Acute Hematogenous Osteomyelitis and Septic Arthritis in Children: Clinical Characteristics and Outcomes Study

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Objective: *To evaluate the clinical features, causative pathogens and outcomes-related to acute hematogenous osteomyelitis and septic arthritis in pediatric patients.*

Material and Method: *The authors conducted a retrospective cohort study of patients under 15 years of age with diagnosis of acute hematogenous osteomyelitis (AHO) and /or septic arthritis (SA), treated at Queen Sirikit National Institute of Child Health from 1996 to 2006. Demographic data, clinical characteristics, bacterial spectrum, and outcomes were collected. Potential risk factors for osteoarticular sequelae in the patients who had more than 2 years of follow-up were analyzed.*

Results: *One hundred and twenty-nine patients met the diagnostic criteria which included 51 cases with SA, 35 cases with AHO and 37 cases with both SA and AHO. The patient's age ranged between 1 day and 13 years 4 months, comprising 37 (28.6%) of newborns, 28 (21.7%) of > 1-12 months, 18 (14%) of > 1-3 years and 46 (35.7%) of > 3-15 years. Causative bacteria were found in 103 of 129 patients (80%), the two most common pathogens were methicillin-sensitive Staphylococcus aureus (MSSA) in 48 (46.6%) and methicillin-resistant Staphylococcus aureus (MRSA) in 18 (17.5%) cases. The initial temperature on admission day was high (> 37.5°C) in only one-third of newborns, one-half of infants and two-thirds of the older group. The duration of antibiotic administration ranged between 21 and 56 days (mean 42 days). Arthrotomy or drainage and bone or joint aspiration underwent in 62% and 17% of cases respectively. Outcomes of 79 patients who had more than 2 years of follow-up identified osteoarticular sequelae in 23 patients (29%) that consisted of avascular necrosis of epiphysis, limb-length discrepancy and pathologic fractures. Univariate analysis for potential risk factors compared between sequelae and without sequelae groups demonstrated significant association with more than 1 week duration of presenting symptoms, newborn age group, hip joint infection, infection with MRSA and more than 3 days delayed treatment with appropriate antibiotics.*

Conclusion: *MSSA was the most common bacterial pathogen causing pediatric osteoarticular infections in all age groups but was second to MRSA in the newborn group. Osteoarticular sequelae were avascular necrosis of epiphysis, limb length discrepancy, and pathologic fracture which were significantly related to longer duration of presenting symptoms, newborn age group, hip joint involvement, MRSA infection and delayed administration of appropriate antibiotics.*

Keywords: *Acute hematogenous osteomyelitis, Septic arthritis, Osteoarticular infection, Causative bacteria, Outcome, Osteoarticular sequelae*

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Successful treatment of the pediatric osteoarticular infections remains a major challenge regarding the eradication of infections and management of long term sequelae[1-4]. The clinical outcomes of this condition were reported to be associated with various factors including, patient's age, health and socio-economic status, type of causative pathogens, accessibility to and timeliness of the appropriate treatment[5,6]. In neonates, the clinical presentations

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when compared to other ages are usually unspecific, resulting in delayed recognition and leading to serious musculoskeletal sequelae[1,7]. Recent reports have shown some changes in the disease patterns, an increase in the severity of the causative bacterial pathogens, and in resistance to antibiotics and reduction of *Hemophilus influenzae* type B osteoarticular infection after vaccination[8-12]. The purpose of the present study was to evaluate the clinical findings, spectrum of bacterial pathogens and prognostic factors of pediatric osteoarticular infections, receiving care at an urban tertiary care Children's Hospital, Bangkok, Thailand.

Material and Method

Medical records of hospitalized children under 15 years of age with discharged diagnosis of acute hematogenous bacterial osteomyelitis and/or septic arthritis or both, at Queen Sirikit National Institute of Child Health (QSNICH), between 1996 and 2006 were retrospectively reviewed. Acute hematogeneous osteomyelitis (AHO) and septic arthritis (SA) were defined by diagnostic criteria that included symptoms and signs of inflammation at affected bones or joints (swelling, local tenderness and limitation of motion) together with one or more of the other findings: pus aspirated from bones or joints and/or positive bacterial culture from blood, joint fluid, or other fluid at bone area from aspiration or surgical drainage, and/or typical radiographic findings (deep soft tissue swelling, periosteal reaction, bone destruction). The authors excluded AHO and SA resulted from penetrating injury and *Mycobacterial* infection.

The data collected from the patients who met the diagnostic criteria included: gender, age, history, and duration of presenting symptoms, underlying diseases and co-morbid conditions, clinical findings, laboratory and bacteriological findings, antibiotic therapy, surgical interventions and treatment outcomes.

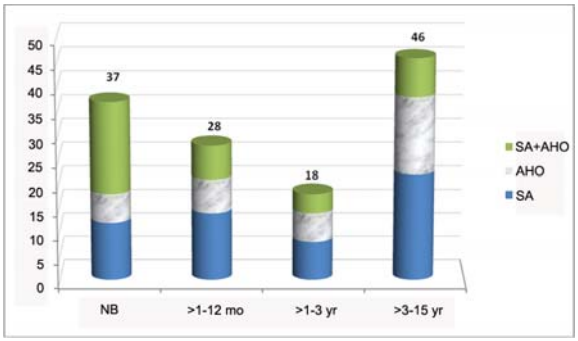
The authors classified patients into four age groups: newborn (1-30 days), infant (>1-12 months), toddler (>1-3 years) and school-age child and adolescent (>3-15 years). For clinical signs: fever was indicated by a body temperature of more than 37.5 degrees Celsius. Initial temperature on admission was defined as the highest temperature within the first 24 hours after hospitalization. As for laboratory findings: the upper normal limits for peripheral white blood cell count, Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) were 11 x 10^9/L, 10 mm/hr, 5 mg/L, respectively. Aspiration of joint or bone was usually done on the first day of consultation by orthopedists. Operative arthrotomy or surgical drainage would be performed if pus was seen after aspiration and in the case of no clinical improvement after administration of antibiotics. Empiric antibiotics were usually administered after specimen for bacterial culture was obtained. The appropriate antibiotics were generally given 3-4 days later when the culture results and susceptibility patterns became available. The duration between suspicious of osteoarticular infections during hospitalization and the time at which appropriate antibiotics were given usually represented the duration between empiric and appropriate antibiotic institutions, defined as duration before receiving appropriate antibiotics.

Osteoarticular sequelae were analyzed from patients who had been followed up for at least 2 years, since changing in the bone or joint structures from infective processes could be better identified. The statistical analysis used for comparison in the present study was relative risk and 95% confidence interval (CI) in univariate analysis and p-value of < 0.05 was considered statistically significant.

Results

One hundred and twenty-nine patients met the diagnostic criteria which consisted of 72 males and 57 females. The patient's age ranged between 1 day and 13 years 4 months. In terms of age group distribution, there were 37 (28.6%) newborn cases, 28 (21.7%) infants (>1-12 months), 18 (14%) toddlers (>1-3 years), 46 (35.7%) pre-school children, school-age children and adolescents (>3-15 years) (Fig. 1). There were 57 cases that were diagnosed with septic arthritis, 35 cases with acute osteomyelitis and 37 cases with both septic arthritis and acute osteomyelitis. The sites of infected bones and joints are shown in Table 1. The two most commonly infected bones were the tibia: 40 out of 92 (43.5%) and the femur: 31 out of 92 (34%). The two most commonly infected joints were the hip joint: 39 out of 98 (39.8%) and the knee joint: 35 out of 98 (35.7%). Multifocal sites of infections were demonstrated in 21 out of 37 cases (56.7%) in newborns, 7 out of 28 cases (25%) in infants, 4 out of 18 cases (22.2%) in toddlers, and 8 out of 46 (17.4%) in those 3 years or older.

The first complaint symptoms were pain or limitation of mobility in 119 out of 129 cases (92%) and fever in 93 out of 129 cases (72%). Twenty-seven patients (20.9%) reported falling or minor blunt trauma prior to the disease onset while 11 patients (8.5%), 9



NB = newborn, SA = Septic arthritis, AHO = Acute hematogenous osteomyelitis

Fig. 1 Diagnosis and age group distributions of pediatric osteoarticular infection (n = 129 cases)

Table 1. Distribution of joint and bone involvements

Involved joints or bones	n (%)
Joint (Total)	98 (100)
Hip	39 (39.8)
Knee	35 (35.7)
Ankle	10 (10.2)
Shoulder	9 (9.2)
Elbow	5 (5.1)
Bone (Total)	92 (100)
Tibia	40 (43.5)
Femur	31 (33.7)
Humerus	9 (9.8)
Radius/Ulna	4 (4.3)
Rib	2 (2.2)
Pelvis	2 (2.2)
Foot	2 (2.2)
Fibula	1 (1.1)
Vertebra	1 (1.1)

patients (7%) and 3 patients (2.3%) reported diarrhea, chronic skin infection, and otitis media respectively. In newborns, the co-morbid conditions included low birth weight (n = 16), prematurity (n = 14), gastroschisis (n = 8), respiratory distress syndrome (n = 6), pneumonitis (n = 5), infected umbilicus (n = 2) and esophageal atresia (n = 1). Sixty-eight patients had received antibiotics prior to hospitalization, mainly from drug stores or community health services.

The duration of presenting symptoms before hospitalization ranged from 1 day to 18 days (mean 7.5 days, median 7 day). Fever (more than 37.5 degrees Celsius) was identified in 78 out of 129 cases (60.46%) comprising 14 out of 37 (37.8%) newborns, 14 out of 28 (50%) infants and 50 out of 64 (78.1%) in the older group. Duration of fever during hospitalization ranged from 1 day to 42 days (mean 6.8 days) while 34 patients did not develop during hospitalization. Laboratory diagnosis revealed 85 out of 123 patients (69%) had a high peripheral white blood cell count, 83 out of 88 patients (94%) had a high ESR level and 40 out of 42 patients (95%) had a high CRP level. Appropriate antibiotics were administrated (intravenous and oral routes) in between 3 weeks and 8 weeks (mean 42 days).

Mean duration before receiving appropriate antibiotics was 2.4 days (range 1-13 days). Appropriate antibiotics were administrated (intravenous and oral route) in between 3 weeks and 8 weeks (mean 42 days). Surgical intervention with bone or joint aspiration was performed in 22 cases (17%) while operative arthrotomy or surgical drainage was performed in 80 cases (62%). Twenty-seven cases (21%) were treated with only appropriate antibiotics.

Bacterial culture yielded causative bacteria in 103 out of 129 cases (80%). Bacteria were found in 59 out of 94 cases (62.8%) from joint fluid culture, 36 out of 50 cases (72%) from bone culture and 40 out of 99 cases (40.4%) from blood culture. The most common causative bacteria was methicillin-sensitive *Staphylococcus aureus* (MSSA) which was found in 48 out of 103 cases (46.6%) followed by methicillin-resistant *Staphylococcus aureus (*MRSA) in 18 out of 103 cases (17.5%), *Streptococcus group A*, *Streptococcus pneumoniae*, *Enterobacter*, and *Salmonella* species in 5 out of 103 cases in each pathogen, and *Hemophillus influenzae* in 4 out of 103 cases etc. (Table. 2). All patients were improved after treatment and no fatality case from condition related to AHO or SA was reported.

Seventy-nine out of 129 patients (61%) had more than 2 years of follow-up, ranging from 2 years to 9 years and 2 months (mean 4 years and 6 months). Osteoarticular sequelae were observed in 23 out of 79 patients (29%) including 11 cases (14%) of avascular necrosis of epiphysis (10 cases, type I B and II A, deformed femoral head of Choi's classification of sequelae and one case with deformed humeral head); 9 cases (11.4%) of limb-length discrepancy or angular deformity that usually presented in less than 3 cm of limb undergrowth or overgrowth; and 3 cases (3.8%) with osteomyelitis who had pathological fractures consisting of 2 cases of femoral fracture from fall accident and one case of partially collapsed vertebra

without neurological deficit (Table 3). The percentage of newborn patients among those with sequelae was 60.9% (14 out of 23) whereas the percentage among those without sequelae was 21.4% (12 out of 56) (Table 3).

The potential risk factors were compared between patients with sequelae and without sequelae as shown in Table 4. Factors significantly associated with developing osteoarticular sequelae by univariate analysis were duration of presenting symptoms for more than 1 week; duration before receiving appropriate antibiotics for more than 3 days; involvement of the hip joint; MRSA infection; and infection occurring in newborns. High body temperature on admission day; positive blood culture; or high peripheral white blood cell count was not associated with poor outcome (Table 4).

Discussion

According to the present study, pediatric osteoarticular infections occurred in all age groups. One half of the patients, however, were less than one year of age. This age group distribution pattern is rather comparable with a report from Japan[13], but rather differs from the one from Switzerland[14]. Newborn was the most common age group which accounted for 28.6% of all cases and 0.28% of all newborn cases hospitalized during the study period. Neonates are generally vulnerable to this type of infection due to multiple factors, including an immature immune system, transphyseal blood vessels connection between metaphysis and epiphysis and multiple procedures may be required for their underlying conditions. In the present study a substantial proportion of neonates had co-morbidity including prematurity, low birth weight, visceral organ defects and other concomitant infections.

The hip and knee were the two most common joints that accounted for 75% of all infected joints, while the tibia and femur were the two most commonly infected bones (77.5%). Multifocal bone or joint involvements were observed in more than one-half of newborn cases, followed by approximately one-fourth of infants and toddlers and lower percentage in older children. Awareness of the possibility of multiple sites of osteoarticular infection that may appear later in the course of illness, especially among in the newborn cases, is essential in clinical assessment.

The duration of presenting symptoms before hospitalization ranged from 1 day to 18 days (mean 7.5 days, median 7 day). This duration was comparable to a report by Chang et al[15]. The initial body temperature on admission day was higher than 37.5 degrees Celsius in 61% of the patients, approximately one-third of newborns, one-half of infants, and more than three-

Table 2. Spectrum of causative bacterial pathogens related to age groups

Bacterial pathogens	n (%)	Newborn n (%)	>1-12 months n (%)	>13-36 months n (%)	>37-168 months n (%)
Methicillin-sensitive *S. aureus*	48 (46.6)	8 (24.2)	6 (31.6)	9 (56.2)	25 (71.4)
Methicillin-resistant *S. aureus*	18 (17.5)	17 (51.5)	1 (5.3)	-	-
Streptococcus grA	5 (4.9)	-	-	1 (6.25)	4 (11.4)
Streptococcus pneumoniae	5 (4.9)	-	4 (21.1)	-	1 (2.85)
Enterobacter species	5 (4.9)	3 (9.1)	1 (5.25)	-	1 (2.85)
Salmonella species	5 (4.9)	-	4 (21.1)	1 (6.25)	-
Hemophilus influenzae	4 (3.9)	-	-	4 (25)	-
Escherichea coli	3 (2.9)	2 (6.1)	1 (5.25)	-	-
Streptococcus grB	2 (1.9)	1 (3.03)	1 (5.25)	-	-
Staphylococcus coagulase neg	2 (1.9)	-	-	1 (6.25)	1 (2.85)
Streptococcus viridans	1 (0.97)	-	-	-	1 (2.85)
Pseudomonas aerugenosa	1 (0.97)	-	-	-	1 (2.85)
Klebsiella pneumoniae	1 (0.97)	1 (3.03)	-	-	-
Acinetobactor species	1 (0.97)	-	-	-	1 (2.85)
Neisseria species	1 (0.97)	-	1 (5.25)	-	-
Pastuerella multocida	1 (0.97)	1 (3.03)	-	-	-
Total	103 (100)	33 (100)	19 (100)	16 (100)	35 (100)

Table 3. Bacterial pathogens in 79 patients with more than 2 years of follow-up

Causative bacteria	Sequelae: n = 23			No sequelae: n = 56
	Pathologic fx n (newborn)	LLD or AD n (newborn)	AVN + LLD n (newborn)	n (newborn)
MSSA	3 (0)	5 (3)	1 (0)	20 (4)
MRSA	0	3 (3)	5 (5)	4 (3)
Salmonella species	0	0	2 (0)	2 (0)
Streptococcus group A,B	0	0	2 (1)	3 (0)
Other bacteria	0	0	0	14 (3)
Culture negative	0	1 (1)	1 (1)	13 (2)

LLD = limb-length discrepancy, AD = angular deformity of limb, AVN = avascular necrosis of epiphysis, fx = fracture

Table 4. Potential risk factors of osteoarticular sequelae

Risks	Sequelae n	No sequelae n	Univariate analysis RR (95% CI)	p-value
Age: Newborn	13	13	3.38 (1.12-10.16)	<0.05
Age: >1-12 month	2	16	0.42 (0.08-2.24)	NS*
Hip joint	12	13	6.46 (1.53-27.32)	<0.05
Shoulder joint	1	5	1.40 (0.12-16.46)	NS*
MSSA	9	20	2.03 (0.53-7.73)	NS*
MRSA	8	4	9.00 (1.79-45.34)	<0.01
Duration of presenting symptoms >1 week	17	17	6.50 (2.18-19.36)	<0.01
Duration before receiving appropriate antibiotics > 3 days**	10	6	5.00 (1.48-16.95)	<0.05
Temperature on admission day > 37.5°C	10	37	0.41 (0.15-1.11)	NS*
WBC on admission day > 11,000 x 10^6/L	16	34	2.47 (0.73-8.40)	NS*
Positive blood culture	9	21	1.79 (0.55-5.84)	NS*

NS* = not significant
** Count after hospitalization and suspicious of AHO or SA

quarters in older age group, represented that fever sign of systemic infection would not be obviously shown in newborns and infants compared to older children. In addition, approximately a quarter of the presented patients did not have fever during hospitalization.

Causative bacterial organisms were identified in 80% of cases from blood, bone and joint specimens. The rate of positive bacterial identification from joint fluid, bone tissue/fluid, and blood were 62.8%, 72%, and 40.4% respectively. MSSA was the most common pathogen in all age groups, except in the newborn. MRSA was the second most common pathogen and was the most common in neonates where it was present in all but one infant. In contrast to older children, various causative bacteria were found in less than 1 year of age patients. Thus empiric antibiotics should be considered initially and physicians then should attempt to identify causative pathogen in the newborn and infants with osteoarticular infection. The proportion of *Hemophilus influenzae* osteoarticular infection was identified only in 3.9% of toddlers. This finding is in agreement with several reports[14,16]. The authors are not certain whether this could be influenced by the availability of *Hemophilus influenza*e type B vaccination, since this vaccine has not yet been introduced into the Thai National Immunization Program.

Data for more than 2 years follow-up were available in 61% of all study subjects. Osteoarticular

sequelae were identified in 29% of the follow-up cases which was comparable to a previous report[13].

The authors found that the potential risk factors significantly associated with osteoarticular sequelae ($p < 0.01$ and $p < 0.05$ respectively) in the patients with long duration of presenting symptoms before diagnosis for more than 1 week and with delay in receiving appropriate antibiotics administration after suspicion of osteoarticular infection for more than 3 days. Arnold et al reported the patients with MRSA infection were less likely to receive appropriate empirical antimicrobial therapy at the time of admission compared to those infected with MSSA[8]. Yamagishi et al suggested the use of antimicrobial agents against MRSA in the initial empirical treatment of SA and AHO[13]. Given the existing evidence and the present study result indicating that MRSA osteoarticular infection appears to be associated with poor outcome, the authors strongly suggested antimicrobial agent with the coverage against MRSA be included in the empirical antimicrobial regimen for this condition especially among neonates.

Newborn age group, hip joint involvement, and MRSA as a causative pathogen were also identified as significant prognostic factors of unfavorable outcome based on univariate analysis. These findings are consistent with existing reports[5,13]. Those with these identifiable prognostic factors should receive particular attention and timely intervention to minimize their long-term sequelae.

Conclusion

In the present study, *Staphylococcus aureus* was the most common causative bacteria of pediatric osteoarticular infection, comprising MSSA the most common in all ages but was second to MRSA in the newborn group. The outcome sequelae were limb-length discrepancy, angular deformity, avascular necrosis of epiphysis and pathologic fracture. Prognostic factors of this condition included long duration of presenting symptoms and delayed treatment with appropriate antibiotics, infection with MRSA, hip joint involvement and infection occurring during neonatal period.

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Potential conflicts of interest

None.

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โรคติดเชื้อจากทางกระแสเลือดของกระดูกและข้อในเด็ก: การศึกษาลักษณะทางคลินิกและผลลัพธ์

พิศิษฐ์ สุกไสว, ดุล โกวิทวณิชชา, วีระศักดิ์ ธรรมคุณานนท์, ทวี โชติพิทยสุนนท์, วราภรณ์ แสงทวีสิน, ยงยส จีระธัญญาสกุล

วัตถุประสงค์: *เพื่อประเมินลักษณะทางคลินิกเชื้อแบคทีเรียที่เป็นสาเหตุ และผลลัพธ์ของการรักษาโรคติดเชื้อจากทางกระแสเลือดของกระดูกและข้อในเด็ก*

วัสดุและวิธีการ: *ทำการศึกษาย้อนหลังและติดตามผลการรักษาผู้ป่วยเด็กอายุน้อยกว่า 15 ปีที่วินิจฉัยเป็นโรคติดเชื้อผ่านทางกระแสเลือดของกระดูกและข้อ และได้รับการรักษาที่สถาบันสุขภาพเด็กแห่งชาติมหาราชินีในระหว่างปี พ.ศ. 2539-2549 โดยรวบรวมข้อมูลทั่วไป ลักษณะทางคลินิก เชื้อแบคทีเรียสาเหตุ และวิเคราะห์ปัจจัยเสี่ยงที่อาจมีผลต่อการเกิดข้อแทรกซ้อนของกระดูกและข้อในผู้ป่วยที่ติดตามการรักษาได้อย่างน้อย 2 ปี*

ผลการศึกษา: *ผู้ป่วยเด็กจำนวน 129 ราย ผ่านการตรวจสอบคุณสมบัติเป็นโรคติดเชื้อของกระดูกและข้อ มีอายุระหว่างแรกเกิดถึง 13 ปี 4 เดือน แบ่งกลุ่มได้เป็นทารกแรกเกิดอายุ 30 วันแรกจำนวน 37 ราย อายุระหว่าง 1-12 เดือนจำนวน 28 ราย อายุระหว่าง 1-3 ปี จำนวน 18 ราย อายุระหว่าง 3-15 ปีจำนวน 46 ราย การตรวจเชื้อพบเชื้อแบคทีเรียสาเหตุในผู้ป่วยจำนวน 103 ราย (ร้อยละ 80) โดยเชื้อที่พบมากที่สุดคือ Staphylococcus aureus ชนิดที่ตอบสนองดีต่อยา methicillin (MSSA) จำนวน ร้อยละ 46.6 รองลงไปคือ Staphylococcus aureus ที่ดื้อต่อยา methicillin (MRSA) จำนวนร้อยละ 17.5 ในวันแรกรับพบมีเพียงหนึ่งในสามของผู้ป่วยวัยทารกแรกเกิด และครึ่งหนึ่งของเด็กอายุน้อยกว่า 1 ปี ที่มีไข้อุณหภูมิร่างกายสูงกว่า 37.5 องศาเซลเซียส ระยะเวลาที่ผู้ป่วยได้รับยาปฏิชีวนะมีพิสัยระหว่าง 21-56 วัน (เฉลี่ย 42 วัน) หัตถการที่ทำโดยการผ่าตัดหรือการเจาะข้อ มีร้อยละ 62 และ 17 ตามลำดับ ผู้ป่วยที่ติดตามการรักษาได้นานกว่า 2 ปี มีจำนวน 79 ราย ในจำนวนนี้มีผู้ป่วย 23 ราย ที่พบข้อแทรกซ้อนของกระดูกและข้อตามมาประกอบด้วย หัวกระดูกขาดเลือดเลี้ยง แขนขาสั้นยาวผิดปกติ และกระดูกหักจากโรค การวิเคราะห์ทางสถิติแบบ univariate พบว่าความผิดปกติเหล่านี้เกี่ยวข้องอย่างมีนัยสำคัญกับปัจจัยต่างๆดังนี้คือ ระยะเวลาตั้งแต่เริ่มมีอาการโรคจนเข้ารับการรักษาที่นานกว่า 1 สัปดาห์, ระยะเวลารอคอยให้ยาปฏิชีวนะที่เหมาะสมกับเชื้อที่นานกว่า 3 วัน, การติดเชื้อในเด็กทารกแรกเกิด, การติดเชื้อที่ข้อสะโพก และในผู้ป่วยที่ติดเชื้อ MRSA*

สรุป: *MSSA เป็นเชื้อสาเหตุที่พบมากที่สุดในทุกกลุ่มอายุ ยกเว้นในทารกแรกเกิดที่ MRSA เป็นเชื้อที่พบได้มากที่สุด ความผิดปกติหลังการรักษาที่พบคือ การขาดเลือดเลี้ยงของหัวข้อกระดูก แขน/ขาสั้นยาวกว่าข้างปกติ และกระดูกหักจากโรคความผิดปกติเหล่านี้เกี่ยวข้องอย่างมีนัยสำคัญทางสถิติกับ ระยะเวลาที่เริ่มมีอาการจนเข้ารับการรักษาที่ล่าช้า, ระยะเวลาได้รับยาปฏิชีวนะที่เหมาะสมล่าช้า, การติดเชื้อในทารกแรกเกิด, การติดเชื้อที่ข้อสะโพก และ MRSA เป็นเชื้อสาเหตุ*