Indian Academy of Pediatrics Consensus Statement on Diagnosis and Management of Bone and Joint Infections in Children

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ABSTRACT

Justification: Osteoarticular infections are fairly common in children but often these are associated with underdiagnosis, delayed diagnosis and improper management. This leads to an increased incidence of complications and poor outcomes. Given the paucity of standard protocols for the management of these children in the Indian context, Indian Academy of Pediatrics (IAP) has taken the initiative to formulate guidelines for the early diagnosis and rational management of bone and joint infections (BJIs).

Objectives: To critically evaluate the current evidence and formulate consensus guidelines for the diagnosis and management of BJIs in children.

Process: A committee comprising of eminent national faculty from different parts of the country who are experts in the field of Pediatric Infectious Diseases, Pediatric Orthopedics and Musculoskeletal Radiology was constituted and duly approved by the IAP. On Jan 16, 2021, a virtual meeting was held and a detailed discussions were carried out regarding the need to formulate these guidelines. Subsequently, the expert group defined the key questions in the first stage followed by collection and review of scientific evidences including available national and international recommendations or guidelines. This was followed by detailed deliberation among group members and presentation of their recommendations. The same were finalized in an online meeting on Aug 01, 2021, and a consensus statement was developed and adopted by the group.

Statement: BJIs are medical emergencies that need early diagnosis and appropriate therapy to prevent long term sequelae like limb deformities. Bacterial infections like *Staphylococcus aureus* is the most common etiological agent. Nonspecific and subtle clinical manifestations make the diagnosis of pediatric BJIs more challenging. Diagnosis of BJIs is primarily clinical, supplemented by laboratory and radiological investigations. The choice of antibiotic(s), mode of administration and duration of therapy requires individualization depending upon the severity of infection, causative organism, regional sensitivity patterns, time elapsed between onset of symptoms and the child's presentation, age, risk factors and the clinical and laboratory response to treatment. There is paucity of appropriate guidelines regarding the diagnosis and management of BJIs in children in Indian context. Hence, the need for this expert consensus guidelines in Indian settings.

Keywords: *Empirical antibiotics, Osteomyelitis, Septic arthritis, Staphylococcus aureus*

BACKGROUND

Acute osteomyelitis in children is almost always a result of hematogenous (bacteremia) infection. As per available data, *Staphylococcus aureus* is the most common organism responsible for osteomyelitis which is seen in more than 50% of all culture-positive cases. Gram negative organisms are more frequent in infants compared to adults and older children [1,2]. Although data is lacking to prove *Kingella kingae* as causative agent of BJIs in children in India, 30-50% of musculoskeletal infections in children below 5 years in Europe, are due to this bacterium; isolated joint infections 65%, osteoarticular infection 30%, isolated bone infections 12% and spine

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infections 4% [3]. The prevalence of methicillin resistance in *Staphylococcus aureus* (MRSA) varies from 10-40% in different studies [4]. The incidence of *Streptococcus pneumoniae*, and *Hemophilus influenzae* type b (Hib) infections has declined with increasing immunization [5]. Multidrug resistant (MDR) and extensively drug resistant (XDR) gram negative bacilli and candida are important pathogens in neonates and critically ill children, especially those with indwelling vascular lines [6]. *Pseudomonas aeruginosa* and non-tuberculous mycobacterium are unique pathogens following penetrating injuries [6]. In patients with implants, coagulase negative Staphylococci, gram negative pathogens and fungi are encountered. Brucellosis and tuberculosis are important causes of BJIs in India, especially in cases with insidious onset. Gonorrhea is seen in sexually active adolescents [7].

NEED FOR GUIDELINES

There is a paucity of scientific guidelines for the management of BJIs in children in India. These are intended for use by pediatricians as well as orthopedicians who take care of children with BJIs.

OBJECTIVES

1. To critically evaluate the current evidence and formulate a consensus statement on the diagnosis and management of BJIs in children in India.
2. To provide consensus-based practice recommendations developed in a systematic manner with clinical applicability.

TARGET AUDIENCE

These guidelines are intended for use by primary care pediatricians and orthopedic surgeons in India who manage children with BJIs.

PROCESS FOR GUIDELINE FORMULATION

A group of experts comprising of pediatric infectious diseases specialists, pediatric orthopedicians and musculoskeletal radiologists were selected by the Indian Academy of Pediatrics (IAP) based on their experience and expertise in the respective fields. The experts are from different regions of India and comply with the policy of conflict of interest by IAP. On the Jan 16, 2021, a virtual meeting was held and detailed discussions were carried out regarding the requirements of the guidelines. Defining key questions was the first stage; it involved collecting evidence and data and conducting evaluations. The recommendations in these guidelines were developed after a review of the available literature from European Society of Pediatric Infectious Diseases (ESPID) guidelines and guidelines of the Infectional Diseases Society of America (IDSA). Special attention was given to publications made from the Indian subcontinent so as to make these recommendations applicable to local needs and clinical circumstances. All relevant papers and statements were discussed by all the expert group until a consensus was arrived at. The panel of experts based the final recommendations on the best available Indian data, global evidence, as well as the socioeconomics of healthcare. After reviewing the available scientific evidence, the committee formulated a few key questions. This was followed by detailed deliberation among group members and presentation of their recommendations. This was finalized in the meeting on Aug 02, 2021. The following Consensus Statement was adopted.

CONSENSUS STATEMENT

1. CLINICAL PRESENTATIONS THAT WARRANT EVALUATION FOR BJIs:

The following clinical scenarios mandate evaluation for BJI

- A child who presents with refusal to use a limb OR restricted range of movements OR limping with / without fever
- Child has discomfort when touching or moving the joint e.g. while changing diaper
- Neonates with pseudoparalysis characterized by limited or absent limb movement without neurological involvement or excessive crying while using a limb
- Neonates with fever without a focus and irritability should have a high index of suspicion for BJIs apart from a CNS infection
- Any child with proven *Staphylococcus aureus* bacteremia
- Patients with trauma where loss of movements cannot be attributed to trauma alone
- A child with history suggestive of bleeding disorder with joint swelling associated with persistent pain with fever
- Patients with risk factors such as immuno-compromized child, known case of inflammatory joint disorder, post procedures like intraarticular injection, or arthroscopy, or prosthetic joints

Joints and long bones of the lower extremities such as tibia and femur are more frequently involved, although any bone in the body may be affected [8,9].

2. INITIAL INVESTIGATIONS FOR A CHILD WITH SUSPECTED BJIs

Recommendations

- We recommend sending a complete blood count including a differential white blood count, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), serum creatinine and blood culture (at least two sets to increase the yield) in all patients with suspected BJI as a part of first line investigations [10].
- Routine assessment of procalcitonin is not recommended

Rationale

Though the diagnosis of acute osteomyelitis/ septic arthritis is usually made based on clinical findings, every effort should be made to obtain a microbiological diagnosis in order to optimize treatment. CRP is a good marker for the diagnosis and prognosis of the disease. Although ESR takes a longer time to rise and has reduced significance for this condition, the combination of both these tests (CRP and ESR) results in better sensitivity. A set of blood cultures with appropriate volume (which is 1% of circulating blood volume) should always be sent before initiating antibiotics. Blood cultures are positive in about one out of three cases [11]. Serum creatinine should be determined especially for a child who will be prescribed vancomycin or a child who needs contrast CT/ MRI [9]. There is no evidence to support the routine estimation of procalcitonin in children with BJIs [3,4].

3. EVALUATION OF BONE/ JOINT FLUID IN BJIs

Recommendations

- Joint fluid evaluation is mandatory in all patients with suspected septic arthritis
- Bone /tissue/ pus evaluation whenever possible in acute osteomyelitis prior to starting antibiotics
- Non-response/ worsening while on adequate treatment
- Neonates and critically ill children with suspected BJIs

Rationale

Synovial fluid evaluation is necessary for establishing the diagnosis of septic arthritis and for differentiation from transient synovitis and rheumatologic causes. The specimen should be sent for cell count, gram stain, aerobic culture. Inoculation of synovial fluid samples additionally into blood culture bottles instead of agar has been demonstrated in multiple studies to increase the yield [12]. If tubercular infection is suspected, then the specimen should also be sent for acid fast bacilli (AFB) stain, cartridge based nucleic acid amplification test (CBNAAT) and mycobacterial culture. In case of clinically stable patient when the diagnosis cannot be established by initial investigations, synovial aspiration/ biopsy should be attempted. In case of sick patient or rapidly progressive infection, antibiotics can be started followed by obtaining a synovial specimen as soon as possible [11].

Gram staining of bone, tissue or pus and aerobic cultures are recommended in acute osteomyelitis whenever possible since the yield is higher than blood cultures [13-16]. In neonates and immunocompromized patients, bone/pus cultures are mandatory since the etiology is diverse and often multidrug resistant. Histopathology can be helpful if tubercular osteomyelitis is suspected; mycobacterial cultures and CBNAAT of the specimen are recommended in such cases [17-23]. In 87.5% of children diagnosed with septic arthritis, PCR successfully identified the presence of a pathogen. Additionally, a lower rate of joint fluid culture positivity was observed in cases where antibiotic pretreatment occurred [24]. The yield of molecular tests is higher than cultures and these may be requested if validated and approved tests are available (e.g., Biomerieux bone and joint panel) [16].

4. RADIOLOGIC APPROACH

Recommendations

- We recommend an initial plain radiograph of the involved site as a screening test.
- Ultrasonography (USG) has a high sensitivity for the diagnosis of septic arthritis [6]. Ultrasound may be performed if there is soft tissue edema or suspicion of septic arthritis.
- Imaging finding can be normal within first 24 hour of the illness. Hence, it is recommended to repeat USG or MRI in case of a high suspicion of underlying BJI [25].
- Magnetic resonance imaging (MRI) is the most reliable imaging modality for the diagnosis of BJI. MRI can be used as a confirmatory investigation for early diagnosis of osteomyelitis in cases with high clinical suspicion and also to grade the extent of disease involvement in confirmed cases [6].

Rationale

4a. Plain radiographs

Plain radiography is considered as an important baseline test in all patients for comparison of disease progression/ treatment response and also to rule out other underlying conditions.

- Acute osteomyelitis: *X*-rays are frequently normal at baseline (< 2 weeks of symptom onset). Delayed

imaging may show appearance of osteolytic changes or periosteal elevation, mostly 10-21 days after onset of symptoms [6].

- Subacute osteomyelitis: *X*-ray changes can frequently be confused with malignancy; hence, MRI or histopathological correlation will be required for a definitive diagnosis.
- Septic arthritis: Limited usefulness of plain radiographs; soft tissue swelling may be seen along with blurring of fat planes, increased joint space with effusion and even joint dislocation.

4b. Ultrasonography

USG is most commonly indicated for septic arthritis because it has a high sensitivity for the diagnosis of joint effusion, although with a lower specificity. It should be performed in all suspected cases of septic arthritis, unless easily diagnosed by physical examination. It provides guidance for diagnostic or therapeutic aspiration and/or drainage. Doppler USG may provide early detection of a high vascular flow in the infected bone [26].

4c. Magnetic Resonance Imaging (MRI)

MRI is the gold standard imaging modality for acute osteomyelitis, because it can detect signs of osteomyelitis as early as within 3-5 days of disease onset. MRI provides greater details of the bone and soft tissue involvement, including the formation of abscesses, sequestra or associated pyomyositis or contiguous venous thrombosis. It is useful for appropriate preoperative planning for diagnostic and/or therapeutic purposes. MRI may not be necessary in certain situations where other clinical and diagnostic tools are strongly suggestive of the diagnosis [27,28].

- Septic arthritis: Although MRI is generally not indicated for isolated SA, it is valuable if OM associated with SA is suspected [29].
- Spondylodiscitis and vertebral OM: MRI is the most useful test for spinal infections as it provides excellent details of bone and soft tissue involvement in these complex areas. MRI aids in exclusion of other conditions such as malignancy.

Disadvantages of MRI include logistics, high cost, long scan times and need for sedation or anesthesia in young children. Presence of metallic foreign bodies, metal implants and MRI incompatible pacemakers are contraindications for performing MRI [30].

4d. Computerised Tomography (CT)

CT is not generally recommended in children as it is less sensitive compared with MRI in detecting early osseous lesions and exposes children to high doses of radiation [31].

- It should be reserved for settings where MRI is not feasible and USG is unremarkable with high clinical suspicion.
- Valuable for guided procedures, such as aspiration or drainage, and may not need sedation because of the short time needed.

4e. Bone Scintigraphy or Bone Scan Technetium Radionuclide Scan (99mTc)

It is used to identify multifocal osseous involvement and to document the site of OM when local skeletal symptoms are ill defined. It has a high sensitivity but low specificity [32] and both sensitivity and specificity are lower in neonates. It may also give false negative results in infancy and with virulent pathogens (MRSA).

5. REFERRAL TO ORTHOPEDIC SURGEONS

Recommendation

- We recommend that all patients with suspected BJI be referred to orthopaedic surgeon as early as possible. The management of such children should be by the combined team of pediatrician and orthopedic surgeon.

Rationale

All acute BJIs are emergencies need immediate and aggressive treatment. Many a times this aggressive treatment could only be empiric/appropriate broad-spectrum antibiotic/medical therapy but surgical intervention at an appropriate/early time is not only limb saving but lifesaving. A few hours of delay can mean a catastrophic outcome with permanent disability/deformity [33,34]. The decision to intervene must be made by a competent orthopedic surgeon [35,36].

6. EMPIRIC ANTIMICROBIAL THERAPY

Recommendations

- We recommend intravenous (IV) cefazolin/ cefuroxime as empiric therapy in children aged 3 months to 5 years.
- We recommend IV cefazolin/cloxacillin as empiric therapy in children aged 5 years or older. Anti-MRSA therapy including vancomycin/ teicoplanin may be added in those with high suspicion for MRSA. We do not recommend linezolid as empiric therapy.
- In sick neonates and critically ill children, IV meropenem and vancomycin is recommended till culture results are available.

Rationale

Choice of empiric therapy depends on the likely etiology and antimicrobial susceptibility and should be parenteral. In children aged 3 months - 5 years, the common culprits are *S. aureus*, *K. kingae* [7,8], *S. pneumoniae* and *H. influenzae*. The disadvantage of antistaphylococcal penicillins as empiric therapy for this age is that they do not cover for *K. kingae*, Hib or pneumococcus. In children aged 5 years and above, antistaphylococcal penicillins (cloxacillin/ flucloxacillin) or cefazolin is the drug of choice. The key decision is about initiation of anti-MRSA therapy. Empiric therapy for MRSA should be initiated if the prevalence of MRSA is more than 10-20%. The prevalence of MRSA varies in different settings, however, Indian data about the prevalence of CA-MRSA in pediatric BJIs is limited [3]. Hence, knowledge of local or institutional antibiogram is very crucial before starting MRSA therapy. Empiric therapy for MRSA may be added in very sick children, if the local experience so indicates, or if specific clinical indicators for MRSA are present such as high fever, bone abscess, multifocal involvement, fracture and deep vein thrombosis (DVT) or severe disease where either joint is involved and patient with poorly controlled comorbidity or organ damage [37,38].

It is mandatory to obtain blood and bone/ joint fluid cultures before initiating antibiotics for SA in neonates and critically ill children. Reviewing data about neonatal intensive care unit (NICU) cultures for that baby and the epidemiology of neonatal sepsis in the NICU where the baby was admitted may also help if available. Empiric therapy if indicated in a sick baby, can be initiated with a carbapenem (meropenem/ imipenem cilastatin), or a beta lactam plus beta lactamase inhibitor combination (piperacillin-tazobactam) along with vancomycin till cultures are available.

7. MODIFICATION OF ANTIBIOTICS BASED ON CULTURE REPORTS

Recommendations

- The choices for definitive therapy are based on the isolate, susceptibility, availability, bone penetration, cost considerations and whether or not there is concomitant bacteremia. Parenteral therapy may be given as outpatient parenteral therapy (OPAT) in some patients.
- **Table I** and **Table II** describe the choices of antibiotics with their doses for definitive therapy of BJI [17].

Rationale

- Methicillin sensitive *Staphyloccus aureus* (MSSA): The drug of choice for treating MSSA isolates in BJIs are either antistaphylococcal penicillins (cloxacillin/ nafcillin/flucloxacillin) or cefazolin. While the antistaphylococcal penicillins are the gold standard, disadvantages include erratic availability, four times a day dosing, thrombophlebitis and nephrotoxicity. The first-generation cephalosporin cefazolin is a good alternative with lower cost, thrice daily dosing but there is a concern about lower efficacy of cefazolin due to inoculum effect. Published data have reported similar efficacy of antistaphylococcal penicillins and cefazolin [39-41]. If the patient does not have bacteremia, other alternatives for MSSA include ceftriaxone dosed once/ twice daily or cefuroxime sodium dosed twice daily (suitable for OPAT). Preliminary studies show efficacy of cefazolin dosed twice daily also. If serious beta lactam allergy is present then daptomycin/fosfomycin can be used.
- MRSA: The drug of choice for MRSA isolates in BJIs is either vancomycin and teicoplanin. While vancomycin is the gold standard, problems include need for 3 to 4 times daily dosing, infusion-related side effects and nephrotoxicity and suboptimal tissue (bone) levels [42-44]. Teicoplanin, the other glycopeptide, has better bone levels than vancomycin, can be dosed once a day, has lesser nephrotoxicity and infusion related side effects [45-47]. A third alternative is daptomycin; availability and lack of pediatric data are limitations. Other anti-MRSA drugs such as linezolid, clindamycin and cotrimoxazole are the options for oral switchover therapy and not for initial parenteral therapy, especially, if coexistent bacteremia is present.

8. CHANGING FROM PARENTERAL TO ORAL ANTIMICROBIALS

Recommendations

- This decision should be individualized.
- It should be initiated once there is resolution of symptoms and signs and improvement in the white cell count and CRP.

Rationale

The change from parenteral to oral therapy depends on many factors including the presence/absence of bacteremia, age of the patient, severity of disease, causative pathogen, clinical and laboratory response, presence and absence of complications and availability of suitable oral option. Hence, this decision of oral switchover should be individualized for each patient. In patients with staphylococcal bacteremia, parenteral therapy for atleast 2 weeks is recommended. When this is

Table I Definitive Antibiotic Regimens in Bone and Joint Infections Based on Etiology

Organism	*Parenteral*		*Oral*
	Ist line	*Alternative*	
MSSA	Cloxacillin/Cefazolin	Daptomycin/Ceftriaxone/ Cefuroxime	Cephalexin/ Cloxacillin/ Clindamycin
MRSA	Teicoplanin/ Vancomycin	Daptomycin/ Fosfomycin	Linezolid/ Cotrimoxazole/ Clindamycin with/ without rifampicin
Kingella/ Pneumococcus/ Hib	Ceftriaxone	Cefuroxime/Co-amoxiclav	Cefuroxime
Salmonella/ susceptible Gram negative	Ceftriaxone Cotrimoxazole	Ciprofloxacin	Cefixime/ Ciprofloxacin/
ESBL producing gram negative	Meropenem/ Imipenem	BL-BLI combinations (Piper-callin-Tazobactam, Cefopera-zone sulbactam)/Ertapenem	CiprofloxacinCotrimoxazole
Candida	Fluconazole	Amphotericin B Deoxycholate/ Liposomal Amphotericin B/ Micafungin/ Caspofungin	Fluconazole/ Voriconazole (for C. krusei)
Carbapenem resistant gram negatives	Polymyxins (Polymyxin B/Colistin) with tigecycline/ Fosfomycin/ Cotrimoxazole		
Brucellosis	Children < 8 y: Cotrimoxazole and Rifampicin for 3 mo and Gentamicin/ Streptomycin for 7 d Children older than 8 y: Doxycycline and rifampicin for 3 mo and Gentamicin/Streptomycin for 7d		
Tuberculosis	Isoniazid, Rifampicin, Pyrazinamide, Ethambutol for 2 mo and then Isoniazid, Rifampicin with/ without Ethambutol for 10 mo		

BL-BLI Beta-lactam and beta-lactamase inhibitor, ESBL Extended spectrum beta-lactamases, MRSA Methicillin resistant Staphylococcus aureus, MSSA Methicillin sensitive Staphyloccus aureus

not possible due to logistic reasons, earlier switch may be considered in children who clear their bacteremia within 72 hours or serial blood culture become negative in 1-2 days of starting therapy. In patients with blood culture negative osteomyelitis, studies and meta-analysis show similar efficacy of early parenteral to oral switch versus prolonged intravenous therapy [48]. Prolonged intravenous therapy can actually be detrimental with increased drug adverse effects and infusion-related complications. Therefore, therapy should be switched to oral when the child becomes afebrile, the symptoms and signs are resolving, there are no complications, and the CRP is returning to normal, provided a suitable oral option is available and the child can take the antibiotic and if the parent/caregiver can administer the oral antibiotic to the child reliably. The cut-offs of CRP recommended to transition to oral therapy vary between 20-30 mg/L or a level 30-50% of the peak level [49-51].

Patients with MRSA infection, delayed response and complications may need prolonged parenteral therapy. Similarly, infants less than 3 months of age are best treated with parenteral therapy for the total duration of antibiotic therapy and so are patients for whom oral options are not available.

9. DURATION OF THERAPY

Recommendation

- We recommend the length of total therapy should be 2-3 weeks for septic arthritis and 3-4 weeks for osteomyelitis; prolonged therapy upto 8 weeks may be needed in MRSA osteomyelitis, neonates, involvement of pelvis and spinal column.

Rationale

Acute uncomplicated hematogenous osteomyelitis due to MSSA with good clinical response and rapid normalization of the CRP can generally be treated with 3-4 weeks of antibiotics. This recommendation is supported by prospective randomized trials in MSSA osteomyelitis where 20 days of therapy was noninferior to 30 days of treatment [48]. However, in osteomyelitis with complications (such as 2 or more bones involved with or without additional soft tissue involvement, slow response to therapy, requiring more than one surgery, persistent bacteremia after 3 or more days of therapy, complications like thrombosis, thrombophlebitis, endocarditis and pathological fracture, potential impact on bone growth) or pelvic/ spine infections, treatment for 6 weeks may be

Table II. Doses of Commonly Used Drugs in Pediatric Bone and Joint Infections

Drug	*Route*	*Dose*	*Maximum dose/ day*
Cloxacillin	IV	200 mg/kg/day q 6 h	12 g
Cefazolin	IV	100-150 mg/kg/day q 8 h	6 g
Ceftriaxone	IV	100 mg/kg/day q 12-24 h	4 g
Cefuroxime	IV	75 mg/kg/day q 12 h	3 g
Vancomycin	IV	45-60 mg/kg/day q 6-8 h	3 g
Teicoplanin	IV	8-12 mg/kg 12 hourly for 3 days and then 8-12 mg/kg/ day q 24 h	1200 mg
Daptomycin	IV	8-10 mg/kg/day q 24 h	700 mg
Clindamycin	IV	20-30 mg/kg/day q 8 h	2700 mg
Cephalexin	IV	100-150 mg/kg/day q 6-8 h	4 g
Cefuroxime	Oral	20 mg/kg/day q 12 h	1 g
Cloxacillin	Oral	30-50 mg/kg/day q 8 h	3 gm
Clindamycin	Oral	20 mg/kg/day 2 8 h	1200 mg
Linezolid	IV, oral	30 mg/kg/day q 8 h	1200 mg
Cotrimoxazole	IV, oral	8-12 mg/kg/day of TMP q 8-12 h	640 mg of Trimethoprim
Rifampicin	Oral	10-20 mg/kg/day q 12-24 h	1200 mg
Meropenem	IV	60-120 mg/kg/day q 8 h	6 g
Imipenem	IV	60-100 mg/kg/day q 6-8 h	3 g
Ertapenem	IV	40 mg/kg/day q 12 h	1 g
Piperacillin tazobactam	IV	300-400 mg/kg/day of piperacillin q 6-8 h	16 g of Piperacillin
Cefoperazone sulbactam	IV	100 mg/kg/day of cefoperazone q 12 h	4 g of Cefoperazone
Ciprofloxacin	IV	20-30 mg/kg/day q 12 h	1200 mg
Ciprofloxacin	Oral	30 mg/kg/day q 12 h	1500 mg
Fluconazole	IV	Neonates: 25 mg/kg loading and then 12 mg/kg/day q 24 h Older children: 12 mg/kg loading and then 6 mg/kg/day q 24 h	Loading 800 mg and Mmaintainence 400 mg
Liposomal Amphotericin B	IV	3 mg/kg/day q 24 h	None
Amphotericin B deoxycholate	IV	1 mg/kg/day q 24 h	None
Micafungin	IV	Neonates: 10 mg/kg/day q24 h; Older children: 2-4 mg/kg/ day q24 h	100 mg
Caspofungin	IV	70 mg/m^2 loading and then 50 mg/m^2 maintenance q24h	70 mg
Polymyxin B	IV	20,000-25,000 units/kg loading and then 20000-30000 units/kg/day q 12 h	2 million
Colistin	IV	4.5 million units/kg loading and then 4.5 million units/kg/day q 8-12 h	9-12 million units
Tigecycline	IV	3 mg/kg loading and then 3 mg/kg/day maintenance q 12 h	Loading 200 mg and maintenance 200 mg
Fosfomycin	IV	200-300 mg/kg/day q 6-8 h	16 g

needed. In MRSA osteomyelitis, treatment for up to 8 weeks may be needed. Candida osteomyelitis needs treatment for up to 6 months. In children with implant- or prosthesis-associated infections (where the implant or prosthesis has been retained), chronic suppressive therapy may need to continue for even up to 3 to 6 months, depending on the joint involvement [52-54].

In infants and children with uncomplicated septic arthritis (single joint involvement with rapid response within 3 to 5 days, resolution of bacteremia in 1-2 days, no signs of late sequelae), the treatment duration is dependent on the clinical response to therapy and the suspected organism. *S. pneumoniae*, *Hib*, *K. kingae* and *N. gonorrhoea*e are treated with appropriate antibiotics for 2-3 weeks. Infections with *S. aureus* and gram-negative organisms are treated longer for 3-4 weeks [55-59]. If there is associated osteomyelitis (complicated septic arthritis), the duration of antibiotics would be as for osteomyelitis. An MRI is the ideal imaging technique to detect coexistent osteomyelitis. However, in resource-

limited settings an *X*-ray of the affected joint to look for bony changes consistent with osteomyelitis may be done at the end of 2-3 weeks of therapy or before stopping treatment.

10. MANAGEMENT OF CULTURE NEGATIVE BJIs

Recommendations

- We recommend continuing the initial empiric regimen in patients with culture negative BJI, provided there is clinical response.
- When there is no growth in culture, all efforts should be made to rule out tuberculosis and fastidious organisms as one of the possibilities.

Rationale

Most of these BJIs respond to empirical therapy with cefazolin/ cefuroxime/cloxacillin. Duration of antibiotic therapy depends on the response to antibiotics and laboratory response using ESR and CRP. Once inflammatory markers are normal and patient has shown clinical improvement, antibiotics can be stopped [60]. In patients who are not improving with the initial regimen, repeat bone/ joint cultures should be obtained before adding an MRSA cover/ broadening therapy. When there is no growth in culture, all efforts should be made to rule out tuberculosis as one of the possibilities.

11. FAILURE OF THERAPY

Recommendation

- Treatment failure should be suspected when there is absence of clinical improvement after 72 hours of antibiotic therapy, persistence of fever more than 72-96 h duration, or its reappearance (unexplained by other common causes), elevated WBC count and raised CRP even after 7 days of antibiotic therapy, or development of a pathological fracture [60,61].

Common causes of treatment failure include inappropriate drug and/or improper dose, drug resistant organisms and lack of source control.

12. MANAGING A PATIENT WITH SUSPECTED TREATMENT FAILURE

Recommendations

- We recommend repeating blood/ bone/ tissue/ pus cultures, MRI imaging for assessing metastatic infection/ subperiosteal abscess, and evaluation for DVT in patients with treatment failure.
- Treatment will depend on the underlying cause of treatment failure and may include upgradation or change of antibiotics and surgical intervention.

Rationale

A delay in the diagnosis and initiation of appropriate treatment can lead to potentially devastating morbidity including sepsis, chronic infection, disruption of longitudinal bone growth and angular deformity.

13. LONG-TERM FOLLOW UP OF A CHILD WITH BJIs

Recommendations

- We recommend follow up by orthopedic surgeons and pediatricians at 2 weeks, 4-6 weeks, 3 months, and 12 months after discharge [62].
- Close monitoring of the range of motion at joint and limb length should be done.
- Pain-free normal activity is one of the important end points to consider prior to discharge from follow up.
- The need for radiological investigations during follow up should be decided by the orthopedic surgeon on a case-to-case basis.

Rationale

Early diagnosis and appropriate treatment are associated with an excellent outcome of BJIs in children. Common sequelae include limping gait, dysmetria, chronic pain, stiffness with or without the presence of growth arrest, leg length discrepancy and deformity. Parents and care takers should be educated to look for signs such as limp, pain, deformity or leg length difference and to seek early medical attention if any concerns irrespective of scheduled appointments [63].

In the true sense, the long term follow up starts with normalization of inflammatory markers (ESR and CRP) and after cessation of antibiotics, both parenteral and oral. Clinically this is evidenced by the child walking and playing without pain and limp. In the initial period, blood investigations for inflammatory markers and radiographs should be included. Clinical examination during every visit, whilst carefully looking for sequelae is very important. If epiphyseal arrest is suspected, an MRI with or without CT scan of affected physis is recommended. Customization may be dictated by the causative organism; certain organisms such as Salmonella, MRSA or Panton-Valentine-Leucocidin (PVL) producing bacteria will need a closer follow up as they are associated with a higher rate of complications and/or sequelae like DVT [62,64].

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