

Neonatal septic arthritis: Indian perspective

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Abstract

Objective: To delineate the pattern of joint involvement in neonatal septic arthritis, assess the prognosis, and determine significant predictors of unfavorable outcome.

Methods: Subjects were recruited through purposive sampling after obtaining parental consent. A detailed history and examination findings with perinatal data were recorded. Ultrasound and magnetic resonance imaging data of affected joints and blood culture and aspirated joint fluid culture data were recorded along with management received. Cases were followed-up every 3 months from discharge up to minimum 12 months. An unfavorable outcome indicated by permanent joint deformity or restricted range of movement of the affected joint, limb length discrepancy, and persistent joint deformity upon radio imaging at the end of the follow-up period were also included.

Results: The hip joint involvement (59.2%) was the commonest with predominance of the monoarticular pattern of affliction (74.4%). An overall outcome was favorable in 70.3% subjects with prompt diagnosis and management. A delay in seeking treatment was found to be an indicator of unfavorable outcome. In addition, disease detection by ultrasound at presentation predicted unfavorable outcome.

Conclusion: Neonatal septic arthritis is a rare disease with predominant hip or knee involvement. Outcome is favorable with early detection and institution of appropriate management. A delay in treatment worsens prognosis.

Keywords: Indian, neonate, septic arthritis

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Introduction

Septic arthritis in neonates is defined as the inflammation of the synovial membrane with purulent effusion into the joint capsule due to suppurative infection of a joint. It is regarded as one of the deep-seated infections in neonates. Global incidence of the disease is approximately 0.3 per 1000 live births, whereas in India, it has been reported as 0.6 per 1000 live births (1, 2). Due to paucity of signs and symptoms, neonatal septic arthritis often goes unrecognized at the beginning with the potential to cause devastating complications, including death of the newborn. *Staphylococcus aureus* is reported to be the commonest culprit for this condition worldwide, while other organisms isolated in culture include *Klebsiella pneumoniae*, Group B streptococci, *Escherichia coli*, *Enterobacter* sp., *Kingella kingae*, and *Candida* sp. (3). Secondary hematogenous seeding of infective organisms is the well-known mode of this infection. The rich vascular supply and lack of synovial basement membrane in the joints of newborn infants (4) is what leads to predisposition to this condition. The immature immune system in neonates means that the condition has the propensity to progress rapidly and lead to several dreaded settings such as sepsis, osteomyelitis, meningitis, abscess formation in tissue spaces, urinary tract infection, etc., in addition to the destruction of the articular cartilage and ossification centers. The latter complication accounts for long-term morbidity in such patients by restricting a normal movement of the affected joint (5).

This multicentric prospective observational study aimed to delineate the frequency and pattern of the joint involvement in this disease and to determine significant predictors of outcome in addition to an assessment of overall prognosis.

Methods

Ethical approval and participant selection

This prospective observational study was conducted during 2016-2018 in the Department of Pediatrics of two distantly established medical colleges in eastern part of India. Newborn infants presenting at the outpatient clinic with suspected infective joint pathology were screened for inclusion as elaborated below.

Sampling was purposive, and as far as feasible consecutive babies that met the inclusion criteria were selected independently at the two centers. Included subjects were followed-up for minimum 12 months.

Due approval for the study was obtained beforehand from the institutional ethics committees. Informed consent was obtained from a parent or legal guardian, in writing, after giving them reasonable time to comprehend the participant information sheet and to clarify any doubts.

Diagnostic criteria

Although it does not have florid presentation during the initial phase of illness, septic arthritis in neonates is primarily a clinical diagnosis. It differs in presentation from septic arthritis at an older age in that a wide spectrum of vague systemic and joint signs and symptoms may be present that can mimic other joint pathologies such as transient synovitis, developmental dysplasia of bones forming the affected joint, osteomyelitis, pyomyositis, localized abscess, cellulitis, nonspecific arthritis, etc. There is lack of consensus on diagnostic criteria for neonatal septic arthritis. Some studies have used Morrey's diagnostic criteria of septic arthritis, which were proposed originally in the year 1976 (6-8). However, it was not proposed for neonatal septic arthritis per se, nor has been it updated further appropriately. With the advent of newer investigational tools and radio imaging methods, these criteria alone probably lack relevance in the present-day scenario. We laid down a screening scheme for detecting neonatal septic arthritis, provided in Table 1, which was used alongside Morrey's diagnostic criteria to determine inclusion of the subjects. Signs and symptoms of systemic infection (refusal to suck, inconsolable cry, lethargy, irritability, inability to maintain body temperature, etc.) along with evidence of inflammation in the affected joint (e.g., redness, swelling, warmth, restricted movement, pseudoparalysis, crying on handling the affected limb, etc.) were looked for.

A case was considered to be neonatal septic arthritis if (i) both the criteria from Block A and

any one from Block B were fulfilled, or (ii) at least one criterion from Block A and two from Block B were fulfilled, or (iii) met Morrey's diagnostic criteria of septic arthritis (9). A possibility of the diagnosis overlap with infective bone pathology is the drawback here, but a careful approach and neutral insight for the exclusion of closest differentials was maintained in case of any ambiguity (10). Neonates with congenital skeletal deformities and other congenital anomalies were excluded from this study.

Data collection

Relevant information was captured using a predesigned case report form. Significant perinatal history was recorded in addition to history of present illness. The onset and duration of illness before coming to medical facility, mode of presentation, and any co-morbidities and complications were elaborated. Management received for the illness was recorded. Cases were followed-up every 3 months from discharge, for minimum 12 months. Restriction of the movement, permanent deformity in the afflicted joint, and limb length discrepancy were looked for at every visit. At the 12-month follow-up visit, plain roentgenographic evaluation of the afflicted joint was carried out for confirming any bone deformity.

Measures of outcome

At the end of the stipulated minimum follow-up period, the cases were assigned to two groups: the one with favorable and unfavorable outcome. Unfavorable outcome was defined as the presence of one or more of the following at the end of follow-up: permanent joint deformity, joint contracture or stiffness, dislocation or restricted movement at the affected joint or limb length discrepancy of more than 1 cm, and/or persistent bone/joint deformity revealed on imaging. Favorable outcome implied none of the above and no medical complications.

Data analysis

Information collected was compiled using the Microsoft Excel 2016 software. Data were summarized by routine descriptive statistics, namely the mean and standard deviation (SD) for numerical variables that are normally distributed, median and interquartile range for skewed numerical variables, and counts and percentages for categorical variables. Key variables were expressed with 95% confidence intervals (CI). Numerical variables were compared between favorable and unfavorable outcome subgroups by Student's independent samples t-test, if normally distributed, or by the Mann-Whitney U test, if otherwise. Fisher's exact test or Pearson's chi-squared test was employed for intergroup comparison of categorical variables. A p-value < 0.05 was considered statistically significant. Statistica version 6 (Tulsa, Oklahoma: Stat Soft Inc., 2001) and MedCalc version 11.6 (Mariakerke, Belgium: MedCalc Software, 2011) software were used for statistical analysis.

Results

Forty-three neonates made up the initial study cohort with the male-to-female ratio of 1.3, contributing a total of 54 cases that were evaluated for septic arthritis. The mean (SD) birth weight of this cohort was 2.37 (0.59) kg. Distribution of the gestational age at birth was 23 (53.4%) preterm, i.e., <37 weeks, 17 (39.5%) term, and 3 (7.0%) postterm, i.e., >40 weeks. The mean (SD) age at the onset of illness was 15.7 (6.82) days and the mean (SD) age of seeking medical attention for the illness was 21.4 (7.08) days of life. There were 12 (27.9%) subjects with a history of previous intravenous cannulation in the affected limb for some other illness, and among these, 5 (11.6%) also had history of umbilical catheterization, while 3 (6.9%) subjects were on ventilator support for significant time period.

In the whole cohort, 32 (74.4%) subjects had monoarticular and the rest had polyarticular pattern of joint affliction. Among total 54 joints evaluated in this study, the hip joint (59.2%) in-

Table 1. Screening tool for neonatal septic arthritis.

Block A	Block B
1. Systemic signs and symptoms of infection.	1. Positive sepsis screen or growth of micro-organisms on blood culture.
2. Joint signs and symptoms of inflammation.	2. Afflicted joint fluid examination demonstrates pus cells under microscopy.
	3. Afflicted joint fluid culture shows growth of culprit organism.
	4. Evidence of septic arthritis upon radioimaging of afflicted joint.

Main Points

- A delay in the detection and institution of appropriate management significantly increases the risk of joint sequels in neonatal septic arthritis.
- Detection of joint pathology with ultrasound at initial presentation of the illness predicts unfavorable outcome.

involvement was commonest followed by knee joint (22.2%). Six (13.9%) subjects had bilateral hip joint involvement. In addition to plain roentgenographic evaluation at the beginning, ultrasonographic examination was done for all the affected joints, while magnetic resonance imaging (MRI) was done for 45 joints. Considering these modalities of radio imaging individually or in conjunction, septic arthritis was diagnosed in 38 of the 54 (70.4%, 95% CI 58.2%-82.6%) joints. Ultrasound individually demonstrated septic arthritis in 32 (59.2%) afflicted joints, and the MRI report corroborated in 22 joints, while others were reported to be normal. Forty-three joints and 34 subjects were managed conservatively with antibiotics according to the culture and sensitivity report where available, while 11 joints in 9 subjects required surgical intervention in the form of guided needle aspiration or incision and drainage; 1 joint had to undergo arthrotomy. Those who were managed conservatively for septic arthritis received 2 weeks of intravenous antibiotic followed by 2 weeks of oral therapy as per accepted practice (2, 5, 11). Following collection of blood samples and joint aspirate wherever possible under ultrasound guidance for culture and antibiotic sensitivity testing, empirical antibiotics were administered and continued till the reports became available. As septic arthritis in newborns is classified as deep-seated infection, in an attempt to give coverage for gram-negative organisms and methicillin-resistant *Staphylococcus aureus*, we had chosen cefotaxime (100 mg/kg/day in divided doses, intravenously) and vancomycin (45 mg/kg/day in divided doses, intravenously) combination as empiric therapy. On occasions where culture of both the blood and joint fluid aspirate yielded no growth, we needed to step-up intravenous antibiotics to piperacillin-tazo-

bactam, meropenem, and vancomycin on six of such instances. In the rest of the cases, intravenous antibiotics were chosen later as per culture and sensitivity report obtained from joint aspirate and blood sample or either of them. Gram-negative organisms such as *Klebsiella pneumoniae* (11/17), *Escherichia coli* (3/3), and *Proteus mirabilis* (1/1) were found sensitive to cephalosporins and carbapenems, while the rest of gram-negative organisms such as *Klebsiella pneumoniae* (6/17), *Pseudomonas aeruginosa* (1/1), and *Acinetobacter baumannii* (1/1) were found sensitive to antibiotics such as extended spectrum beta-lactams and monobactams. We decided to continue oral antibiotic therapy with cefuroxime or cefixime after initial 2 weeks of intravenous antibiotics as per protocol in cases where gram-negative organisms were yielded. Gram-positive organisms like *Staphylococcus aureus* (6/8) and *Streptococcus pneumoniae* (2/3) were found to be sensitive to cloxacillin and cephalosporins, while rest of the gram-positive organisms *Staphylococcus aureus* (2/8), *Streptococcus pneumoniae* (1/3), and *Staphylococcus epidermidis* (1/1) were found to be sensitive to vancomycin and linezolid. We decided to continue oral antibiotic therapy with linezolid after initial 2 weeks of intravenous antibiotics as per protocol in cases where gram-positive organisms were yielded.

The follow-up cohort who completed at least 12 months observation comprised 37 of the initial 43 subjects. Among the rest, 2 deaths were recorded despite aggressive management during the acute phase of illness while 4 were lost to follow-up. In accordance with the predetermined outcome measures, the follow-up cohort was divided into favorable and unfavorable outcome subgroups; 26 of 37 (70.3%) subjects and 33 of 45 (73.3%) joints

had favorable outcome. The rest had unfavorable outcome in the form of functional or radiological deficits. Subjects who had multiple joint involvement initially and subsequently had unfavorable outcome of at least one of the joints, were put into unfavorable group. Joint sequelae noticed in the unfavorable outcome group were limb length discrepancy (4 of 12 joints; 33.3%), restricted range of movement (3; 25.0%), joint stiffness with deformed bones on radio imaging (3; 25.0%) and joint subluxation (2; 16.7%). Figure 1 depicts distribution of joints as per outcome at the end of the follow-up period.

Taking the initial cohort of 43 subjects into consideration, the prenatal history in 9 (20.9%) subjects revealed that the mother suffered from illness during pregnancy such as genital tract infection (14%), preeclampsia (2.3%), and rubella infection (2.3%). Some (2.3%) were carriers of hepatitis B virus, while 13 (30.2%) subjects had adverse perinatal history of obstructed labor (11.6%), delayed labor (9.3%), pre-labor rupture of the membrane (7%), and placenta previa (2.3%) that are often associated fetal distress at birth. Twenty-seven (62.7%) subjects were diagnosed with co-existing morbidities such as pathological neonatal jaundice (11.6%), neonatal sepsis (11.6%), birth asphyxia (9.3%), congenital heart disease (7%), cephalohematoma (4.7%), intrauterine growth restriction (4.7%), hepatitis B infection (2.3%), and respiratory distress syndrome (2.3%). During subsequent course, osteomyelitis (16.2%), development of soft tissue abscess (16.2%), and avascular necrosis (4.3%) were found as local complications of the illness in this study, besides systemic complications such as neonatal sepsis, meningitis, diarrhea, and urinary tract infection.

Table 2 presents a comparison of study subjects showing favorable or unfavorable outcome at the end of 1-year observation. Birth weight and time taken in presenting to a medical facility were found to be significantly different between the two subgroups. The outcome appeared to be less favorable with increased birth weight and with a greater delay in seeking medical care. Detection of septic arthritis with ultrasound of the affected joint during acute presentation was found to be a significant predictor ($p=0.027$) of unfavorable outcome, as well as cesarean delivery ($p=0.016$). However, other potential predictors of unfavorable outcome, namely prematurity at birth, hip joint involvement, previous intravenous (IV) cannulation in the affected limb, specific co-morbidities and complications, and restriction of joint movement at discharge were not

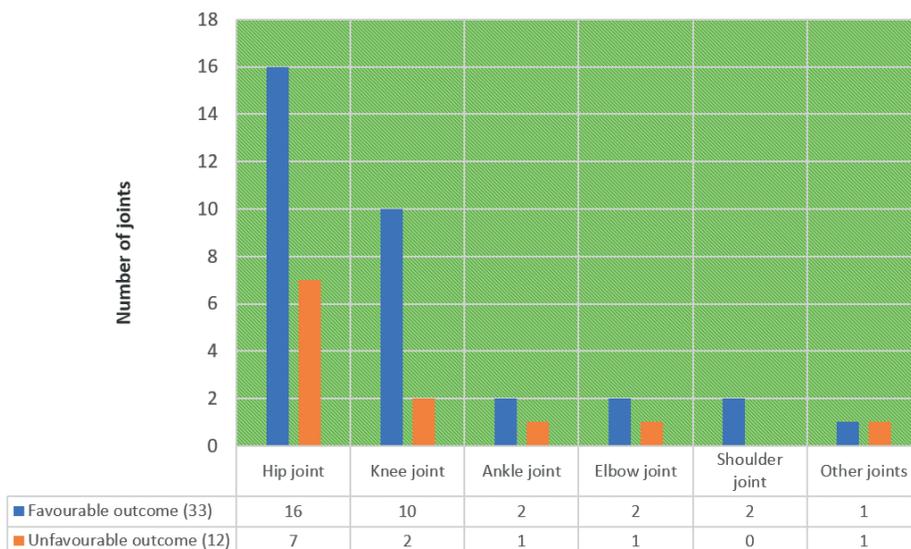


Figure 1. Showing distribution of joints as per outcome in follow-up cohort.

Table 2. Comparison of clinical variables between septic arthritis afflicted neonates showing favorable and unfavorable outcome at the end of one-year observation.

Clinical variable	Favorable outcome [n=26]	Unfavorable outcome [n=11]	p
Birth weight (kg)			
Range	1.2-3.3	2.2-3.0	
Mean (SD)	2.1 (0.47)	2.6 (0.28)	0.009
Gender			
Male (%)	15 (57.69%)	5 (45.45%)	
Female (%)	11 (42.31%)	6 (54.55%)	0.719
Gestational status at birth			
Term (%)	8 (30.77%)	7 (63.64%)	
Pre-term (%)	17 (65.38%)	3 (27.27%)	
Post-term (%)	1 (3.85%)	1 (9.09%)	0.104
Onset of illness (day)			
Range	5.0-27.0	6.0-21.0	
Mean (SD)	16.0 (6.30)	15.3 (4.78)	0.326
Time taken to present to medical facility (day)			
Range	1.0-9.0	3.0-14.0	
Mean (SD)	4.6 (2.28)	9.2 (3.37)	< 0.001
Joints affected per subject			
Range	1.0-2.0	1.0-2.0	
Median (IQR)	1.0 (1.0-1.0)	1.0 (1.0-2.0)	0.455
Joint USG corroborative			
Yes (%)	13 (50.00%)	10 (90.91%)	
No (%)	13 (50.00%)	1 (9.09%)	0.027
Joint MRI corroborative			
Yes (%)	13 (50.00%)	8 (72.73%)	
No (%)	13 (50.00%)	3 (27.27%)	0.285
Hip joint involvement			
None (%)	14 (53.85%)	3 (27.27%)	
One hip joint (%)	10 (38.46%)	7 (63.64%)	
Both hip joints (%)	2 (7.69%)	1 (9.09%)	0.321
Previous IV cannulation in affected limb			
Yes (%)	8 (30.77%)	3 (27.27%)	
No (%)	18 (69.23%)	8 (72.73%)	1.000
Primary management			
Conservative (%)	21 (80.77%)	8 (72.73%)	
Surgical (%)	5 (19.23%)	3 (27.27%)	0.672

Figures in parentheses indicate percentages within respective group.

found to be significantly associated with unfavorable outcome. Further, comparison of the primary mode of management (conservative vs surgically managed) also did not yield a significant difference.

Routine blood investigations along with blood culture and antibiotic sensitivity testing were done for all 43 subjects from the initial cohort, but only 19 (44.19%) reports showed decisive growth of organisms. The gram-negative bacillus *Klebsiella pneumoniae* (20.9%) was found to be the commonest organism. *Staphylococcus aureus* (9.3%), *Escherichia coli* (4.7%), *Streptococcus pneumoniae* (2.3%), *Staphylococcus epidermidis* (2.3%), *Pseudomonas aeruginosa* (2.3%), and *Acinetobacter baumannii* (2.3%) were among the other isolates. Thirty joints (55.6%) among total 54 afflicted underwent the joint fluid examination. Twenty-three (76.6%) of these joints revealed the presence of pus cells, and 18 (33.3%) samples showed the growth of

microorganisms in the culture. Majority were gram-negative, which was consistent with other study findings (12). Here 9 joint fluid isolates did corroborate with the blood culture report of respective subject whereas in 8 instances, blood culture yielded no growth, but the presence of pathogenic organism was established through gram-staining and microbiological culture of involved joint fluid. In one case, blood culture showed suspected growth of skin commensal, yet joint fluid revealed growth of pathogenic organisms. On seven occasions, both the blood and joint fluid culture yielded no growth. Table 3 presents microbiological findings in relation to the potential causative organism of the septic arthritis in the two outcome groups. Here also, no statistically significant differences were noted.

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Table 3. Comparison of microbiological profile between favorable and unfavorable outcome groups.

Organism on culture	Favorable outcome (n=26)	Unfavorable outcome (n=11)
Blood		
<i>Klebsiella pneumoniae</i>	8 (30.77%)	1 (9.09%)
<i>Escherichia coli</i>	2 (7.69%)	0
<i>Staphylococcus aureus</i>	1 (3.85%)	1 (9.09%)
<i>Streptococcus pneumoniae</i>	1 (3.85%)	1 (9.09%)
<i>Staphylococcus epidermidis</i>	1 (3.85%)	0
<i>Pseudomonas aeruginosa</i>	1 (3.85%)	0
<i>Acinetobacter baumannii</i>	0	1 (9.09%)
NO GROWTH	12 (46.15%)	7 (63.64%)
Joint aspirate		
<i>Klebsiella pneumoniae</i>	6 (23.08%)	2 (18.18%)
<i>Staphylococcus aureus</i>	1 (3.85%)	5 (45.45%)
<i>Streptococcus pneumoniae</i>	1 (3.85%)	0
<i>Escherichia coli</i>	1 (3.85%)	0
<i>Proteus mirabilis</i>	1 (3.85%)	0
NO GROWTH	8 (30.77%)	3 (27.27%)

Figures in parentheses indicate percentages within respective group.

Culture of joint fluid aspirate was not done in 8 subjects in the favorable outcome group and 1 in the other group.

Discussion

Neonatal septic arthritis is an uncommon clinical entity, and subtle clinical signs and symptoms make the diagnosis even more difficult. In this study, subjects presented with different complaints though refusal to suck and reduced movement of the affected limb were common alongside joint swelling, inconsolable crying, or crying on handling the affected limb. The present cohort showed predominantly monoarticular pattern of affliction with the hip joint as the commonest site involved. Earlier studies report the knee or the hip as the common sites of involvement.

Table 4 summarizes the findings of some earlier published studies on neonatal septic arthritis, with the present study for comparison. In our study, 70.3% of the subjects and 73.3% of the affected joints had favorable outcome. This is comparable to the study by Li et al. (2), but better than results reported by Devi et al. (7) and Halder et al. (13). By contrast, much better

Table 4. Comparison of published studies on neonatal septic arthritis with the present study.

Authors (Year of publication)	Size of follow-up/ initial cohort (subjects)	Average age at presentation (days) [Mean (Range or SD)]	Average delay in seeking medical attention (days) [Mean (Range or SD)]	Commonest joint affliction (% of all joints studied)	Minimum follow-up period after discharge	Favorable outcome in % out of all joints affected
Narang A et al. (1) [1998]	- / 9	26 (7-64)	-	Hip (48)	-	-
Li Y et al. (2) [2016]	44 / 52	17.5 (7.6)	14.9 (8.7)	Knee (39.2)	12 months	72.9
Devi et al. (7) [2017]	52 / 70	18.8 (7.1)	13.7 (3.8)	Hip (40)	15 months*	63.5##
Kabak et al. (12) [2002]	13 / 14	34.7 (17- 60)	4.2 (1-9)	Hip (42.9)	24 months	92.3
Pittard et al. (13) [1976]	7 / 9	-(3-54)	-	Knee (100)	10 months	100
Halder et al. (14) [1996]	5 / 10	15.6 (9-18)	2.4 (1-5)	Knee (60)	3 months	60
Present study	37 / 43	21.4 (7.1)	6.08 (3.9)	Hip (59.2)	12 months	73.3

*Depicts mean age of follow-up; ## Expressed in % of total subjects followed-up due to inadequate elaboration.

results to the tune of >90% favorable outcome have been reported by Kabak et al. (14) and Pittard et al. (15). This discordance between studies indicates that outcome of septic arthritis in babies is likely to depend on various circumstantial factors, and the duration of follow-up is not directly related to the outcome status.

Favorable outcome in neonatal septic arthritis will, however, depend on diagnosis and treatment latency. In our case, the time taken to present to medical facility was on average around 5 days longer in the unfavorable outcome cohort. Lee et al. (6) reported that delay in the institution of appropriate management is a negative prognostic factor for septic arthritis of the hip in neonates and infants. Two additional findings in this study were that the birth weight can affect the final outcome significantly and that the disease detection on ultrasound is associated with unfavorable outcome. Prematurity and low-birth weight might be an important risk factor for development of neonatal septic arthritis (16), but so far as the outcome is concerned, in our case, the unfavorable outcome cohort had a higher mean birth weight than their favorable outcome counterpart. Some other studies had also reported the mean birth weight in the unfavorable outcome group to be >2.5 kg, but they were not statistically significant (2, 7).

We also found that the disease detection by ultrasound, but not by MRI, is an unfavorable prognosis indicator. Recovery of the bone from an insult is dependent on its stability, in addition to the bone mass and bone mineral accretion (17). Early in the disease process, factors such as the echogenic debris, and fluid collection in the soft tissue and periosteal region, can obscure findings such as joint effusion, and ultrasound might miss neonatal septic arthritis at the onset. However, with the progression of the disease, the findings become clear (3, 18). Thus, the ultrasound detection at presentation signifies advanced disease that is likely to have a poor outcome. It is interesting that in our favorable outcome cohort, both ultrasound and MRI allowed disease detection in 50% cases. It is important to mention that in our study, the hip joint involvement did not show any prognostic significance amounting to outcome on follow-up.

Our study has its share of limitations. The observation period was limited to 12 months due to logistical constraints. The initial size of our study cohort and the numbers of patients who completed 1-year follow-up compares favorably to

several earlier studies, but it is still quite limited to permit logistic regression analysis on the outcome. Such analysis could have provided us estimates of risk posed by individual prognostic indicators as adjusted odds ratios. The sample size was not very big in our study due to a low incidence of the illness. A joint fluid examination of all the afflicted joints could not be done due to the unavailability of parental consent. Ultrasound and MRI could not be done in all the patients due to severity of illness limiting their transport. As we have conducted this study at the tertiary-care center, thus a significant number of patients we got were actually referred from hospitals where they have already been administered antimicrobials. We suppose this might have resulted in negative initial blood and joint fluid culture report in few patients.

Despite these limitations, we can conclude that septic arthritis is a rare infection in newborns that commonly involves the hip or knee joints and predominantly follows monoarticular pattern of affliction. Microbial etiology cannot always be detected. Overall outcome is good with prompt diagnosis and appropriate management. However, a delay in seeking medical attention worsens the prognosis. Disease detection by ultrasound at presentation also indicates that there is a chance of a less favorable outcome.

Ethics Committee Approval: Ethics committee approval was received for this study from the North Bengal Medical College Institutional Review Board.

Informed Consent: Written informed consent was obtained from parents or legal guardians of the patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - R.M., A.R., B.M.; Design - A.N., T.M., A.H., A.R.; Supervision - R.M., D.C., A.H., B.M.; Data Collection and/or Processing - S.B., A.R., A.N., D.C.; Analysis and/or Interpretation - R.M., A.H., B.M., D.C.; Literature Search - A.N., D.C., A.R., T.M.; Writing Manuscript - A.N., D.C., A.R., T.M.; Critical Review - R.M., A.H., S.B., B.M.

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