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DINOSAUR
Duration of Intravenous antibiotic therapy for Septic Arthritis or acUte osteomyelitis in a paediatRic population.

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1. Hypothesis and aims

Currently there is little international or UK consensus regarding the route or duration of antibiotic treatment for acute osteomyelitis (OM)/septic arthritis (SA) in children. Data regarding paediatric bone and joint infections in the UK are scarce and outdated. This study will be used to:

1. determine the feasibility of performing targeted molecular tests (multiplex PCR) on routinely collected samples and throat swabs in paediatric bone and joint infections.

2. collect a 5ml blood sample from patients with bone and joint infection and store these for possible future analysis of genetic and immunological factors associated with susceptibility to serious infection in patients presenting with OM/SA.

The results of this molecular epidemiological study conducted at 5 or more sites will be linked to a national service evaluation conducted at approximately 40 sites in the UK (including all sites participating in this study)

2. Background

Osteomyelitis and Septic Arthritis in Children

Osteomyelitis (OM) is inflammation of the bone accompanied by bone destruction (1), usually due to bacterial infection. It is an acute process but if not treated effectively, the inflammation can become chronic, leading to the development of sequestrae and fistulae (2). Osteomyelitis and septic arthritis can both be divided into three types according to the source of the infection: haematogenous, secondary to contiguous infection and secondary to direct inoculation. Haematogenous OM can present acutely or as a more indolent, progressive process subacutely, with symptoms present for more than 2 weeks (3). In children osteomyelitis most often affects long bones (femur 36%, tibia 33%, humerus 10%, pelvis 2.8%) (4). Single site infection is most common, but 5-20% of children have multifocal osteomyelitis (5). Septic arthritis (SA) is acute infection of synovial joints (6, 7), usually secondary to bacteraemia. The infection affects the synovial membrane and the joint space. In younger children, the capsule of the joint often extends to the metaphysis, which when the cortex is damaged can lead to septic arthritis secondary to osteomyelitis and vice versa. The epiphyseal growth plate can also be affected, causing growth discrepancies and long term disability or permanent joint destruction if the acute infection is not treated promptly (2).

The estimated incidence for both OM and SA arthritis in Western populations is between 5 to 12 cases per 100,000 children per year (2). Half of the children with acute haematogenous osteomyelitis are under the age of 5 (2, 7). Boys are 1.2-3.7 times more likely to be affected by osteoarticular infection (OAI) than girls (2). The incidence in Southampton from 1979-1997 was between 1.4 to 10.5 cases per 100,000 per year (8) and in Newcastle from 1991 to 1999 was 7 per 100, 000 for SA and 11 per 100, 000 for OM (unpublished data). Recent unpublished national data from England shows the admission rate for osteomyelitis in children 0-18 year of age has varied between 0.048 and 0.070 per 1000 child years (M. Sharland, personal communication). Subacute OM appears to be increasing over recent

years (9), reported to be found in 5 per 100, 000 children in Norway (10). Neonatal infection can occur in preterm or term babies and is associated with a wider range of causative organisms (table 1, (11)) and potential complications. Neonatal vascular anatomy allows infection within bone to reach the growth plate or joint in 76%(12).

From the current literature, the pathogens implicated in paediatric bone and joint infections:

commonly include *Staphylococcus aureus* (MSSA) (44-80%) (7, 13, 14) and *Kingella kingae* (14- 50% (increased <36 months)) (7, 14-18);

rarely include Methicillin-resistant *S. aureus* (MRSA) (40-50% in USA, rare in UK (19, 20)), Panton-Valentine Leukocidin (PVL) MSSA (21, 22), Group A streptococci (GAS) , Group B streptococci (GBS) (neonates) (11, 23), Non-typeable *Haemophilus* spp. (incidence unknown), *Haemophilus influenzae* type b (non-immunised or immunodeficient), *Escherichia coli* (neonates) (11, 23), *Streptococcus pneumoniae* (24), Coagulase-negative *staphylococcus* (subacute);

very rarely (most in immunocompromised individuals) include *Pseudomonas aeruginosa* (usually inoculation injuries therefore > 1 year old), *Neisseria gonorrhoeae*, *Neisseria menigitidis* (neonate, adolescent), *Mycobacterium tuberculosis* (older children as OAI develops 2 years from primary infection), *Salmonella* spp. (sickle cell disease) (25), *Bartonella henselae*, *Neisseria gonorrhoreae*, *Non tuberculous mycobacteria* (associated with defects of IFNg/IL12 pathway), *Klebsiella* spp, *Bartonella henselae*, *Fusobacterium* (often multifocal), Aspergillus and *Candida albicans* (neonate, damaged bone).

The pathogens most frequently seen according to age are:

Neonate: GBS, MSSA, *Escherichia coli* and other gram negatives, Candida alibicans
< 2 years: MSSA, *Kingella kingae*, *S. pneumoniae* , *Haemophilus influenzae* type b , Non-typeable *Haemophilus* spp., *E. coli*, MSSA PVL

2-5 years MSSA, *Kingella kingae*, GAS, *S. Pneumoniae*, *Haemophilus influenzae* type b, Non-typeable *Haemophilus* spp., *Pseudomonas* spp., Coagulase-negative staphylococcus (subacute), MSSA PVL

> 5 years MSSA, MSSA PVL

Clinical features

The clinical features of OM and SA are dependent on age, site of infection and type of disease. The diagnosis and management of osteoarticular infection in children should ideally be multidisciplinary, including paediatricians and orthopaedic surgeons with radiologists and microbiologists. The diagnosis of OM or SA is made on the basis of the clinical presentation, laboratory tests, imaging and where available microbiology results.

White Blood Cell Count, CRP and ESR

The white blood cell count (WBC) is an unreliable indicator of an OAI as in many cases it remains normal throughout the infection (26). The inflammatory markers erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) are more reliable, although normal values also do not exclude osteomyelitis (27). CRP levels are most sensitive (elevated in up to 98% of cases) (6, 7) but not specific for bone or joint infection. Two studies have shown that CRP increased and also decreased faster than ESR, predicting recovery with more

sensitivity than the ESR or the white cell count (27, 28). Differences in the causative organism may also cause differences in the acute phase markers. Patients with osteomyelitis caused by PVL-expressing *Staphylococcus aureus* isolates had significantly higher mean values for ESR at admission, and higher maximum CRP, ESR and absolute neutrophil counts at presentation compared with patients whose isolates werePVL-negative (22). Other markers remain unproven. In a small study, procalcitonin has not shown benefit over CRP (29).

Imaging

Imaging is of great importance in the diagnosis of acute osteomyelitis.
Where available, *Magnetic Resonance (MR) Imaging* with enhancement show the best results regarding sensitivity and specificity of diagnosis of both OM and SA (sensitivity 97% and specificity 92% (30, 31), sensitivity 97-100% in OM) (6)) However as young children often require a general anaesthetic to undergo an MR scan, and MR imaging is not immediately available in all UK centres, MR is not widely used in the UK in the initial diagnosis.

Technetium radionuclide bone scan (^{99m}Tc) also has high sensitivity and specificity in the diagnosis of OM (32), but due to the radiation burden is now used less often except in difficult cases and is not useful in discitis. In SA, bone scan may be used to exclude underlying OM following aspiration and commencement of empirical therapy. Bone scan is especially useful where there is a suspicion of multifocal disease, but may give false negative results in infancy, and sensitivity is reduced for the first 48 hours. New nuclear medicine technologies are available in some centres to combine bone scan with low dose CT (SPECT CT) which may be useful in increasing the resolution of nuclear medical images (33).

Plain radiographs are less helpful compared with other imaging techniques as osteolytic changes or periosteal elevation occur most often 10 to 21 days after the onset of symptoms (1, 7, 34). However, once apparent, the extent of bony change provides a good correlate to the severity of the disease. Plain radiographs also provide a baseline for comparison of subsequent change. Radiographic changes are frequently seen in subacute OM, but can be confused with malignancies such as Ewings sarcoma or osteiod osteoma (12). In SA, plain radiographs are of limited use. In discitis, lateral radiographs of the spine 2-3 weeks into the illness often will reveal disc space narrowing with erosion of the vertebral end plates of the contiguous vertebrae. In vertebral OM, radiographs initially show localised rarefaction of a single vertebral body then anterior bone destruction.

Ultrasound is useful in SA for identifying the presence of deep effusions and in OM for subperiosteal collections, but cannot differentiate between purulent and non-purulent material (6, 35).Ultrasound may also be used to distinguish infection from other causes of similar symptoms or to direct fine needle aspiration (36).

Computed tomography (CT) is most valuable for guided procedures, such as aspiration or drainage of the infected bone or joint (37). It effectively demonstrates air and sequestra and cortical destruction in chronic OM (35), but gives non-specific results in discitis.

Microbiological investigation

Identification of the pathogenic organism by culture should be attempted with samples preferably taken prior to starting antibiotic therapy, as where positive it allows targeted antibiotic therapy. Blood cultures, joint fluid (from aspiration), periosteal pus or bone biopsy can all be used. Samples from the infected bone or joint require an invasive procedure but are more likely to be positive (40- 50% positive) than blood cultures (9-22% positive) (14, 26). Yield is generally not high for identification of bacteria in children with OM (26), as unless therapeutic operative intervention is required, bone biopsy is infrequently necessary for diagnostic reasons alone.

New molecular techniques including PCR and broad-range 16s rDNA PCR (38, 39) have established the basis for more rapid and sensitive microbiological diagnosis (17), although these methods currently do not provide information on specific organism antibiotic resistance profiles.

Blood cultures (minimum 4 ml aerobic culture sample in older children, 2 ml in specific neonatal aerobic bottle (40)) should therefore be taken, and where available samples from infected bone orjoint placed in a sterile universal container and sent for culture and sensitivity testing. Older reports suggesting an increase in *K. kingae* recovery is gained from inoculating synovial fluid or bony exudates directly into blood-culture bottles have not been replicated in UK practice (16). *K. kingae* is detectable using new PCR techniques from cultures where conventional direct plating of specimens on solid media has been used (17, 18).

Surgical management

There is little current high quality evidence on which to base current surgical practice.

Osteomyelitis

Surgical drainage in acute OM is indicated if the patient is not responding to antibiotics after 48-72hours (although this may be due to resistance) or if there is radiological evidence of a substantial pus collection (6). Best practice is to immobilise any surgically treated limb or focus of infection.

Occasionally, where a soft tissue or sub-periosteal collection is clearly demonstrated by ultrasound or MRI, needle aspiration can be performed prior to starting intravenous antibiotics. The procedure should be carried out under sterile conditions. If there is bony destruction or pus aspirated, surgical debridement is usually required. With only early radiographic signs, intravenous antibiotic therapy may suffice.

Historically, the role of surgery is poorly defined. Cole (41) identified three groups of patients: in the group of patients older than one year but who presented within 48 hours, antibiotic therapy alone was sufficient. In a group aged more than one year, five days after the onset of illness, patients usually required surgery and possibly multiple procedures. In infants less than one year in whom the exact diagnosis was difficult to make, a single operation and antibiotic therapy usually sufficed.

In current practice, the relative roles of bacterial virulence and host age and immunity are unclear. More invasive surgery appears more common when bacteria have specific virulence genes, for example PVL (21). While most children recover rapidly with simple medical management, a small proportion require repeated debridement.

Septic Arthritis

In SA, prompt drainage and washout of the affected joint (either arthroscopic or open) is advocated by some for both diagnostic and therapeutic purposes as the articular cartilage is damaged early (6). The role of surgery in the treatment of septic arthritis is in fact poorly defined except in relation to the hip, where prompt surgical drainage is absolutely necessary. Open capsulotomy to allow continuing drainage of septic material is advocated, and if the arthrotomy does not provide turbid material drilling the femoral neck may decompress a proximal femoral osteomyelitis. The anterior approach is preferred as this also allows open reduction of any displacement of the femoral head.

The indications for surgical drainage of septic joints other than the hip remain controversial. Where there is a large effusion, drainage is usually advocated although in some joints arthroscopic irrigation may be appropriate, such as the knee or ankle. However, with arthroscopic treatment joint visualisation is less complete. Overall, for joints other than the hip, aspiration, irrigation and IV antibiotic therapy is the preferred first line of treatment. If the patient fails to respond then the joint should be surgically drained, usually by formal open arthrotomy rather than arthroscopic drainage.

Medical Management and Antibiotics

Current evidence for how to initiate treatment:

Intravenous antibiotics are started empirically as soon as the clinical diagnosis of acute OM or SA is made, as delaying therapy until the bacterium is identified increases the risk of complications. In septic arthritis, where urgent surgery is indicated, a widespread pragmatic approach has been to start antibiotics following surgery unless it will take longer than 4 hours to get to theatre. As soon as organisms are isolated, antimicrobial treatment should be adjusted and optimised. In subacute OM with no systemic reaction, oral antibiotics can be used from the start.

Although there has not been a definitive randomised controlled trial, a number of observational and retrospective studies in the literature show several different antibiotic regimes have been effective in treating acute haematogenous osteomyelitis in children, including the use of beta-lactam and macrolide antibiotics (8). The initial antibiotics should always include potent cover against MSSA and GAS, and in younger children against *Kingella kingae*, although the choice will vary according to the age of the child, route of infection and local resistance patterns (7). Activity against *H. influenzae* type b is essential in children who have not been fully immunised against it.

Switch to oral antibiotics and total duration of treatment:

Currently there is no international and little UK consensus regarding the route or duration for antibiotic treatment of acute OAI in children.

a) Oral switch

Sequential intravenous and oral therapy has become usual as it is less inconvenient and painful for the patient, has fewer complications and is cheaper (2, 6, 7). There is no current evidence to aid the clinical decision of when to switch from intravenous to oral therapy, which is widely accepted and usually occurs when the patient has shown a marked clinical improvement (8). A Canadian systematic review of short (≤7 days) versus long course (>7 days) parenteral antibiotic treatment for acute haematogenous OM in children due primarily to *Staphylococcus aureus* showed no difference in the overall cure rate after 6 months

between short course and long course parenteral antibiotic therapy (42). A recent retrospective cohort study of 1969 children in the USA found that early switch to oral therapy (median 4 days) was as effective as prolonged intravenous treatment 43), a finding also suggested in a smaller retrospective study of 186 children with septic arthritis (44). The laboratory or clinical parameters that would determine the decision to switch to oral therapy remain undefined. Most clinicians continue intravenous antibiotics until the child shows clinical improvement, is afebrile and oral fluids and medication could be established.

Additionally, observing a decrease in inflammatory markers such as white blood count (WBC), C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) is thought to be of value (2). Studies have shown that serum CRP level decreased more rapidly than ESR in children recovering from acute osteomyelitis, and that children with a raised CRP level were more likely to have symptoms or extensive radiographic abnormalities(27, 45, 46). A recent Finnish clinical trial showed apparently good long term results and apparently no failure rates using CRP as the biological marker of infection (45, 47).Failure to improve necessitates repeat blood culture, additional imaging for metastatic infection, assessment for deep vein thrombosis, and consideration of unusual pathogens such as PVL *Staphylococcus aureus* or *Fusobacterium.*

No UK consensus currently exists to guide the criteria for oral switch for use in clinical practice or a clinical trial, which will be determined as part of this feasibility study. Currently there is no consensus about the route or duration for antibiotic treatment of acute osteomyelitis in children.

b) Total duration of antibiotic therapy

The suggested duration for parenteral antibiotic treatment ranges from 3 days up to 6 weeks, resulting from several, mainly observational studies with relatively poor level of evidence (8, 48). In the past, the overall duration of antibiotic treatment has been considered an important factor to improve outcome and reduce relapse. Several paediatric textbooks recommend at least 4 to 6 weeks of treatment (2, 49).

Although there are encouraging data from a recent clinical trial in Finland (45, 47) and from other review papers and case series, no recent formal randomized controlled trial has been conducted to show good evidence for shorter courses of parenteral antibiotic treatment. There are a number of reasons why the recent Finnish data may not be directly applicable to practice in the United Kingdom or other countries in 2011 (50). Some historical observational studies showed an association between short duration of antibiotic therapy and 15-19% poor outcome or relapse with courses of 3 weeks or less (51-53).

c) Oral antibiotic choice and dose

Many different regimens are used as oral therapy following switch from oral antibiotics, including co-amoxiclav, flucloxacillin and clindamycin. Although flucloxacillin and clindamycin have good oral bioavailability and excellent tissue penetration, both drugs have to be given orally 4 times per day and both have poor taste and therefore poor drug adherence of the suspension in small children (54). Although clindamycin rarely leads to *Clostridium difficile* disease in children, there is no current evidence or consensus regarding oral antibiotic choice that will be acceptable to children and parents both in terms of palatability and dose frequency.

d) Continuation of intravenous antibiotics for more than 2 weeks

Complex disease requiring continuing intravenous therapy poses problems of vascular access, hospitalisation and schooling. Most children will require central or peripherally-inserted central venous long line (CVL/PIC) insertion for long term antibiotic treatment. Delivery of subsequent care is either in hospital, or at home dependent on local services and the ability to provide outpatient parenteral antibiotic therapy (OPAT), although OPAT services for children are not yet well developed in the UK. Central venous lines (CVL) or peripherally-inserted central catheters (PICC) and OPAT has attendant risks, with 3-11% CVL associated infection noted in the USA (55, 56).

e) Additional or 2nd line antibiotics for complex disease or where resistant pathogens are identified

Where cases are complex, additional antibiotics may be advised by local microbiologists, clinical infectious diseases specialists or national guidelines, for example PVL positive *S. aureus* infection (57). Organisms that cause complicated disease may be more readily identifiable using molecular techniques, which may allow antibiotic therapy to be adapted accordingly.

Complications

Deep venous thrombosis and thromboembolism have been seen in up to 30% of children with OM and is associated with a higher risk of disseminated infection (58). In addition, joint stiffness, limb shortening, dislocation (acutely neonates) and avascular necrosis of affected epiphysis may occur. Routine follow-up allows most children with simple disease to be discharged without the need for long-term care or further assessment of growth or function. In the context of clinical audit or clinical trials, outcome measures may include length of stay in hospital, total length of therapy, operative procedures required as well as formal assessment of growth and function.

3. Aims and objectives

We aim to understand the current UK molecular epidemiology of UK paediatric bone and joint infections using a novel targeted multiplex polymerase chain reaction (PCR) test. Currently the principal method for ascertaining what organism is causing the bone and joint infection is by conventional culture and microscopy. Although the literature (of selected cases in many reports) suggests 9-60% microbiological diagnosis where culture of blood and tissue combined (most *Staphylococcus aureus),* UK microbiology laboratories report microbiological identification in far fewer OM/SA cases, for example Southampton HPA laboratory between 2003-06 defined pathogen in only 8% of approximately 1200 “fluid” or “tissue” specimens from bone or joint sent for microscopy and culture (adult and children’s services). New molecular microbiological methods have been used to increase the bacterial diagnostic yield in paediatric bone and joint infections. One such multiplex PCR assay has been validated at the South-East Health Protection Agency Regional Laboratory and will be used to further establish range of organisms causing paediatric OM/SA in the UK.

Certain organisms, in particular *Kingella kingae* are difficult to grow from samples. This means that the true spectrum of organisms causing bone and joint infections in the UK is not known, and that treatment is usually empirical. The PCR study will also give an indication of the incidence of PVL *S. aureus* incidence in the paediatric population, which causes

complicated disease. PCR is more sensitive than conventional culture and microscopy, although it does not allow testing for antibiotic resistance. We aim to show that this technique is sensitive and cost effective and would allow antibiotic therapy to be focused to specific organisms effectively if it were routinely available.

We also aim to understand the pathophysiology of *Kingella kingae* by using PCR to test throat swabs (taken from patients who have provided consent) for *K. kingae.* It is likely that children who have *K. kingae* bone and joint infections have pharyngeal colonisation with this organism. Testing throat swabs taken from these children using PCR will determine whether this is truly the case.

This study will inform the future design of a possible randomised controlled trial (RCT) investigating short vs long courses of antibiotic therapy for paediatric bone and joint infections, of the range of organisms causing OM and SA in paediatric populations. The results will be used to achieve consensus regarding the antimicrobial agents to be used in different ages within the RCT. Although the literature quotes a high proportion of *S. aureus* causing OM and SA, as described in our response to reviewers these case series and trials are for the most part highly selected and do not represent the UK case population in 2012. In particular, the incidence of *K. kingae* and other non-staphylococcal cases of OM and SA, and in which age groups these occur, will be of fundamental importance to the future trial design in terms of antimicrobial choice and length of therapy. The PCR study will also give an indication of the incidence of PVL *S. aureus* incidence in the paediatric population, as if found in a high proportion of cases of detected *S. aureus* OM or SA this will impact significantly on the potential feasibility of a future trial.

In addition we will collect and store a 5ml blood sample from all patients who provide consent with a view to testing in future for genetic and immunological factors that may affect susceptibility to bone and joint or other serious infections. This will be done in conjunction with a separate study requiring additional funding.

4. Study design

The range of organisms causing paediatric OM/SA will be established in 5 or more tertiary centres linked to a database from a concurrent national service evaluation being conducted at approximately 40 centres including those participating in this microbiology study. .

The participating centres will collect and store small aliquots of “routine” microbiological culture samples (bone, tissue, fluid, blood). We will seek consent from parents, and where appropriate patients to do PCR analysis on these samples. These are routinely collected clinical samples, with no additional sample collection and we will compare PCR results with culture results on the same sample. Results will not be available to clinicians in real time and will not affect clinical management.

We will also seek consent to take a throat swab, and an additional 5ml blood sample at a time when blood is being taken routinely for clinical reasons. The throat swab will be tested using PCR to determine what organisms are colonising the pharynx and whether these are implicated in the bone or joint infection. This is principally intended to answer the question whether children subsequently found to have *Kingella Kingae* OM/SA also have detectable

Kingella Kingae in the nasopharynx, which has recently been published in a study in the United States (*Ceroni et al, Detection of Kingella kingae Osteoarticular Infections in Children by Oropharyngeal Swab PCR. Pediatrics Volume 131, Number 1, Jan 2013 p e230*).

The blood sample will be stored and we aim to test these for genetic and immunological factors associated with serious infection in childhood in conjunction with another European study.

Samples will be linked anonymised (linked to study number but no identifiable patient data attached), batched and sent to the SE Regional HPA laboratory for processing. The results will be made available to the treating consultants when available for information to be placed in the medical records.

As part of a national service evaluation, we will also record demographic details and details of hospitalisation(s) including transfers between hospitals; type and site of disease; routine haematology, biochemistry and microbiology; radiological procedures; surgical procedures; length of IV therapy; antimicrobials used, route and duration; reason/criteria; used for oral switch (if any); and clinical outcomes at 3 months

Participant selection

All patients presenting to participating centres with bone and joint infection will be approached. The following eligibility criteria will be applied:

Inclusion criteria

1. Children between the ages of 1 month and 16 years with a clinical diagnosis of osteomyelitis or septic arthritis.

2. Written informed consent of participant or parent/legal guardian, and assent where appropriate for

a) PCR to be done on routine samples taken for culture and microscopy;
b) Throat swab to be taken for PCR and culture and microscopy
c) additional 5ml blood sample to be taken and stored for future tests.

Exclusion criteria

Patients for whom informed consent is not obtained (parents/patients may decline consent for certain procedures, e.g. additional blood aliquot but still give consent for others e.g. PCR on routine samples).

Participant identification and recruitment

Posters displayed on admitting wards will notify parents and patients that the centre is participating in a service evaluation of children's bone and joint infections. A different version of the poster will be used for centres that are participating in this microbiological study.

Parents and patients will be approached by a member of the local research or treating team, and will be given information leaflets detailing PCR on routine samples, PCR on throat swab samples and storage of 5ml blood sample for future testing relating to patient susceptibility to bone and joint infections. Once they have had time to consider the study and to discuss it with a member of the local team they will be asked to provide consent.

Withdrawal of participants

Parents can ask for their child's data and samples to be removed from the study at any time without giving a reason. A withdrawal notification will be completed and submitted to the CTU who will remove all relevant records and liaise with HPA to request destruction of samples.

Confirmation of completion of the request will be returned to the centre. If withdrawn from the study, parents/children will have the option of samples remaining in the study for analysis without clinical information (providing data on different microbiology tests alone) or whether all samples are to be destroyed.

Study sponsorship

The sponsor will be University Hospital Southampton NHS Foundation Trust

Data Capture and Confidentiality

Demographic and clinical data will be collected by appropriately trained delegated staff within participating centres and entered into a secure database via a web based system, as part of a national bone and joint infection database involving around 40 participating centres.

Records will be assigned a unique study number and centres will maintain a separate log locally for patient tracking purposes. No data that is identifiable outside of the research team will be kept and the database will be password protected. PCR and throat swab results will be linked to the database.

Electronic Records

Managed as part of a national service evaluation, the data will be stored and managed by the MCRN Clinical Trials Unit, a division of the UKCRC fully registered Clinical Trials Research Centre based at the University of Liverpool.

Data will be collected using a custom web based data entry system written in c# .Net, using JQuery. These data collection pages will be designed and implemented in the same way as the data collection that was used for the NASH (National Audit of Seizure Management in Hospitals) study - http://www.nashstudy.org.uk/. The NASH study collected data from 130 hospitals, with each hospital entering data for between 20 and 30 participants. The data collection system will allow data to be validated on input, provide help/additional information as required for questions and allow for the hiding of questions that do not need to be answered by the clinician.

Sample collection and tracking

a) Samples of blood culture bottles for PCR analysis will be collected according to set study Standard Operating Procedures in the microbiology departments of sites participating in the

molecular analysis. Samples will be given study specific numbers and stored according to NHS microbiology protocols prior to transfer to the Southampton site for analysis.

b) Throat swabs taken as study specific samples will be labelled with study and site identifiers and sent directly to the Southampton site for storage and analysis according to study Standard Operating Procedures.

c) 5ml blood sample taken for storage will be labelled with study and site identifiers and stored according to study Standard Operating procedures.

Data analysis

Descriptive statistical techniques will be used to analyse the data.

7. Research governance, monitoring and Ethics and R&D approval

The research will comply with the Research Governance Framework and International Conference on Harmonisation Good Clinical Practice (ICH GCP).

The study will be sponsored by University Hospital Southampton NHS Foundation Trust, subject to the relevant governance approvals. The Sponsor will delegate appropriate responsibilities to the Chief Investigator, and to the NIHR Medicines for Children Clinical Trials Unit (study co-applicants) who will co-ordinate the study.

There are several ethical considerations with this study. It requires trained researchers not directly involved with the patients' medical care to have access to confidential information. There is no direct benefit to the individual patients of having PCR done on routine samples or throat swab as any significant findings, such as organisms identified by PCR would not be received in time to alter management in most cases. Relevant clinical information will be given to the treating medical team.

8. Finance

This study is supported by the NIHR HTA project 10/146/01 - Duration of intravenous antibiotic therapy for children with acute osteomyelitis or septic arthritis: a feasibility study

9. Reporting and Dissemination

We will use the normal channels of journal publication and conference presentations. In addition, we are committed to ensuring that our research is available via open access and we will have a dissemination strategy that includes rapid web-based publishing of lay summaries once research articles have undergone peer-review and links to University and Trust press offices.

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