

Duration of intravenous antibiotic therapy for children with acute osteomyelitis or septic arthritis: a feasibility study

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Scientific summary

IV antibiotic therapy in children with OM or SA

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Scientific summary

Background and aims

Acute bacterial osteomyelitis (OM) and septic arthritis (SA) in children cause significant morbidity and use of health-care resources. Limited data on disease spectrum and case load are available, and there is currently little international or UK consensus regarding the route or duration of antibiotic treatment for acute OM/SA in children.

This study comprised four components to assess the feasibility and inform the potential design of a randomised controlled trial (RCT) to determine the safety of early oral switch from intravenous (i.v.) to oral antibiotic therapy. We aimed:

1. to understand the current case load, disease spectrum and clinical practice in the diagnosis and treatment of OM/SA in secondary and tertiary UK care by conducting a service evaluation of OM/SA in children aged 1 month (the lower limit of the clindamycin licence) to 16 years
2. to assess whether or not a new molecular test is an appropriate tool to assess the molecular epidemiology of children's bone and joint infections by conducting a substudy at six of the service evaluation centres
3. to understand parents' and children's views and experiences of bone and joint infection, and gather their views and perceptions of both participating in a clinical trial and potential trial outcomes by conducting a qualitative study
4. to develop a core outcome set for use in a future RCT using a systematic literature review of previously used clinical trial outcomes in children's bone and joint infections, a web-based clinician survey and results of the qualitative study to inform a stakeholder consensus meeting.

Methods

Service evaluation

Clinical data from all paediatric patients presenting at 44 UK centres with presumed OM/SA were collected via an electronic web-based database for a 6-month period at each centre, with 3 months' clinical follow-up. Briefly, simple cases were defined as first presentation of OM/SA with no comorbidities. Complex cases were defined as those involving infection with a resistant or virulent organism (retrospectively allocated), infection of an implant or the presence of comorbidity.

Microbiology substudy

In six of the participating centres, children were recruited for a molecular microbiology substudy. After informed consent, routinely collected blood and tissue samples were transported to the central laboratory (Southampton Public Health England South East Regional Laboratory) for polymerase chain reaction (PCR) analysis after being processed locally. Results were compared with clinical data collected as part of the service evaluation.

Qualitative interviews with families and children

Semistructured interviews were employed to explore the views and experiences of children treated for bone and joint infections within the previous year and their parents. Topics included in the interviews covered (1) experiences of becoming ill and diagnosis, (2) understandings and perceptions about aspects of antibiotic therapy, (3) understandings and perceptions about aspects of antibiotic therapy and (4) views about participation in a hypothetical future RCT. Thematic analysis was used.

Development of a core outcome set

A systematic literature review, two rounds of Delphi clinician survey and a consensus meeting informed by the qualitative interviews with families and children were used to develop a core outcome set to use in a future RCT of shortened duration of antibiotic therapy for paediatric bone and joint infections; to identify the oral switch criteria for use in a future RCT; and to make an overall assessment of the feasibility of a future RCT.

Results

Service evaluation

Data from 356 children were recorded, of whom 313 were confirmed as having OM or SA, or both OM and SA. A total of 54% (of 313) children were male and the median age was 3.4 years [interquartile range (IQR) 1.4–9 years]. There were 218 (61.2%) simple infections and 95 (26.7%) complex infections. The most likely joints/limbs affected in simple disease were the hip (21.1%), the knee (24.8%) and the ankle (13.3%). Complex cases showed similar proportions of joints/bones affected (23.2%, 20% and 17.9%, respectively), although often with multiple rather than single joint/bone infections.

At presentation, C-reactive protein (CRP) was higher in complex disease than simple cases (simple cases: median 32 mg/l, IQR 11.8–66.7 mg/l; complex cases: median 54 mg/l, IQR 24–141 mg/l). Total white cell/neutrophil count and erythrocyte sedimentation rate were less often used to confirm SA or OM. Overall, a radiological diagnosis was obtained for 51.8% of simple cases (at a median of 1 day post presentation, IQR 0–3 days) and 52.6% of complex cases (median of 1 day post presentation, IQR 0–4 days). Diagnostic surgery was more common in SA than in OM prior to starting i.v. antibiotics [for SA, 39/107 (36.4%) simple and 15/35 (42.9%) complex cases; for OM, 21/109 (19.3%) simple and 14/56 (25%) complex cases]. A total of 144 out of 218 (66.1%) children with simple OM or SA, and 59 out of 95 (62.1%) with complex OM or SA, had at least one test from either blood culture or tissue diagnosis (bone, joint aspirate or periosteal pus).

Among 103 children with simple SA, the median total duration of antibiotic treatment (i.v. and oral) was 30 days (IQR 18–41 days), and the median duration of i.v. antibiotic treatment was 7 days (IQR 4–13 days). Among 105 children with simple OM treated with antibiotics, the median total treatment duration was 40 days (IQR 21–48 days), and the median duration of i.v. antibiotic treatment was 9 days (IQR 6–16 days). The most commonly used i.v. antibiotics were flucloxacillin and ceftriaxone. A total of 27% of simple cases and 42% of complex cases were discharged home on i.v. antibiotics. Overall, 40.4% of simple cases received a higher formulary initial dose of antibiotics, compared with 29.5% of complex cases. Only 30 (13.8%) simple cases and nine (9.5%) complex cases received the higher formulary dose of antibiotic treatment throughout. Overall, among children with simple OM and SA combined, the median length of hospital stay was 7 days (IQR 4–12 days), with 50% of children staying for ≥ 6 days but no longer than 12 days. Of 73 initially defined simple cases in whom oral switch took place very early (after < 1 week of treatment with i.v. antibiotics), 9.6% experienced a defined treatment failure, compared with 16.1% in whom switch took place between 1 and 2 weeks and 18.2% in whom switch took place after 2 weeks.

Microbiology substudy

A total of 151 samples were received from 50 patients. Of these, 113 were bone, fluid and blood culture samples that were collected from 44 patients across six geographical sites. The remaining 38 samples were from throat and wound swabs. In five (of 50) patients only throat swab samples were obtained, and in one patient only a skin swab sample was obtained.

Overall, excluding any data from skin or throat swabs, 32 out of 44 patients (72.7%) were PCR positive for one or more of the target organisms included in the reverse transcription PCR panel. In 24 of 32 simple cases (75%) and 8 of 12 complex cases (67%) in which the test was used, a pathogen was detected.

Using PCR, *Staphylococcus aureus* is the most commonly detected pathogen (16 cases). *Kingella kingae* (seven cases) and group A *Streptococcus* (four cases) were also common causes of OM/SA.

Qualitative interviews with families and children

Twenty-six families were recruited to the qualitative study and interviewed. One of the most striking issues to emerge during the course of interviews was the length of time reported to have elapsed between children first presenting with symptoms and a diagnosis being given/treatment starting. Participants understood the need for the use of i.v. antibiotics and identified the positive benefits of making them/their child better in the fastest, most effective way possible. Parents expressed enthusiasm about participation in a theoretical trial, although the concerns of those potentially unwilling or not sure reflected anxiety about reduced courses of treatment or that rigid trial protocols might put their own child at risk. Key or 'pinch' points of anxiety for parents included lead-up to diagnosis (especially in case of delays); occasions during which their child experienced distress (e.g. during insertion of cannula); fears about their child receiving a general anaesthetic; and some follow-up anxiety around potential for future impacts, or recurrence of infection.

Development of a core outcome set for use in clinical trials and potential oral switch criteria for use in a clinical trial

A systematic review identified 10 relevant papers to inform potential clinical trial outcomes. The key outcomes were combined, and summarised and discussed with study clinical co-investigators, who also had the opportunity to review the papers, and consensus was gained that all of the available outcomes had been extracted. In two rounds of Delphi process 37 general paediatricians, 38 paediatric orthopaedic specialists, 34 paediatric infection specialists, four paediatric microbiologists and 13 paediatric radiologists took part. The results of the service evaluation and the Delphi process were presented in a consensus meeting. The oral switch criteria and outcomes reported are a product of clinician and researcher choices during the Delphi and consensus meeting, informed by the qualitative findings.

Outcomes reaching consensus included rehospitalisation or recurrence of symptoms while on oral antibiotics, treatment failure/recurrence of infection, disability at follow-up, being symptom free at 1 year, limb shortening or deformity, chronic OM or chronic arthritis, amputation or fasciotomy, death, need for paediatric intensive care, and line infection.

Oral switch criteria considered important by consensus following the meeting voting were resolution of fever for ≥ 48 hours, tolerating oral input (medicines and food/drink) and pain improvement (rather than resolution). Although there was much variability in the Delphi survey and consensus meeting regarding what the CRP criteria should be, there was agreement that CRP is an important parameter in around 60% of respondents in both round 1 and round 2 of the Delphi survey, and by approximately 70% of those at the consensus meeting.

Discussion

A core outcome set for future clinical trials in paediatric bone and joint infections was established by a Delphi survey and consensus meeting. The same process established agreement on the criteria needing to be met for oral switch from i.v. therapy in any clinical trial.

A service evaluation, qualitative study and consensus meeting discussion provided information to inform the feasibility of a RCT, and of potential RCT designs.

1. A RCT of very early oral switch to i.v. antibiotics would be supported by the service evaluation data and was supported by the clinicians at the consensus meeting. However, the qualitative study suggested that parents might have considerable concerns regarding participation if asked to consent to early oral switch before what would currently be considered standard of care. In addition, the strict oral switch

criteria identified, together with low numbers of cases of simple OM and SA likely to meet switch criteria in the first week of i.v. treatment, means that such a study would not be likely to be feasible in a single country (UK) trial.

2. A RCT of reduced total therapy duration after clinician-directed oral switch (based on the criteria determined in this study) would be feasible but was not the first-choice study of the consensus meeting participants. It would be possible to explain the study to parents and children, and feasible to recruit in terms of numbers of cases and clinician willingness. It is unlikely that such a study design would make an enormous impact on the overall cost to the NHS of treating bone and joint infections in children or on the overall antibiotic burden of children in the community.
3. A RCT in simple OM and SA comparing shorter and longer courses of i.v. therapy, with no reduction in total (i.v. and oral course combined) duration of antibiotic therapy, would be feasible if children are included and randomised only if oral switch criteria are met after 7 days of i.v. therapy. Children would be excluded from the trial if they met the criteria for oral switch in the first week of i.v. therapy as the service evaluation suggests that this group are less likely to experience treatment failure than those in whom oral switch occurs later. This study design meets clinician preference and addresses parental concerns about randomising children before they meet currently used oral switch criteria. It would also provide important information on whether or not i.v. therapy can be reduced without increasing treatment failure compared with longer-course i.v. therapy, or whether or not outcomes are worse in those treated with more i.v. antibiotics as a result of treatment failures being caused by the treatment modality itself.

Regardless of RCT design, the qualitative study has demonstrated remaining gaps in the understanding of parental and family decisions to participate in clinical trials that could be explored prospectively alongside any future trial.

Conclusion

The epidemiology of paediatric OM/SA in this study was consistent with existing European data. Species-specific PCR provides important additional information compared with using culture-based microbiology methods alone. Clinicians have implemented early oral switch for selected patients with simple disease without formal clinical trial evidence of safety. However, the criteria by which decisions to make the oral switch are made are not clearly established or evidence based.

This study established a potentially feasible design for the reduction of a course of i.v. antibiotics in a group of children with simple OM or SA. Agreement was reached regarding a core outcome set for use in a future RCT and for oral switch criteria for use in a clinical trial.

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