■ ANNOTATION

Diagnosing acute bone and joint infection in children

HOW DOES IMAGING ALTER THE PROBABILITY OF INFECTION?

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Acute bone and joint infections in children are serious, and misdiagnosis can threaten limb and life. Most young children who present acutely with pain, limping, and/or loss of function have transient synovitis, which will resolve spontaneously within a few days. A minority will have a bone or joint infection. Clinicians are faced with a diagnostic challenge: children with transient synovitis can safely be sent home, but children with bone and joint infection require urgent treatment to avoid complications. Clinicians often respond to this challenge by using a series of rudimentary decision support tools, based on clinical, haematological, and biochemical parameters, to differentiate childhood osteoarticular infection from other diagnoses. However, these tools were developed without methodological expertise in diagnostic accuracy and do not consider the importance of imaging (ultrasound scan and MRI). There is wide variation in clinical practice with regard to the indications, choice, sequence, and timing of imaging. This variation is most likely due to the lack of evidence concerning the role of imaging in acute bone and joint infection in children. We describe the first steps of a large UK multicentre study, funded by the National Institute for Health Research, which seeks to integrate definitively the role of imaging into a decision support tool, developed with the assistance of individuals with expertise in the development of clinical prediction tools.

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Background

Osteomyelitis is typically haematogenous and usually affects the metaphyses of long bones. Acute haematogenous osteomyelitis presents with symptoms of less than two weeks, including pain, loss of limb function, raised temperature, and malaise. The infection frequently 'breaks out' into the adjacent joint, causing septic arthritis, although joint sepsis can also occur through a haematogenous mechanism without concomitant bone infection.[1] Osteomyelitis and septic arthritis are inextricably linked and considered together as osteoarticular infection (OAI). The burden of OAI is significant, with NHS Digital 2017/18 suggesting that approximately 1,800 children (aged 0 to 16 years) are admitted with this diagnosis to hospitals in England each year.[2]

OAI presents two key challenges: to establish the diagnosis promptly and start antibiotic treatment, and to decide whether surgical drainage of the infection is required. Untreated OAI rapidly progresses to irreversible cartilage and/or physeal damage and bone destruction, which can lead to a limb- or life-threatening situation. Early differentiation of OAI from less urgent conditions mimicking the symptoms is essential. The most common differential diagnosis is transient synovitis (i.e. irritable hip), a childhood disorder, which spontaneously resolves over several days. Other differential diagnoses include occult fracture, benign or malignant bone tumour, bone marrow disease, inflammatory arthritis, non-infective osteitis, and soft-tissue infections.

With the onset of relevant symptoms (spontaneous limb pain, limp, and loss of function), most patients present to the emergency department (ED).[3] Clinical investigation typically includes history, clinical examination, blood tests, and radiographs. Currently, clinicians have been taught to consider the child's ability to bear weight, their temperature, white blood count, CRP, and (where available) ESR, in a bid to quantify the likelihood of OAI. Several rudimentary, yet simple, risk stratification tools have been developed to help clinicians quantify the risk and inform their decision.[4–6] While helpful, the development of these tools has been simplistic in that they were based on small single-centre studies with insufficient statistical power and used dichotomized continuous variables. Importantly, they did not consider the role of imaging in the risk predictions, i.e. how the presence of positive imaging alters the pretest

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probability of infection, and how the type of imaging affects this. The clinical value of these tools is, therefore, limited.

Modern clinical practice dictates that in the face of diagnostic uncertainty related to the diagnosis of OAI, advanced imaging should be included in the investigation. Ultrasound scanning (USS) is more readily accessible and can identify organized fluid collections within joints or tissues. However, findings can be non-specific, as the presence of a fluid collection does not necessarily represent infection and neither does the absence of fluid exclude infection. Furthermore, the overall diagnostic value of USS for OAI is unknown. A recent systematic review, commissioned by the UK National Institute for Health and Care Research (NIHR), showed MRI to have a sensitivity and specificity of 95.6% and 80.7%, respectively, for diagnosing OAI in adults.[7] However, MRI often requires sedation or anaesthesia in children. Access to MRI in the acute setting for children represents a significant challenge for most hospitals treating OAI.

NIHR has previously been interested in childhood OAI, and 2016 saw the conclusion of the NIHR "Duration of intravenous antibiotic therapy for children with acute osteomyelitis or septic arthritis: the DINOSAUR" study.[8] The DINOSAUR study sought to understand the current caseload, disease spectrum, and clinical practice in the diagnosis and treatment of OAI in children. The DINOSAUR study investigated inpatient cases of children with suspected OAI: USS was undertaken in approximately one-third of children and MRI in one-fifth. The sequence and timing of these investigations varied.[3] Abnormalities were identified on 70% to 80% of USS and 75% to 90% of MRI. The design of the DINOSAUR study does not allow evaluation of the diagnostic accuracy of imaging techniques and the study reflects practice which may be outdated. Qualitative work, undertaken as part of the DINOSAUR study, demonstrated that delays in making diagnoses related to OAI affected the families' experience of healthcare,[3] and recommended that future research should "explore and evaluate strategies to improve the speed and accuracy of diagnosis among non-specialist primary and secondary care providers at the initial point of contact."

Beyond imaging, the DINOSAUR study concluded that polymerase chain reaction provided important additional information compared with culture-based microbiology methods alone. It also noted that clinicians often implemented early switching from intravenous to oral antibiotics for patients with uncomplicated OAI, though there was no formal clinical trial evidence to support this practice.

The need for further research and design of a clinical algorithm

A recent survey of the 'Paediatric Emergency Research in the UK and Ireland' (PERUKI) network indicated that, for every child admitted to hospital with suspected OAI, another five for whom OAI is a differential diagnosis were seen in the ED and discharged. Considering the NHS Digital data of 1,800 admissions per year with suspected OAI, this suggests that more than 10,000 children are investigated for suspected OAI in English EDs each year. Furthermore, after investigation, approximately 30% of children undergo surgical interventions (aspiration, biopsy) to identify or exclude OAI.[3] Many of these procedures may be avoidable, but are undertaken to prevent harm from delayed diagnosis when there is uncertainty. Understanding the sensitivity and specificity of diagnostic imaging, along with a clear decision tool that includes other diagnostic parameters, would be of value to minimize unnecessary procedures.

Prioritization studies from PERUKI, and the equivalent Australian body, have identified that decision support tools to help differentiate OAI from other diagnoses are among their top ten research priorities: "In children with atraumatic limp (suspected infection), what is the best clinical decision rule for observation/investigation/management?"[9,10] Providing clinicians with robust guidance to support their clinical practice is therefore a priority of both clinicians and patients/families.[3,10]

Future work: the PICBONE study

The NIHR has recently commissioned a study to consider the role of imaging in the diagnosis of OAI in children, called the Imaging in Paediatric Osteomyelitis (PICBONE) study (NIHR134125). This is a multicentre cohort study to understand the role of MRI and ultrasound in the diagnosis of acute OAI in children. The primary objective of the study is to calculate the sensitivity and specificity of MRI and USS in the investigation of OAI in children. This study will derive and validate a clinical algorithm, as a prediction tool for the diagnosis of OAI in children, thus determining the role of MRI and USS imaging for use in the emergency, secondary, and tertiary care settings. A parallel qualitative study will explore acceptability of the algorithm to children, parents, and health practitioners.

The study consists of two phases. First, a multicentre retrospective cohort study in 30 UK hospitals will establish the diagnostic accuracy of MRI and USS and will develop the diagnostic clinical algorithm. This will require reviewing approximately 6,000 ED records of children with suspected OAI. Second, a multicentre prospective cohort study, in the same hospitals, will validate the clinical algorithm on a sample of 1,500 ED attendees. The study will recruit children and young people (aged under 16 years) presenting acutely with the diagnosis of OAI suspected by their treating clinician. It will collect details of their medical history, clinical examination, blood tests, and conventional radiographs, along with information about imaging such as the timing of scans, the seniority of the clinician performing/interpreting the scan, the need for any sedation/anaesthesia, and the outcome.

The PICBONE qualitative study will be based on a subgroup of patients from the prospective cohort. Qualitative interviews will be conducted among children and young people, along with their parents, who have undergone clinical investigations for OAI. This is important to learn how patients experience clinical investigations and the diagnostic processes, and to identify ways to avoid delays and enhance patient experience of diagnosis. This will inform the management of children being investigated for OAI, including how best to address their information needs and how to support them during the process. Interviews will also be undertaken among clinicians, to understand the barriers encountered in the diagnostic pathway and to identify how best a decision support tool could be implemented.

While the PICBONE study is seeking to be the definitive guide to the diagnosis of OAI, we acknowledge the challenges encountered in building a tool using previously collected data. However, while a wholly prospective study would offer the most robust data, the timescales and costs are unacceptable. A prospective study on an adequate number of children with suspected infection would have taken four years to complete recruitment. The funding for such a long study would have been a multiple of the current one and probably prohibitive. The optimal way to deliver a reliable and cost-effective solution is to amass a large retrospective cohort from many centres, and then validate the output in a smaller prospective sample, again using many centres. The cohort will ensure that the results are applicable to current practice, and reflect increasing access to and heightened resolution of MRI. This will then reflect contemporaneous clinical practice, which is broadly generalizable across the UK. We have adopted a pragmatic approach, which allows clinicians to decide on the choice, timing, and sequence of the investigations with no change to their routine clinical practice. A study imposing USS and MRI investigation of all participants in a pre-defined order would have been methodologically ideal, although ethically unacceptable given the need for sedation or anaesthesia for MRI in young children.

The PICBONE study will start recruiting in the UK soon. We hope that PICBONE will provide the definitive tool to deal with the uncertainties faced by clinicians treating children with potential OAI, particularly by understanding the role of imaging in the clinical pathway and its role in informing clinicians of the likelihood of OAI.

Take home message

- This annotation describes the beginnings of a large UK multicentre study, funded by the National Institute for Health Research, which seeks to definitively integrate the role of imaging into a decision support tool.

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