establishing the success of the Ponseti method in terms of relapse is the variability of the threshold for diagnosis and the classification of a relapse in the reported literature. This variation makes assessment of actual long-term results and comparison between studies quite difficult. In order to assess the magnitude of the problem and to assimilate reported relapse rates, this systematic review from **London (UK)** examined relapse as a primary outcome measure of the Ponseti method.[8] Studies reporting outcomes for idiopathic clubfoot published between 2012 and 2017 were included in the initial literature search. The authors identified 84 studies reporting the outcomes of over 7000 patients and 10 000 clubfeet, and based their conclusions on review of these results. Reported relapse rates varied widely between 1.9% and 45%. Only 57% of the studies reported here included a definition or criteria for relapse, with the Pirani score the most commonly used method. In all, 45% of the papers included data on further surgical procedures with a tibialis anterior transfer rate of between 0.6% and 48.8%. More invasive techniques, such as posteromedial or posterolateral release, ranged from 1.4% to 53.3%. Clinical assessment and scoring of the corrected and relapsed foot was poorly recorded and defined, and, as the authors point out, where inconsistencies with the definition exist, it is difficult to compare outcomes between studies. The authors therefore sensibly suggest that a consensus definition of relapse is required, and hopefully this will be forthcoming. Ideally, this would be applicable as a tool or score to use at every point throughout the treatment course.

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Research

X-ref ***For other Roundups in this issue that cross-reference with Research see: Spine Roundup 2.***

Machine learning in osteosarcoma histology X-ref

Here at 360, we were delighted to see this study from **Dallas, Texas (USA)** on innovative uses of modern computer analysis for medical diagnosis.[1] The use of machine learning and artificial intelligence (AI) is growing in medicine, particularly in diagnostics, where reproducible patterns and correlations make it an ideal environment for machines to take on data analysis. In this article, the group explore the potential scope of AI in the estimation of tumour necrosis after chemotherapy in osteosarcoma. The authors digitized 40 whole slide images that represented a range of osteosarcoma cells following chemotherapy. In all, 13 machine learning tools and a single deep learning architecture were taught to divide the digitized images into viable tumour, necrotic tumour, and nontumour cells, and the best performing was analyzed using receiver operating characteristics for discrimination of necrotic from viable tissue and tumour from nontumour cells. This paper shows that machine learning tools perform very well, and that the outputs in real, whole slide images are a clinically useful tumour prediction map. This study reports the first fully automated tool to assess viable and necrotic tumour in osteosarcoma, employing advances in histopathology digitization and automated learning, and paves the way for the use of machine learning tools in other types of tumour diagnosis.

Gene therapy for osteosarcoma: is TP53 a potential candidate?

Targeted therapy is one of the promising avenues pursued by oncologists in treating orthopaedic and other tumours. Although there has been some success in the field and there are viable viral vectors, the success of treatment depends to a large extent on the suitability of the candidate gene, as well as the level of transformation. This study from **Los Angeles, California (USA)** reports on the output of a meta-analysis evaluating the clinical relevance of mutant TP53 tumour suppressor gene in patients diagnosed with osteosarcoma, as well as an *in vitro* study of the therapeutic effect of targeting mutant TP53 utilizing CRISPR-Cas9 technology and the TP53 inhibitor N5C59984.[2] The authors report on a meta-analysis of the nine studies they identified through their literature search. The review was undertaken to synthesize all the data available and to establish the relationship between mutant TP53 and the overall survival of patients with osteosarcoma. The output and analysis presented in this review demonstrated that mutations in TP53 predicted poor two-year survival in patients diagnosed with osteosarcoma, and that CRISPR-Cas9 effectively inhibited the consequent mutated protein with subsequent positive results in decreasing proliferation, migration, and tumour formation activity and increasing susceptibility to doxorubicin. The p53 activator NSC59984 showed similar effects. The team go on to show that knocking out the mutant TP53 decreased the expression of the oncogenes, antiapoptotic proteins, and survivin (an inhibitor of apoptosis protein) in osteosarcoma cells. The authors conclude from their review and collected data that targeting TP53 may improve treatment outcomes in osteosarcoma patients.

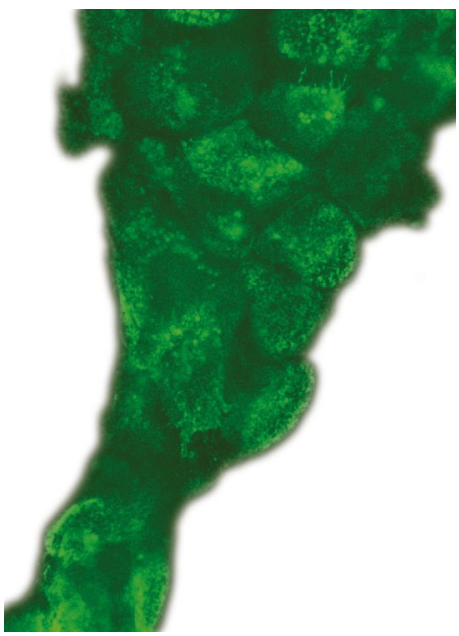
Anticoagulation and venous thromboembolism X-ref

It is now standard practice among surgeons carrying out lower limb arthroplasty to offer chemical thromboprophylaxis postoperatively. Since the recommendations made by the National Institute for Health and Care Excellence (NICE), the debate about appropriate drugs, and the duration of their use, has raged. This article from **Philadelphia, Pennsylvania (USA)** sought to test the hypothesis that low-molecular-weight

heparin (LMWH) or warfarin reduces the incidence of venous thromboembolic events in these high-risk patients.[3] With such a question, large numbers of cases need to be analyzed. In this study, 60 467 primary and revision total joint arthroplasties were isolated from a multi-institutional database. Patients in whom the method of thromboprophylaxis was unclear were excluded. A venous thromboembolism score was then calculated based on 26 individual variables and outcomes were assessed at 90 days. The authors found that thromboprophylaxis with aspirin showed a lower rate of deep vein thrombosis, as well as venous and pulmonary thromboembolism, than warfarin or LMWH. The team went one step further, using propensity scoring to show that LMWH and warfarin gave rise to increased odds of venous thromboembolism in patients who underwent total knee arthroplasty. Finally, the data supports the hypothesis that warfarin increases the likelihood of a prosthetic joint infection when compared with either LMWH or aspirin. There are, of course, some potential caveats to analyzing this kind of data in this way. While a propensity matching system does its best to allow for all potential confounders, propensity matching is only effective in circumstances where all of the confounders can be accounted for and are known. It is certainly conceivable that the majority of very high-risk patients were on warfarin as part of this study preoperatively, which would preclude effective matching for those patients. In summary, despite these limitations, this study shows that aspirin is as effective as other antithrombotics in patients at high risk of thrombus formation. This is an excellent study that provides useful evidence for thrombus prevention and bleeding control after total joint arthroplasty.

Platelet rich plasma: is leucocyte richness important?

One of the treatments that flickers in and out of orthopaedic textbooks is platelet-rich plasma (PRP) for tendinopathies. Although a few randomized controlled trials have been carried out, they have so far shown that PRP is, in most cases, no more effective than saline. There is a plethora of small and large case series that similarly demonstrate a mixed result. Detractors would argue that the overwhelming majority of data currently available suggest there is no role for PRP. Supporters would say that PRP is a biologic, and one that is generated in the operating theatre. As such, it is subject to significant variation in production and application, which would explain the apparent differences in efficacy in the various reports. To date, all of these investigations have failed to use the patellar tendon as the focus of inquiry, and the effect of different PRP formulations on the tendon have yet to be compared. In this interesting study from **Vancouver (Canada)**, a team of investigators sought to determine which of two different PRP formulations, if any, was superior to saline when used to treat patellar tendinopathy under ultrasound guidance.[4] In what is essentially only a feasibility study, the research group recruited 57 patients, each assigned randomly to one of three treatment arms with single blinding. Patients were then enrolled into a rehabilitation programme and assessed at 6, 12, 26, and 52 weeks, with the Victoria Institute for Sport Assessment (VISA-P) functional score at 12 weeks being the primary outcome. Despite the small size of this study, the authors achieved an impressive 93% retention at the primary outcome and 79% after one year. There were no significant differences in any of the outcome measures (VISA-P score, pain, or global rating of change) at any of the follow-up points. Following the completion of follow-up, analysis showed no differences in the functional scores between the three treatment arms at either the primary endpoint of 12 weeks or at one year. The authors conclude that PRP is no more effective than saline when it comes to treatment for patellar tendinopathies, but that rehabilitation should remain the mainstay of care. Here at *360*, our prejudices would lead us to agree with the authors findings, but it is important to recognize that a three-armed study of this scale does not really have the requisite power to establish if there are any real differences in effect size between the interventions.



Is DAIR slightly too daring? X-ref

In the war against prosthetic joint infection (PJI), debridement and implant retention (DAIR) represents one end of the revision spectrum, with the traditional two-stage revision sitting at the other. There is ongoing debate about how effective DAIR is, regarding its advantages in terms of implant retention, lower complication rates, and improved clinical outcomes. Everyday practice suggests that within six weeks of implantation, DAIR is an effective treatment for infection if undertaken comprehensively and by a surgeon familiar with the techniques required. However, this study from **Philadelphia, Pennsylvania (USA)** uses data from 199 patients to explore the rates of failed treatment in DAIR in patients with acute infection (which this team deems to be within three months of implantation) and haematogenous infection (more than three months, with symptoms for less than three weeks).[5] As would be expected from a paper originating at the Rothman Institute, all of the patients met the definition of infection described by the Musculoskeletal Infection Society. The authors found that the rate of failure of DAIR was 38% at one year, with the rate being 52% in those with acute haematogenous infections over acute postsurgical infection. In terms of risks for failure, the authors established that previous revision surgery and increased comorbidities (specifically chronic obstructive pulmonary disease, malignancy, and diabetes) were all associated with subsequently failed DAIR. Interestingly, elevated systolic readings, alongside intra-articular purulence and higher C-reactive protein measurements, were also all associated with failure in this group. We often perform irrigation and debridement for acute PJI, and the literature supporting this has been varied. In the past, the defining timepoint was deemed to be six weeks, but this team has shown that poor results, with regard to infection recurrence, follow if symptoms occur rapidly within three weeks. We should consider one-stage exchange arthroplasty in these patients, instead of just irrigation and debridement and polyethylene exchange due to biofilm bacteria presence.

Plasma fibrinogen better than D-dimer in diagnosis of prosthetic infection

Making a diagnosis of prosthetic joint infection (PJI) is the key step in managing the failing arthroplasty. Many markers have been identified as holding the potential to unlock a diagnosis, with high specificity and sensitivity. However, to date, no individual marker has been evidenced as the holy grail. There has been significant renewed interest in both tissue and plasma biomarkers over the past

few years, largely fuelled by the commercial availability of the bedside Synovasure test. Most existing work looking at plasma biomarkers has used inflammatory markers as a diagnostic adjunct, promulgating their role in establishing this catastrophic diagnosis. In an effort to improve the diagnostic yield of venesection, a group from **Beijing (China)** have examined elements of the clotting cascade as markers for PJI in a large multicentre study.[6] There are subtle changes to the clotting cascade in light of inflammatory conditions, so it is reasonable to suppose that inflammatory markers may be altered. Equally, the changes are subtle and, as such, it is also conceivable that any changes would be missed with a fairly straightforward serological test. Overall, the authors identified 439 hip and knee arthroplasty cases to be enrolled in the study over 2016 and 2017. Of these cases, 76 had proven PJI based on the criteria established by the International Consensus on Meeting on Periprosthetic Joint Infection. Blood samples taken from each patient were correlated with the presence of infection, and the team found that plasma fibrinogen was the most reliably associated with PJI, followed by C-reactive protein and erythrocyte sedimentation rate. D-dimer and white blood cell count were found to be the least reliable. It is worth noting that the team defined the threshold for plasma fibrinogen as 4.01 g/l, at which level good sensitivity, specificity, positive predictive value, and negative predictive value was demonstrated. Overall, this study is not the universal answer to PJI, but it does suggest that plasma fibrinogen is a useful adjunct to the traditional inflammatory markers in reaching this difficult diagnosis. A previous article demonstrated that D-dimer may be a good marker of infection diagnosis and reimplantation. However, this study demonstrates that fibrinogen may be an even better marker, given the inflammation present at the time of PJI, and this marker should be used going forward.

Leucocyte esterase and prosthetic joint infection

Antibiotic administration prior to the biopsy of suspected prosthetic joint infection (PJI) is anathema in most cases. Sadly, many patients with suspected joint infection – be it prosthetic or otherwise – present to family doctors, the emergency room, or junior surgeons first, where often the reflex is to prescribe systemic antimicrobials. Reaching a diagnosis is difficult and giving antimicrobials can challenge current diagnostic techniques, or even render them useless. A tool that is increasingly used in diagnosing PJI is the leucocyte esterase test strip. This simple diagnostic tool appears to be equally effective when compared with other more expensive, bespoke assays. In another excellent PJI paper from the group in **Philadelphia, Pennsylvania (USA)**, the authors sought to identify if the pre-emptive administration of antibiotics influences the diagnostic value of this test.[7] This report focused on the results of a cohort of 121 patients who underwent revision surgery for infected total hip or knee arthroplasty and had a leucocyte esterase test performed during the diagnostic phase of their care. The group found that C-reactive protein, erythrocyte sedimentation rate, and synovial white blood cell count were all significantly lower in those patients who received antibiotics prior to testing when compared with those who had not. In contrast, leucocyte esterase testing was found to be unaffected by antibiotic use. The results also confirmed the higher rate of negative culture in those who received antibiotics. This study demonstrates that the leucocyte esterase test remains sensitive, even when antibiotics are administered. As a result, if the synovial fluid is able to be analyzed, it would be ideal to send for alpha-defensin and leucocyte esterase in patients who have had prior antibiotic administration. While there is clearly further work to undertake in order to establish the sensitivity and specificity of these tests, here at *360*, we think this likely the future of diagnosis in this tricky condition.

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