X-Ref *For other Roundups in this issue that cross-reference with Research see: Hip Roundup 3, 6, 7, 8; Knee Roundup 7, 8, 10; Wrist Roundup 4; Shoulder Roundup 2; Paeds Roundup 6.*

Biomarkers in periprosthetic joint infection

■ The widely-accepted current methods of diagnosing a periprosthetic joint infection (PJI) rely on laboratory tests which are usually highly sensitive but non-specific, or highly specific but not terribly sensitive. The most widely accepted tests are the systemic markers, such as serum erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) and synovial fluid white cell count with differential, which are sensitive but not specific; and direct culture which is less sensitive but more specific. While the Musculoskeletal Infection Society (MSIS) criteria are often used as the gold standard to diagnose a PJI, the diagnosis remains difficult in some cases. The biotech revolution has allowed for 'bedside' testing of a huge range of biomarkers using enzyme-linked immunoflourescent assay-type tests such as those used in pregnancy tests. The revolution has finally reached surgery and an accurate test for synovial fluid defensin is an emerging new biomarker (marketed as Synovasure), but its utility for accurately diagnosing a PJI, both alone and in combination with other tests, has not been studied. While there is some conflict of interest, investigators from **Philadelphia (USA)** sought to further investigate the reported combination of synovial fluid α-defensin and CRP tests being an impressively accurate way to diagnose (or rule out) a PJI, including in patients with systemic inflammatory disease and those on antibiotics.[1] In this prospective study of 149 synovial aspirates, 112 patients had an aseptic cause of pain and 37 patients had a confirmed PJI. The combination of synovial fluid α-defensin and CRP tests demonstrated a sensitivity of 97% and a specificity of 100% for diagnosing PJI, while the synovial α-defensin test alone demonstrated a sensitivity of 97% and a specificity of 96%. In this typically heterogeneous cohort consisting of a typical cross-section of revision hips, patients presenting with wear, instability and metallosis were all tested, including 23% of patients documented with a history of systemic inflammatory disease, 9% taking immune-modulation drugs and/or corticosteroids, and 27% in the PJI group that were on antibiotic treatment at the time of the aspiration. The combination of α-defensin and CRP appears to be a reliable test to diagnose PJI that really should be considered for all patients, including those with a history of systemic inflammatory disease or on current antibiotic treatment.

HbA1c and complications in arthroplasty X-ref

■ There is ample evidence that HbA1c is an excellent predictor of complications in many branches of surgery. While there is a large volume of literature on the topic, it does not yet appear to have reached the general orthopaedic subconscious. In an excellent paper from **Salt Lake City (USA)**, a study team set out to unpick the relative contribution of pre-operative hyperglycaemia and peri-operative HbA1c to post-operative complications.[2] Their paper includes the results of 13 272 patients, all of whom underwent arthroplasty over a ten-year period in their institution. Of these, around a third had an elevated peri-operative HbA1c. This did not appear to predispose towards eventual infection (HR 0.86), although it did impact profoundly on mortality (HR 1.3). The converse was true when looking at pre-operative hyperglycaemia, with a significant association with post-operative arthroplasty infection (HR 1.44), but this had no bearing on mortality. Perhaps the logical conclusion from this paper is that while diabetes itself does not predispose patients to infection (although it increases mortality rates), diabetic control in the peri-operative period does profoundly affect infection rates – an easy to control variable to which we should pay more attention.

Getting to the bottom of biofilms X-ref

■ Biofilms are known to be one of the major difficulties associated with treating periprosthetic infection. Usually associated with *Staphylococcus aureus* infections, a persistent biofilm protected by a glycocalyx coating is the single biggest challenge to clear surgically, and as yet there are few effective pharmacological or implant technologies to combat this. A key to understanding the pathophysiology of a biofilm is comprehension of the evolution of the process. Research into this area has been limited by the lack of a valid animal model to understand the evolution of the process. Basic scientists in **Rochester, New York (USA)** report their development of a murine tibial implant model, which they have coupled with *ex-vivo* imaging with electron microscopic technology to quantify the development of the biofilm.[3] The authors report successful development of a biofilm in C57BL/6 and Balb/c mice with a variety of strains of *Staph. aureus*. Their model was able to successfully develop a biofilm in three distinct phases. Proliferation of the *Staph. aureus* starts at day 3 and peaks by day 7. The formation of the biofilm then occurs and stabilises by day 14 with around 40% coverage. Given the similar characteristics to *in vivo* biofilms, we would expect this model to be exploited to make strides in treatment of human biofilms, which is one of the great challenges in orthopaedic infection of the next decade.

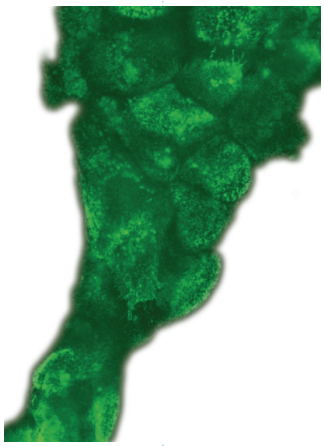
Effective antibiosis for biofilms X-ref

■ While the study of biofilms has been hampered by the lack of a validated model, perhaps the most important question is how best to treat them. Common strategies include the application of topical and systemic antibiotics. The basic science group in **Chapel Hill (USA)** designed an experiment with the aim of establishing which of a number of antibiotics strategy resulted in eradication of biofilms most effectively from inoculated implants *in vitro*.[4] The investigators conducted a series of experiments including *in vitro* inoculation of implants with biofilm-forming bacteria and then treatment with a variety of systemic and local antibiotics. The results were quite clear – effective treatment of biofilm-forming bacteria (in their series, at least) requires both systemic and local antibiotic administration.

Stem cells and avascular necrosis X-ref

■ Stem cell technology is still a technology without an application. In time we are sure this will evolve into a mature and essential tool. However it is, for the moment, in search of an application without any current evidence of clinical success. One of the issues is that a 'stem cell' is one of a variety of different progenitor cells, and this needs to be coupled to harvesting, culture, reimplantation and surgical technologies, all of which are maturing technologies with many alternatives and little evidence to support one over the other. Cellular biologists in **Rochester, Minnesota (USA)** set out to examine some of the multitude of progenitor options.[5] They present their comparative report of the more commonly-used bone marrow-derived mesenchymal stem cells (bmMSCs) and the less commonly-used adipose-derived MSCs (aMSCs) in an *ex-vivo* model of femoral necrosis. The study (like

many basic science studies) actually reports the results of a number of discrete but supporting experiments. The research set out to establish the proliferative potential (and any differences between them) of both aMSCs and bmMSCs in their model. Following this they went on to identify the difference in bone osteogenic differentiation potential and then quantify the molecular signaling pathways expressed in both cell lineages. The *ex-vivo* experiments involved adipose tissue and bone marrow tissue obtained from patients undergoing hip arthroplasty for osteonecrosis. The MSCs isolated from these tissues were then cultured and grown on osteogenic differentiation media. The reported results strongly favour the aMSC cell lineage with a fourfold proliferation advantage and a 2.25-fold differentiation advantage. The authors went on to quantify the RNA expression differences between the two cell lines which may give a clue as to signaling pathways which could be manipulated to result in bone growth. This paper offers a potentially exciting breakthrough in the management of a range of conditions including osteonecrosis of the femoral head.



Predicting LOS in total joint arthroplasty X-ref

■ One of the 'holy grails' of joint replacement is reducing hospital length of stay. The current gold standard is to use standardised care models in an attempt to streamline care, getting everything in place to send the patient (happily) home as quickly as possible. The strength of this model is the lack of variation and the standardisation of outcomes. The weakness is the same. Not all patients are the same and they will not all require the same physiotherapy support or post-operative therapy. The next step in discharge programme development must be creating appropriately tailored programmes to address patient variation and reduce outliers in length of stay. The search for a suitable 'predictor' of needing more support continues, and a study team from **Ottawa (Canada)** has ventured their own take on a potential predictive tool.[6] They investigated the potential of a number of scales including the timed-up-and-go (TUG), Iowa level of assistance scale, post-operative quality of recovery scale, readiness for hospital discharge scale, and the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) in 108 patients. They also collated some outcome measures to assess function post-discharge (Older Americans Resources and Services activities of daily living (ADL) questionnaire (OARS)). The study team used a multiple linear regression model in an attempt to predict the length of stay from the collated data in their study group. The statistical model constructed using the pre-op and day 2 TUG when combined with the WOMAC function subscale was able to account for around 20% of the variance in length of stay. Perhaps not the golden bullet we are all hoping for, but even accounting for one fifth of variation in a complex system such as length of stay is potentially useful if the results can be validated in another external group of data.

Long-term antibiotics reduce recurrence in periprosthetic infection X-ref

■ Dealing with periprosthetic infection is going to become more and more of a focus in the coming years. Although the aging population and revision burden receives much press, here at *360* we have much more concern about the longer-term consequences of infection. The rise in antibiotic resistance combined with increased incidence of diabetes and obesity is likely to make infection more difficult to treat. Throw in the increased revision burden (associated with much higher infection rates) and it seems to us that the infected arthroplasty is likely to be the signature problem of the next decade. There are many factors which influence the clinical outcome of bone and periprosthetic infection treatment, however, a strategy that has fallen somewhat out of favour due to concerns about selecting for bacterial resistance is the long-term suppression strategy. This strategy is the subject of the latest report from a group in **Cleveland (USA)**. Their retrospective study includes the records of 655 infected revision arthroplasty procedures. Within this, a subgroup of 92 patients received suppression with long-term oral antibiotics which was compared with a 1:3 matched cohort of patients who did not receive long-term oral antibiotics.[7] The headline result for this study is a significantly improved, infection-free prosthesis survival rate with a hazard ratio of 0.63 (68.5% *vs* 41.1%) in the antibiotic suppression group. The authors went on to attempt a stratified analysis and suggest that the antibiotic suppression was most effective in those patients who underwent irrigation, debridement and polyethylene exchange as a single-stage procedure (64.7% *vs* 30.4%). While this paper itself is interesting, it is important to set it in context. The infection-free survival reported here is lower than that reported in other series, and those patients selected for antibiotic suppression are not 'randomly allocated' - they could well be patients with more severe clinical infections, or indeed those with sensitive organisms, making inferences to clinical practice from a paper such as this very dangerous. Re-examination of the role of long-term suppression antibiotics is clearly indicated, but perhaps this isn't quite the evidence we are waiting for.

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 DOI: 10.1302/2048-0105.45.360402