an indistinguishable micro-organism. Micro-organisms of the same species were considered indistinguishable if there were two or fewer discrepancies in the antimicrobial susceptibility pattern. A result was considered polymicrobial if two or more distinguishable organisms were each isolated from two or more samples.

Multi-drug resistance (MDR) was interpreted from available antimicrobial susceptibility data for five bacterial types (*Staphylococcus aureus, Enterococcus* spp., *Enterobacteriaceae, Acinetobacter* spp., and *Pseudomonas* spp.) according to the criteria defined by ESCMID.[17] These specify definitions of MDR, extensively drug resistant (XDR) and pan drug resistant (PDR) bacteria owing to resistance against specific antibiotics. All isolates tested for susceptibility to at least 3 antibiotics were included in this analysis.

Specimens for histological analysis

All samples for histological analysis were fixed in formaldehyde. Tissue samples were embedded in paraffin and five-micrometre sections cut and stained with hematoxylin-eosin. All tissue samples were examined by two specialist osteoarticular histopathologists who were blinded to the microbiology results. In all cases, histopathology was reported as either suggestive of infection, inconclusive, or not suggestive of infection. Gram stains were performed on all samples.

Statistical analysis

Statistical analyses were carried out using R in RStudio (RStudio, Inc., Boston, MA URL http://www.rstudio.com/). Proportions of micro-organisms were compared, if relevant to the clinical question, using Fisher's exact test.

Multivariable analysis to investigate possible associations between clinical information and MDR infection was carried out using logistic regression, with patients as the unit of analysis. Two analyses were carried out in parallel: all patients with infection involving organisms that could be classified as MDR according to ESCMID criteria; and all patients. Full logistic regression models were compared with simple models of MDR infection against cohort using the likelihood ratio test. Odds ratios for MDR infection for available clinical information were calculated and reported. Missing data were imputed using Multiple Imputation by Chained Equations (MICE).[12]

Polymicrobial infection, cause of infection (aetiology) and Cierny and Mader grade were not included in the analysis because of co-linearity with other variables and significant missing data in the earlier cohort. Information pertaining to duration of infection, past surgical intervention and pre-operative antibiotic use was not available.

Table 1
Baseline characteristics of 2 cohorts of patients treated operatively for chronic osteomyelitis.

	2013–2017 Cohort	2001–2004 Cohort
Patients included	**223**	**157**
Male	167 (74.9%)	116 (76.7%)
Female	56 (25.1%)	41 (28.3%)
Mean age	51	45
Minimum age	17	12
Maximum age	88	90
Cierny and Mader Grade		
CM I	8 (3.6%)	Not known
CM II	10 (4.5%)	
CM III	174 (78.0%)	
CM IV	31 (13.9%)	
Aetiology		
Fracture	135 (60.5%)	117 (73.6%)
Soft tissue injury or ulcer	14 (6.3%)	
Haematogenous	52 (23.3%)	(~26.5%)
Following an orthopaedic procedure	22 (9.9%)	
Metalwork history		
None	92 (41.3%)	43 (27.0%)
Previous metalwork	99 (44.4%)	59 (37.1%)
Metalwork at time of surgery	31 (13.9%)	53 (33.3%)
Unknown	1 (0.4%)	2 (1.3%)
Specimens for microbiology		
Median per patient	5	5
Mean per patient	4.9	4.5
Patients with >= 5 specimens tested	197 (88.3%)	83 (52.2%)
Histology		
Suggestive of infection	195 (87.4%)	104 (65.4%)
Not suggestive of infection	0	23
Non-diagnostic or equivocal	25	18
Missing	3	12
Clinical features of osteomyelitis		
Sinus	152 (68.1%)	Not known
Purulence reported at surgery	84 (37.7%)	

Results

Patient demographics

A total of 223 patients with a diagnosis of osteomyelitis were included as part of the 2013 – 2017 cohort. These patients were compared to an earlier cohort of 157 patients from between 2001 and 2004 that has been previously reported by Sheehy et al. 2010.[4] Baseline characteristics from both cohorts are described in Table 1.

Anatomical information and surgical management in the 2013–2017 cohort

The most common sites of osteomyelitis were the tibia (100/223; 44.8%), femur (54/223; 24.2%) and the humerus (27/223; 12.1%). Other sites included the forearm (16/223; 7.2%), calcaneum (8/223; 3.6%), pelvis (7/223; 3.1%), ankle (7/223; 3.1%), fibula (4/223; 1.8%), knee (2/223; 0.9%) and clavicle (2/223; 0.9%).

Seventy-two patients (32.3%) had no micro-organisms identified on deep bone culture. Mono-microbial infection comprised 46.1% (103/223). Poly-microbial infection was present in 21.5% (48/223), Fig. 1.

The mean number of deep tissue specimens sent for microbiological culture was 4.9 (median 5 samples) and 87.4% of patients (195/223) had at least five samples analysed. For *Staphylococcus aureus* isolates, a mean of 19.3 antimicrobial susceptibility tests performed (range 0–28) and only one isolate had fewer than 17 susceptibility tests.

The majority of isolates were classifiable by ESCMID MDR criteria (182/231; 78.8%) and this comprised 124 patients (124/223; 55.6%). Supplementary Table 1 shows susceptibility testing.

Table 2
Micro-organisms isolated from deep operative specimens in two cohorts of patients with chronic osteomyelitis.

	2013–2017 Cohort	2001–2004 Cohort
Total number of isolates	232	166
Gram positive bacteria		
Methicillin-susceptible *S. aureus*	77 (33.2%)	36 (21.7%)
Methicillin-resistant *S. aureus* (MRSA)	10 (4.3%)	16 (9.6%)
Coagulase-negative *Staphylococcus*	14 (6.0%)	27 (16.3%)
Streptococcus spp.	19 (8.2%)	13 (7.8%)
Enterococcus spp.	15 (6.5%)	8 (4.8%)
Diphtheroids including *Propionibacterium*	10 (4.3%)	11 (6.6%)
Gram negative bacteria		
Enterobacteriaceae	54 (23.3%)	27 (16.3%)
Aerobic non-fermenting bacilli including *Pseudomonas* spp.	17 (7.3%)	9 (5.4%)
HACEK group	0	1 (0.6%)
Other microorganisms		
Anaerobic bacteria	12 (5.2%)	15 (9.0%)
Mycobacterium spp.	1	1
Fungi	1	1
Others	2 (0.9%)	1

Microorganisms isolated from culture of deep tissue specimens

All isolated micro-organisms are given in Table 2. The most common isolate was *S. aureus* which comprised 37.5% (87/232) of the total number of isolates and occurred in 39.0% (87/223) of patients. MRSA comprised 10.5% (10/95) of all *S. aureus*.

Clinical features of osteomyelitis and microbiology

Endogenous (haematogenous) osteomyelitis was associated with a greater proportion of culture negative infection compared to exogenous osteomyelitis, (44.2% compared to 26.0%, $p = 0.011$; Fig. 3a). Of note, there were no cases of MRSA osteomyelitis identified in patients following elective orthopaedic procedures.

All patients in the 2013 – 2017 cohort were classified according to Cierny and Mader grade, Table 1.[13] Cierny Mader grade did not influence the bacteria culture (Fig. 3b). However, the presence of factors conferring local soft tissue compromise, such as smoking, malnutrition and peripheral vascular disease (Bl or Bsl host status) increased the likelihood of positive bacterial culture (Fig. 3c). The presence or history of metalwork did not influence the pathogens identified (Fig. 3d).

Changes in MDR, including MRSA, osteomyelitis over time

MDR pathogens comprised 15.2% of infections in the 2013–2017 cohort and 17.1% of infections in the 2001–2004 cohort. No significant association was identified between earlier and later treatment period and the risk of MDR infection ($p = 0.10$, MDR-classifiable infection only; $p = 0.44$, all patients.) Adjusted logistic regression models including cohort, history of metalwork, site of infection, age and sex did not demonstrate an association of the odds of MDR infection with treatment period (Fig. 4 and supplementary Fig. 1). There was no salient confounding by these clinical factors ($p = 0.125$, MDR-classifiable infection only; $p = 0.261$, all patients).

MRSA is a subgroup of MDR *S. aureus*. In the 2013–2017 cohort, the proportion of MRSA isolated was lower than in the 2001–2004 cohort (11.4% versus 30.8% of *S. aureus;* $p = 0.007$) despite the overall proportion of *S. aureus* remaining similar (37.5% versus 31.3%; $p = 0.11$). However, the number of methicillin-sensitive *S. aureus* isolates that met the ESCMID criteria for MDR meant that there was no significant difference between *S aureus* MDR isolates overall between the two cohorts (16/52 versus 15/86, $p = 0.09$). In the 2013–2017 cohort, on average an additional 5 antimicrobial susceptibility tests which were able to contribute to ESCMID MDR classification were performed on *S. aureus* isolates (Supplementary Table 1).

In the 2013 - 2017 cohort, 6.7% of *Enterococcus* spp. were vancomycin-resistant (VRE) compared with 12.5% in 2001–2004. Extended-spectrum beta-lactamase-producers (ESBL) comprised 5.6% of Enterobacteriaceae in 2013–2017, compared to 7.4% in 2001–2004. Species with the potential to over-express AmpC-type beta-lactamases (ESCAPPM group)[18] comprised 35.2% of *Enterobacteriaceae* in 2013–2017 compared with 44.4% in 2001–2004.

Effect of metalwork on MDR infection

MDR infection was associated with metalwork in-situ at the time of surgery according to univariate analysis ($p = 0.04$, MDR-classifiable infection only; $p = 0.03$, all patients) but not multivariate analysis ($p = 0.06$, model adjusted for cohort, patient age, anatomic site of infection; MDR-classifiable infection only). The estimated odds ratio for MDR infection in the presence of metalwork in situ compared to no metalwork at the time of surgery was 5.0 (95% CI: 1.15 to 22.0, all patients; Fig. 4).

Empiric systemic antimicrobial regimens

The susceptibility of infections to common antimicrobial regimens were reviewed. All significant isolates from a patient were required to be tested and susceptible to antibiotics in a regimen, for the infection to be 'sensitive' to the regimen (Fig. 5). Susceptibility for some micro-organisms was inferred according to international guidelines.[15,19]

Local antimicrobial therapy

In our cohort, the combination of a glycopeptide (vancomycin) with an aminoglycoside (gentamicin) had the lowest rate of resistance, with 58.3% of patients having confirmed susceptible infections, and only 7.2% having resistant micro-organisms, albeit at susceptibility testing that reflected usual pharmacodynamic targets for systemic therapy.

Systemic antimicrobial regimens

The combination of an anti-pseudomonal carbapenem with a glycopeptide remains the most likely effective systemic combination therapy for the empiric post-operative treatment of osteomyelitis, based on susceptibility of micro-organisms identified (Fig. 5). Only 2.2% of patients had resistant infections in 2013–2017. Micro-organisms resistant to this combination included vancomycin-resistant *Enterococcus* (1/223), *Mycobacterium tuberculosis* (1/223), *Aspergillus fumigatus* (1/223), meropenem-resistant *Proteus mirabilis* (1/223), and meropenem-resistant *Pseudomonas aeruginosa* (1/223). This was not significantly different from 2001–2004, where 2.5% of patients had resistant infection ($p > 0.9$).[6]

For the 223 patients treated in 2013–2017, a targeted oral antimicrobial regimen could be selected for 213 patients (95.5%), based on microbiology alone, although this figure does not take into account allergies, drug interactions or tolerability.

Discussion

This prospective cohort study reviewed the change in microbiology of osteomyelitis in one tertiary referral centre over a ten year period and investigated possible associations with clinical features.

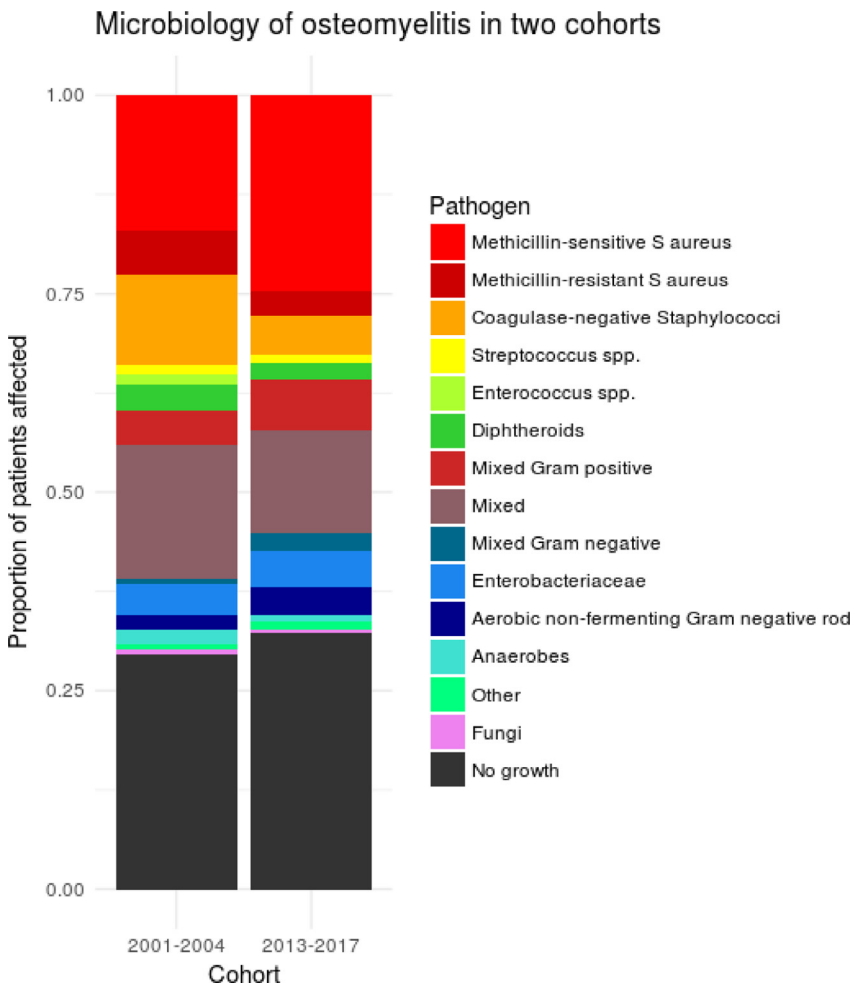


Fig. 2. Microbiology of Chronic Osteomyelitis: Changes in Microbiology of Chronic Osteomyelitis Over Time.
Comparison of microbiology between patients treated in 2001–2004 and 2013–2017. Only significant culture results from deep tissue and bone culture are included. Mixed infection was described when significance culture results from ≥2 micro-organisms were identified.

Clinical features

We observed a similar proportion of bacterial isolates between the two study periods. There was also a similar rate of culture negative osteomyelitis; this was expected based on prior studies.[6,20] The rate of *S. aureus* at 39.0% was comparable to that of other reported studies[20] and that in prosthetic joint infection.[21] A higher proportion of culture-negative infection was observed in patients with endogenous osteomyelitis compared to exogenous osteomyelitis. Furthermore, patients who were free from local tissue compromise had a higher proportion of culture-negative osteomyelitis, compared to those with local compromise such as peripheral vascular disease.

Stratifying patients according to clinical features may be helpful in targeting microbiological tests. For example, in the groups that we identified as being at higher risk for culture negative infection, there may be greater benefit from the use of sensitive molecular techniques. In the three patients in our cohort where 16 s PCR was applied, no micro-organisms were identified. However, identification of fastidious organisms including Kingella in haematogenous osteomyelitis may improve with the use of 16 s PCR from tissue samples.[22]

MDR infection including MRSA

The proportion of MRSA isolated in 2013–2017 fell to approximately one third compared to 2001–2004, despite the proportion of patients affected by *Staphylococcus aureus* remaining similar over the study period. The reduction in the proportion of MRSA chronic osteomyelitis over 10 years parallels the fall in MRSA bacteraemia in the United Kingdom over the same period.[23] This reduction could be attributed to improved hospital infection prevention practices including pre-operative decolonization therapy in orthopaedic surgery.[24] Demonstrating a direct effect of MRSA decolonization prospectively has been challenging due to the long duration of follow-up required[25] and the likely impact on patients who did not receive decolonization therapy themselves, through reduced transmission. The effect of decolonization is supported by the difference in MRSA infection in patients with fracture-related osteomyelitis (where there is no possibility of pre-operative decolonization) compared with those sustaining osteomyelitis following elective orthopaedic procedures (Fig. 2).

There was no evidence of change in the overall rate of MDR infection. The number and proportion of tests relevant to ESCMID MDR classification performed on isolates in the 2013–2017 cohort

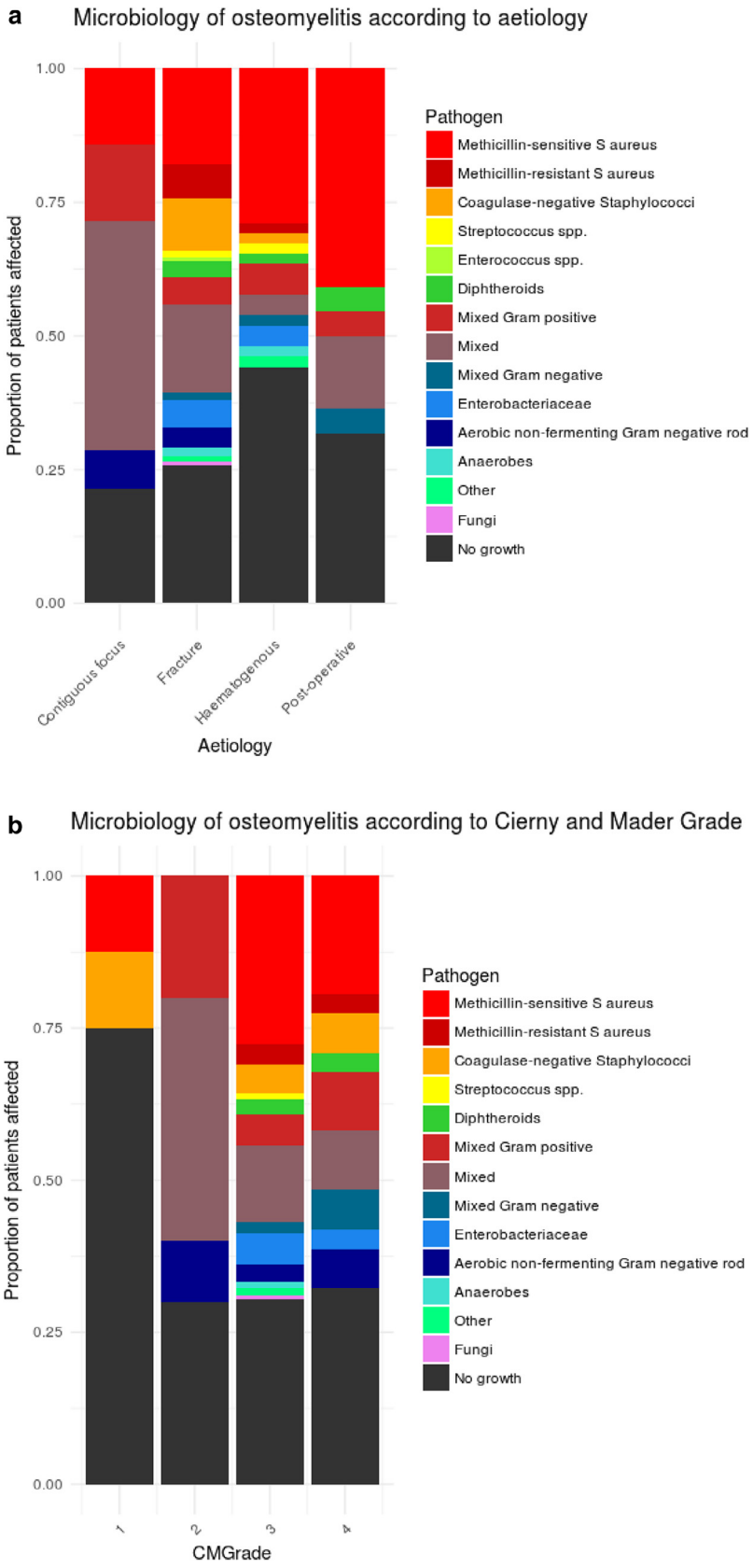
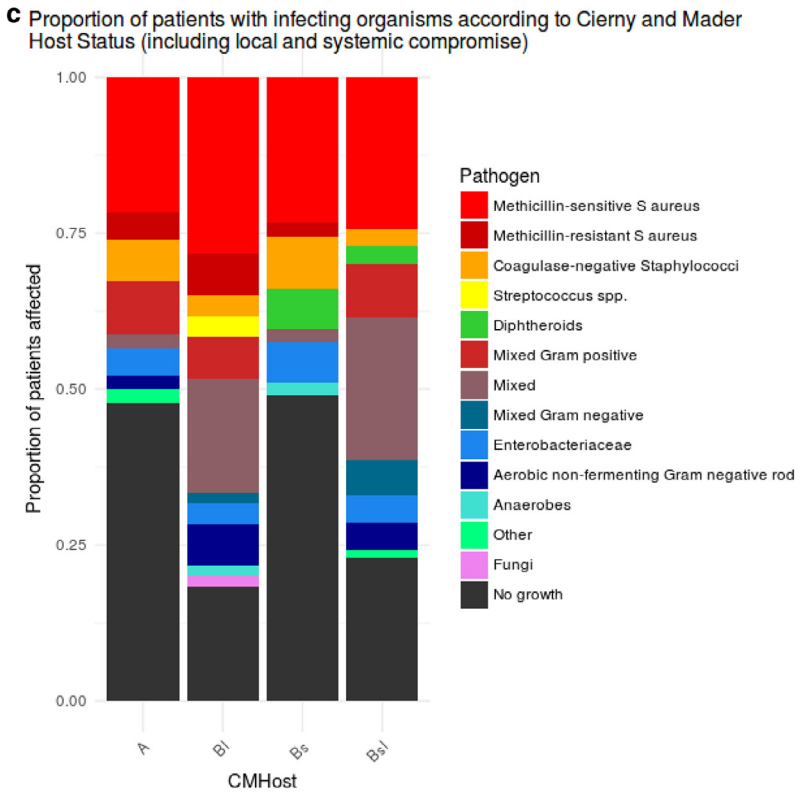


Fig. 3. Proportion of patients with infections where particular significant micro-organisms were identified, according to aetiology of infection.
Microbiology of Chronic Osteomyelitis For Patients Treated between 2013 and 2017 (a) According to cause of infection (aetiology); (b) according to Cierny Mader grade (1 = Superficial, 2 = medullary, 3 = localised and 4 = diffuse)[13] (c) according to Cierny Mader host status (*S* = systemic compromise including significant medical comorbidity; *L* = local compromise including arterial and venous disease) (d) according to history of metalwork (None= no prior history of metalwork; Previous= history of metalwork but none in situ at the time of surgery; In situ= metalwork present at the time of index surgery).



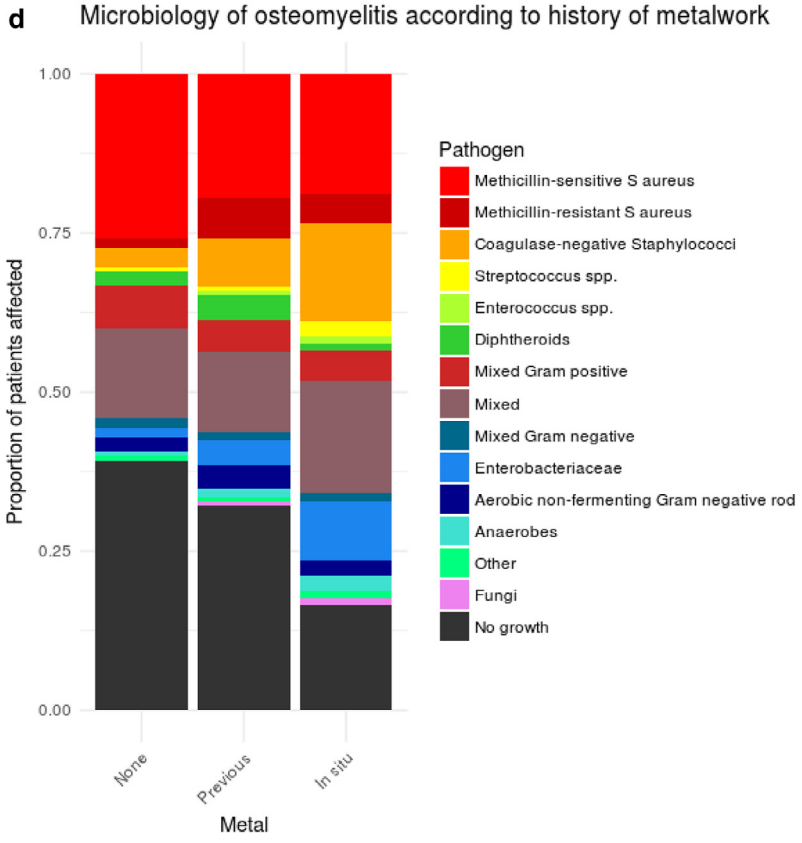


Fig. 3. Continued

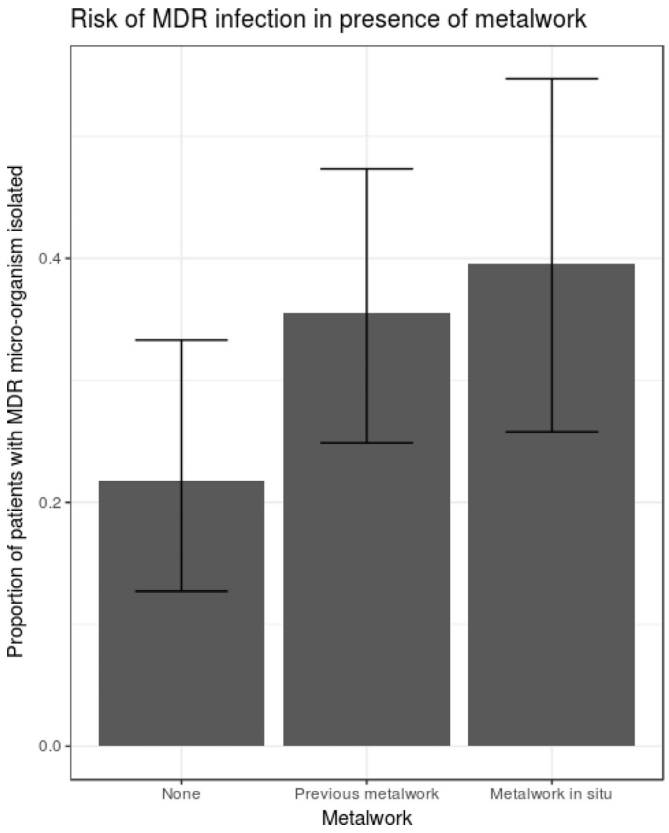


Fig. 4. Risk of MDR infection in relation to History of Metalwork.
Proportion of patients in 2001–2004 and 2013–2017 cohorts with MDR micro-organisms isolated in deep tissue according to history of metalwork. Error bars denote 95% confidence intervals estimated by binomial exact method.

was greater in all cases than for the 2001–2004 cohort, but nevertheless an increase in MDR with time was not observed (Supplementary Table 1). An important limitation is the variation in minimum inhibitory concentration (MIC) breakpoints used to define resistance on antimicrobial susceptibility testing between the two cohorts. For the more recent 2013 – 2017 cohort, EUCAST guidelines were used.[15] The 2001 – 2004 cohort, BSAC guidelines were used.[26] There was a trend for adopting a lower MIC threshold for intermediate antimicrobial susceptibility and resistance in the later cohort (Supplementary Table 2). This substantiates our findings that there has not been a salient increase in the proportion of MDR infections. Furthermore, although other aspects of laboratory investigation have changed between the two periods, including the introduction of automated liquid culture and pathogen identification through MALDI-TOF, these changes are not expected to impact on antimicrobial susceptibility of the pathogens identified. Sonication was used for three patients in the 2013–2017 cohort, but did not identify any additional pathogens. There was no salient change in culture-negative infection rate between the earlier and later cohorts.

History of metalwork may predict MDR infection in our cohort. This analysis was limited by possible confounding between metalwork and the cause of infection. Patients with a history of previous metalwork likely represent a heterogeneous population consisting of those who have persistence of their original metalwork-associated organism and those who have reinfection with a new micro-organism.

Antimicrobial regimens

Finally, the most appropriate empirical antibiotic therapy after surgical debridement remains the combination of an anti-pseudomonal carbapenem with a glycopeptide. This corresponds with prior results from our centre.[6] This broad-spectrum combina-

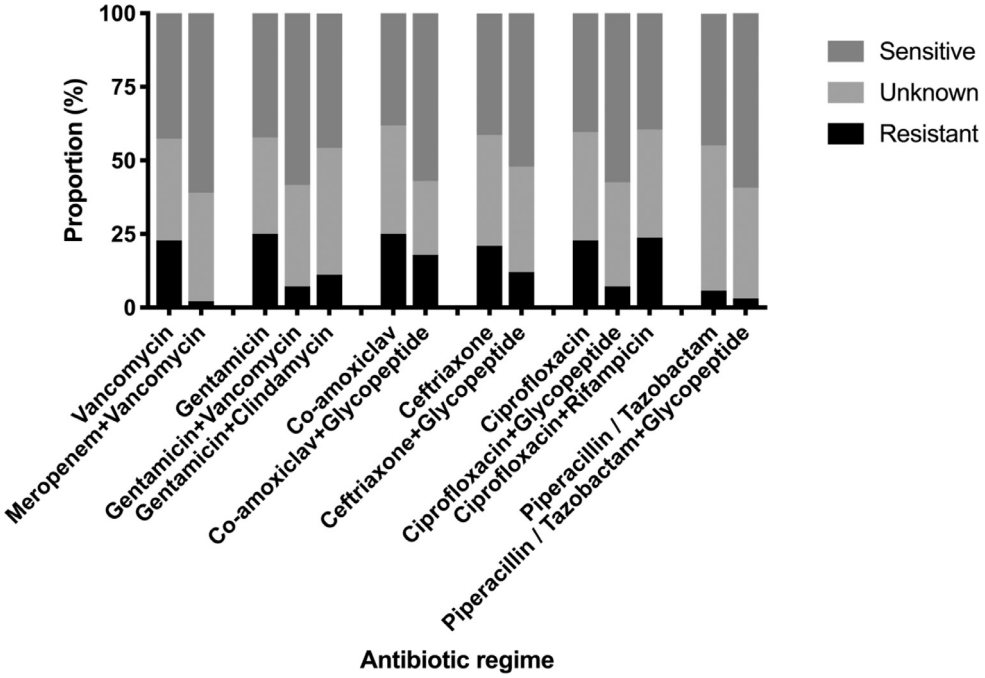


Fig. 5. Predicted Efficacy of Empiric Antimicrobial Regimens for 2013–2017 Cohort.
Proportion of patients in the 2013 – 2017 cohort that had micro-organisms or combinations of micro-organisms identified that were either sensitive, resistant, or had unknown susceptibility to common prophylactic, empiric systemic, and local antibiotic regimens used in the management of chronic osteomyelitis.

tion must be rapidly replaced by a targeted antimicrobial regimen as soon as susceptibility tests are available, or a more appropriate empiric follow-on regime in culture-negative infection, to minimise exposure to broad-spectrum antibiotics. For example, in our centre, meropenem would be discontinued 48 h post-operatively if Gram-negative pathogens have not been isolated at that stage.

The most appropriate local antibiotic combination is a glycopeptide with an anti-pseudomonal aminoglycoside. Inferences regarding local antibiotic therapy are limited by the method of susceptibility testing, which reflects likely pharmacodynamic target attainment with systemic antimicrobial use. Local antibiotic levels at the site of surgery immediately following implantation may be considerably higher, and microbial response may not be accurately predicted by these standard susceptibility tests.[27,28]

Conclusions

In our centre, we have seen a reduction in MRSA osteomyelitis to almost one third of the proportion observed ten years ago; the possible association with pre-operative decolonisation therapy, suggested by the absence of MRSA infection in patients with iatrogenic infection, merits further investigation. We did not observe an increase in MDR bacterial chronic osteomyelitis over the past ten years, despite subjecting classifiable bacterial isolates to more relevant susceptibility tests, and reducing MIC values defining resistance to most relevant antibiotics. Endogenous osteomyelitis and absence of local tissue compromise were predictors for culture-negative osteomyelitis in adults. Consequently, patients in these groups could be selected to receive additional investigations. The presence of metalwork was predictive of MDR infection. We conclude that an anti-pseudomonal carbapenem and glycopeptide remain the combination of choice for empiric post-operative antimicrobial therapy, assuming similar background rates of antimicrobial resistance.

Conflicts of interest

The authors declare no conflicts of interest with this study.

Ethics

Ethical approval was sought and granted by the local research and development committee in our hospital.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jinf.2019.07.006.

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