The future of diagnosis and treatment for Orthopaedic infections

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Bone and joint infections are deep infections, often associated with prosthetic material. This makes treatment particularly difficult due to the poor vascular supply and the formation of Biofilms on the prosthetic material by the bacteria. Long courses of antibiotics are frequently used in conjunction with surgery for prosthesis removal or debridement, antibiotics and implant retention (DAIR) for early/acute prosthetic joint infections.

Infection occurs by two main routes; direct spread and haematogenous seeding. Direct spread is most commonly related to intra-operative acquired or post-operative wound infections adjacent to the prosthetic material. Infection associated with these routes can be mono or poly-microbial compared to haematogenous seeding which can occur if the patient is bacteraemic and tends to be mono-microbial. A Staphylococcus aureus bacteraemia is associated with a 30-40% risk of infection. Haematogenous seeding accounts for 20-40% of prosthetic joint infections with the remainder being due to local spread. The prevalence of infection for elective Orthopaedic surgery is 1%.

Healthcare associated infections are a serious cause of morbidity and mortality for affected patients and they are a major source of cost to the NHS. In Orthopaedics, there is a mandatory requirement for surveillance during each financial year. With increasing worldwide development of resistance, these infections are becoming increasingly difficult to treat. We describe the Microbiology of bone...
Microbiology of bone and joint infections

Bone and joint infections become particularly problematic when prosthetic material is involved as this reduces the size of the inoculum needed to produce an infection. Adherence of bacteria to the avascular prosthetic material and the formation of biofilms by the bacteria allows them to be overlooked by the body’s defense system. Biofilms are communities of bacteria that form on prosthetic material including heart valves, pacemakers, central venous and urinary catheters.

These biofilms result in the bacteria becoming much more resistant to antibiotics, it is estimated that the MIC of an organism in a biofilm is up to 1,000 higher than the planktonic form. The organisms in biofilms are less metabolically active and grow at a slower rate. This reduces uptake of the antibiotics while at the same time down regulating the expression of antibiotic targets making the organism more resistant to treatment. They are therefore often associated with treatment failure and recurrent infection when antibiotic treatment is stopped. They may also cause a delay in the presentation of infection and surgery maybe the only way to remove them. Certain antibiotics such as Rifampicin have the ability to penetrate some biofilms.

The microbes involved in bone and joint infections are numerous. The most common being Gram positive organisms. These include Staphylococci and Streptococci. Staphylococcus aureus (S. aureus) and Coagulase negative Staphylococci (CONS) account for the majority of prosthetic joint infections (PJI’s). Staphylococcus aureus is a highly virulent pathogen which often causes acute early onset infections. Coagulase negative Staphylococci are skin commensals and are therefore much more indolent. Infections with this organism may not become apparent until weeks or months later.

Other Gram positive organisms which commonly cause infections include Streptococci and Enterococci which account for 10% of infections. Gram negative organisms such as Escherichia coli are also capable of causing infections and more commonly cause early onset infection due to their virulent nature. Propionibacterium acnes is a Gram positive bacillus that is part of the normal human flora and has low virulence. It likes to live on the skin on the upper back and shoulders and therefore has a higher association with upper limb replacements compared to lower limb replacements. It causes indolent infections similar to CONS.

Diagnosis

Culture remains the gold standard for Microbiological diagnosis. Initially, a diagnostic pre-operative arthrocentesis can be performed to enable appropriate antibiotic choice. Multiple, deep peri-prosthetic intra-operative samples (5-6) are required to enable true interpretation of the culture results. The bacterial load in these tissues is often low so sending more samples is more likely to yield a positive culture result. Receiving multiple samples brings the false positive rate down to <5% compared to 30% when a single sample is sent. Atkins et al, has shown that the isolation of identical organisms from three or more of the 5/6 specimens sent is highly predictive of infection (Sensitivity 65%, Specificity 99.6%). When five specimens are sent, the chance of all samples being negative is only 1% compared to 3% when four samples are sent. A single positive result in isolation is of no diagnostic value. Sonication of the implant
itself helps to breakdown the biofilm and increase the culture rate (Sensitivity 78.5%)\(^9\).

Each specimen should be taken with a separate set of instruments and placed into a separate sterile universal. All specimens are cultured directly and placed into an enrichment broth\(^8\). Upper limb samples routinely receive 14 days at our institution compared to 7 days for lower limb due to the dominance of Propionibacterium in this area. To ensure that there is a chance of growing the causative pathogen the patient would ideally have had no antibiotics for the two weeks preceding the operation\(^6,8\).

MALDI-TOF (Matrix assisted Laser desorption ionization time of flight) is a new diagnostic technique that uses mass spectrometry in the identification of Micro-organisms. Over 90% of isolates are identified to species level, 98% to genus level and <1% fail to identify\(^10\). It provides accurate and rapid identification of micro-organisms\(^10,11\).

For some patients, who may have received antibiotics prior to samples being taken, the causative organism may fail to grow on both the direct plates and enrichment broth. In these culture negative cases, new molecular techniques may enable us to identify the responsible organism. This is a broad range Polymerase chain reaction based test targeting the 16s rRNA of the bacterial genome\(^12\) and is not reliant on the bacteria being alive. This is an option in patients who have clinical signs and symptoms of infection but are culture negative. Its sensitivity however varies from 50-86%\(^13\). Using specific PCR’s can increase the sensitivity when used on sonicated fluid, in some cases up to 97%\(^13\). This technique does not provide information on antibiotic sensitivities\(^12\).

**Treatment considerations**

The mainstay of treatment continues to be surgical intervention in combination with antibiotics\(^5\). Extensive courses of antibiotics are required for periods of weeks to months. The need for these long courses of antibiotics creates several concerns; the most significant of these is the development of anti-microbial resistance. Exposing patients to prolonged courses of broad spectrum antibiotics selects out multi-resistant organisms. This is not restricted to the UK alone but is a worldwide concern. The Department of Health set out a UK Five year Antimicrobial Resistance strategy 2013-2018 to tackle this threat\(^14\). This highlights the importance of ensuring that appropriate samples are sent from patients at an early stage of their illness so that targeted narrow spectrum antibiotics are used. It is recommended that if patients are systemically well, treatment should be withheld until the culture results are available\(^12\). This negates the need for broad spectrum empirical antibiotics.
Of these emerging multi-drug resistant organisms, the most concerning are the carbapenemase producing enterobacteriaceae (CPE). Enterobacteriaceae constitute part of the normal flora of the human gut and can be responsible for healthcare associated infections. Over the last decade, worldwide increasing resistance has been observed in Gram negative bacteria15. Initially with the development of extended spectrum beta lactamases (ESBL’s). Treatment options for these infections are limited and Carbapenems such as Meropenem are used to combat these more resistant infections. Carbapenemases are enzymes produced by these resistant organisms that are capable of hydrolysing the Beta lactam side chain, rendering the antibiotic ineffective. Due to the increasing prevalence of these infections in countries such as Greece, Italy and India, more and more of these infections are being imported into the UK each year16. Care must be taken to identify these patients early with active surveillance, to slow the spread of these organisms and to ensure that they do not become endemic flora in our hospitals and operating theatres. Screening of high risk patients should be undertaken to help identify carriers of these organisms17, 18, 19.

**The Future of antibiotics**

Between 1940 and 1970, there was a consistent increase in the development of new antibiotics. Subsequently, only three new systemic antibiotics have been discovered14. These include quinupristin-dalfopristin, linezolid and daptomycin. Linezolid and daptomycin are from two new classes of antibiotics, the oxazolidinone and lipopeptides. These target Gram positive infections only and there are few new antibiotics targeting increasing Gram negative resistance.

Unfortunately, there is little incentive for the pharmaceutical industry to invest in the development of antibiotics as they generate little income. This is due to antibiotics being given for relatively short periods of time compared to drugs that are required daily for chronic illnesses17. We are at risk of reaching a stage where antibiotics are ineffective and simple infections such as urinary tract infections are untreatable. This highlights the importance of prudent anti-microbial prescribing to preserve our current antibiotics. The Infectious Diseases Society of America has set up the 10 x '20 initiative to develop 10 new antibiotics by the year 202020, as the rate at which bacteria are developing resistance far outweighs the development of new antimicrobials to combat this. New antibiotics that are being developed include Tedizolid and Ceftobiprole.

**Summary**

The development of antibiotic resistance will continue to be a concern in the future as bacteria continue to mutate. Prudent anti-microbial prescribing will ensure that the antibiotics that we currently have will last longer, but this is dependent upon making an early accurate diagnosis so that the need for broad spectrum empirical antibiotics is eliminated. This relies on the appropriate samples being sent to Microbiology. Antimicrobial stewardship should be a top priority for all prescribers. The need for development of new antibiotics cannot be emphasised strongly enough and there appears to be increasing worldwide recognition of this.

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**References**

References can be found online at www.boa.ac.uk/publications/JTO or by scanning the QR Code.
References

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