

Original Article

Pediatric deep venous thrombosis associated with *Staphylococcus aureus* osteomyelitisLinlin Liu¹, Lingyun Guo¹, Zhuangzhuang Wang¹, Qiang Wang², Jinjin Zeng³, Tianming Chen¹, Gang Liu¹¹ Key Laboratory of Major Diseases in Children, Ministry of Education, Department of Infectious Diseases, Beijing Children's Hospital, Capital Medical University, National Center for Children's Health, Beijing, China² Key Laboratory of Major Diseases in Children, Ministry of Education, Department of Orthopedics, Beijing Children's Hospital, Capital Medical University, National Center for Children's Health, Beijing, China³ Key Laboratory of Major Diseases in Children, Ministry of Education, Department of Radiology, Beijing Children's Hospital, Capital Medical University, National Center for Children's Health, Beijing, China**Abstract**

Introduction: Our objective was to evaluate clinical features of children with deep venous thrombosis (DVT) and acute hematogenous osteomyelitis (AHO) caused by *Staphylococcus aureus*.

Methodology: We analyzed 4 years of medical records of patients with AHO and DVT caused by *Staphylococcus aureus* (*S. aureus*) and compared clinical and biochemical characteristics of AHO with and without DVT, as well as patients whose DVT dissolved in ≥ 3 weeks.

Results: DVT was found in 19/87 AHO individuals (22%). The median age was 9 years (range: 0.5-15 years). 74% (14/19) patients were boys. Methicillin-susceptible *Staphylococcus aureus* (MSSA) was present in 58% (11/19) cases. The femoral vein and common femoral vein were the two most damaged veins (9 cases each). Anticoagulation therapy with low molecular weight heparin was given to 18 (95%) patients. Within 3 weeks of anticoagulation, 7/13 (54%) with available data had completely resolved DVT. There was no rehospitalization due to bleeding or recurrent DVT. Patients with DVT were found to be older and had increased levels of C-reactive protein, procalcitonin, D-dimer, positive blood culture, incidence of intensive care unit admission, multifocal rate, and length of hospital stay. We did not find clinical difference between patients whose DVT dissolved within 3 weeks and those with > 3 weeks.

Conclusions: Over 20% of patients with *S. aureus* AHO developed DVT. MSSA accounted for more than half of the cases. DVT was completely resolved in more than half of the cases after 3 weeks of anticoagulant medication, with no sequelae.

Key words: thrombosis; osteomyelitis; *Staphylococcus aureus*, children.

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Introduction

Deep venous thrombosis (DVT) in children is rare but may lead serious conditions and 5.3 out of 10,000 affected children are hospitalized [1]. Inflammatory mediators contribute to activated blood coagulation; hence infection is a known risk factor during the development of DVT. One of the most serious acute consequences of osteomyelitis is DVT. *Staphylococcus aureus* (*S. aureus*) is the most common cause of osteomyelitis and its virulence factors are important in DVT pathophysiology. DVT is increasingly recognized in various studies [2,3] as an essential acute consequence of staphylococcal osteomyelitis that can result in a longer hospital stay and serious pulmonary problems. In this study, we reviewed our institutional experience by looking into the occurrence of DVT in children with *S. aureus* osteomyelitis and evaluated their characteristics.

Methodology*Study design and patients*

The medical records of children (≤ 18 years) with acute hematogenous osteomyelitis (AHO) caused by *S. aureus* from discharge diagnoses between January 1, 2017 and December 31, 2020 were retrospectively reviewed. The patients and/or their families were informed that data from the case would be submitted for publication, and gave their consent. A case of AHO caused by *S. aureus* was defined as disease compatible with acute osteomyelitis (duration of symptoms less than 2 weeks), in which *S. aureus* was cultured from blood or subperiosteal collection. Cases of infection due to contiguity or secondary to direct inoculation were excluded [4]. Compression and color Doppler ultrasound were performed on the veins of lower and

upper extremities. DVT appeared as filling defects on ultrasound.

Multiple data fields were recorded, including age, sex, risk factors, symptoms at presentation, infection-site, DVT site, methicillin-susceptible *Staphylococcus aureus* (MSSA) / methicillin-resistant *Staphylococcus aureus* (MRSA), intensive care unit (ICU) admission, tracheal intubation, surgery, and anticoagulation treatment. Laboratory findings included white blood cell (WBC), platelet, mean platelet volume (MPV), C-reactive protein (CRP), procalcitonin (PCT), erythrocyte sedimentation rate (ESR), D-dimer, fibrinogen, and antithrombin III. We compared clinical and laboratory characteristics of AHO with and without DVT, as well as those AHO whose DVT dissolved within 3 weeks to those of six patients whose DVT took longer to dissolve.

Statistical Analysis

The means were compared by the Mann-Whitney U test and percentages by Fisher's exact test. The significance threshold was set at $p \leq 0.05$. Data were analyzed with the SPSS Inc. Released 2007. SPSS for Windows, Version 16.0. Chicago, SPSS Inc.

This research was approved by the Institutional Review Board of the authors' affiliated institutions.

Ethical Approval

The study was approved by the Ethics Committee of Beijing Children's Hospital affiliated to Capital Medical University (No.[2021]-E-088-R).

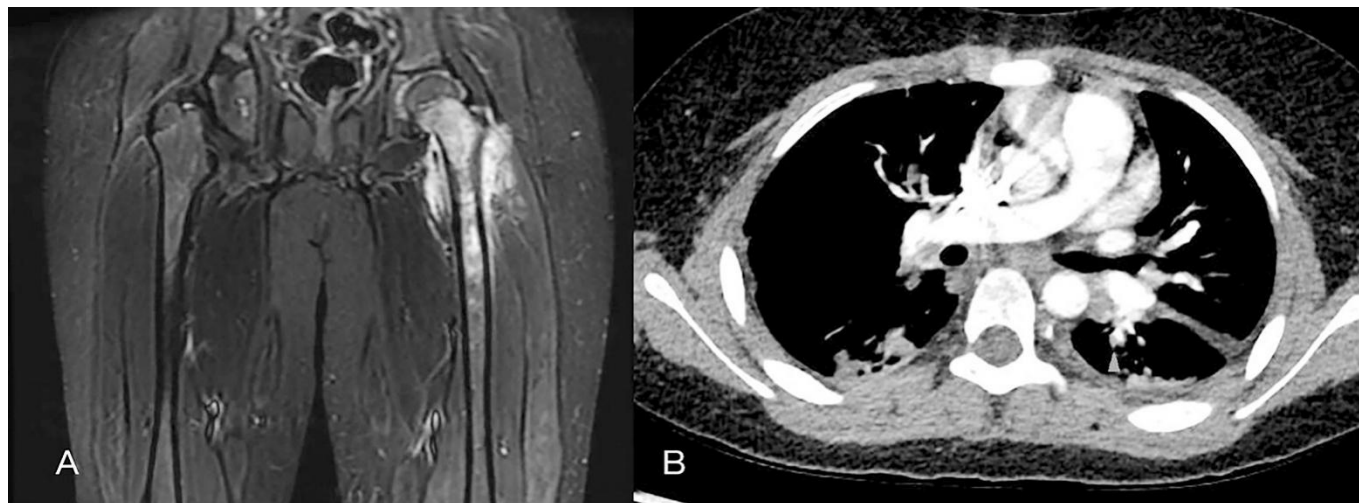
Results

During the course of 4 years, 87 patients were hospitalized with AHO that was proven to be caused by *S. aureus*. The mean age was 5 years (range: 8 days to 15 years). 56% (49/87) were boys. Femur (56%) was the most common infection site. MSSA was found in 55 cases (63%) while MRSA was found in 29 cases (33%). Antibiotic resistance in the three cases infected with *S. aureus* was unknown because data was unavailable.

DVT were detected in 19 patients (22%) by ultrasound. 74% (14/19) patients were male. The median age at the time of diagnosis was 9 years (range: 6 months to 15 years). All of the patients were previously healthy with no underlying chronic illness, immunodeficiency or other risk factors for DVT. None of the patients in this study reported previous thrombophilia or family history of thrombosis. All of the cases were community acquired (CA). MRSA accounted for 42% (8/19), MSSA accounted for 58% (11/19). 90% of the patients (17/19) had a positive blood culture. Thirteen patients had a positive culture of subperiosteal collection.

All the venous thrombus formed adjacent to the infection sites. A total of 36 different sites of veins were involved in the 19 patients. The most commonly affected veins were the femoral vein ($n = 9$) and common femoral vein ($n = 9$), followed by the popliteal vein ($n = 5$), common iliac vein ($n = 4$), external iliac vein ($n = 3$), posterior tibial vein ($n = 2$), great saphenous vein ($n = 2$), brachial vein ($n = 1$), and deep femoral vein ($n = 1$). Eleven patients (55%, 11/19) were found to have conclusive evidence of DVT. Mean time from symptom onset to DVT diagnosis was 7 days (quartile range, 5-10). All the patients had swelling and bone pain causing functional impairment. In four of the

Figure 1. MRI image A: showing extensive abnormal signals in the left femur, and abnormal signals in the surrounding soft tissue; B: Chest CT image showing septic emboli (triangle).



nine cases where a chest computerized tomography (CT) was performed, pulmonary embolism was discovered (Figure 1). None of the patients reported having thrombosis related to central venous catheters.

In total 20 bone sites in 19 patients were infected with AHO and DVT. The femur (65%, 13/20) was the most common site (Figure 1), followed by the tibia (15%, 3/20), and hip, fibula, humerus, and vertebrae (5%, 1/20, each). Magnetic Resonance Imaging (MRI) indicated that nine of the twenty patients (45%) had contiguous pyomyositis/myositis. Pneumonia was found in 70% of the 19 cases of DVT (14/19). Patient number 17 had endocarditis, meningitis, paravertebral abscess and intraspinal abscess, and vertebrae osteomyelitis. The majority of the patients (15/19) underwent surgery. Six children (30%) with DVT and AHO were admitted to the ICU, with two requiring trachea intubations.

Eighteen (95%) patients received anticoagulation therapy with low molecular weight heparin (LMWH). The duration of anticoagulant treatment for DVT ranged from 1 week to 17 months. Seven out of thirteen children (54%) with available DVT resolution data as assessed by vascular ultrasound had complete DVT resolution within 3 weeks of anticoagulant treatment. Four of them experienced complete resolution in less than a week after receiving only 1-2 weeks of LMWH treatment. They did not experience any DVT recurrences. Five cases (39%, 5/13) received anticoagulant therapy for more than 3 months, ranging from 3 to 17 months. We compared age, inflammatory marker, bacteremia rate, MRSA rate and ICU admission rate in 7 patients whose DVT resolved in 3

weeks to 6 patients whose DVT resolved beyond 3 weeks and found no difference. In one patient with DVT flutter, inferior vena cava (IVC) filters were placed to prevent pulmonary embolism. When the DVT disappeared after two weeks of treatment, the filter was removed.

None of the 19 patients died. One patient had post-thrombotic syndrome of localized skin thickening. There was no requirement for the patient to be readmitted due to bleeding or recurrent DVT.

Table 1 summarizes a comparison of various clinical and biochemical data for AHO patients with and without DVT. Comparative analysis showed that patients with DVT were older (9 vs. 4 years old, $p = 0.005$). Patients with DVT had higher CRP, PCT and lower platelet count ($p \leq 0.001$). D-dimer, fibrinogen, rate of admission to ICU, positive blood culture, and multifocal infection were higher in DVT patients ($p < 0.05$). In addition, patients with DVT had longer stays in the hospital (33.5 v. 14.2 days, $p = 0.033$).

Discussion

The association between DVT and osteomyelitis has long been known. According to studies, DVT occurs at a rate of 5% to 30% in patients with osteomyelitis, regardless of pathogen [1,3,5]. We found that 23% AHO patients with proven *S. aureus* infection had DVT. *S. aureus* is the most common pathogen causing osteomyelitis, and *S. aureus* infection is another risk factor for DVT [6]. Our cases were all culture positive. A culture positive case may indicate a more serious sickness, and the severity of the illness is linked to the occurrence of DVT [7]. MRSA was shown

Table 1. Comparison of patients with and without DVT.

	DVT (n = 19)	No DVT (n = 68)	p value
	Median values		
Age (years)	9	4	0.005*
Male (%)	74%	52%	0.117
Length of hospital stay (days)	20	15	0.033*
MRSA (%)	42%	32%	0.428
Positive blood culture (%)	89%	63%	0.047*
Multifocal (%)	74%	21%	0.000*
WBC ($10^3/\text{mm}^3$)	15.26	12.00	0.221
CRP (mg/dL)	200	55	0.000*
PCT (ng/mL)	9.89	0.54	0.001*
ESR (mm/h)	48	40	0.168
Platelet count ($10^3/\text{mm}^3$)	124	322	0.000*
MPV (fl)	10.7	9.5	0.001*
Fibrinogen ($\mu\text{g}/\text{mL}$)	5.81	4.58	0.027*
D-dimer	2.02	1.161	0.010*
AT3	92.0	98.7	0.260
ICU (%)	26%	4%	0.011*
Surgery (%)	74%	74%	1.000

*: $p < 0.5$; MRSA: methicillin-resistant *Staphylococcus aureus*; MPV: mean platelet volume; ICU: Intensive Care Unit; DVT: Deep venous thrombosis; WBC: white blood cell; CRP: C-reactive protein; PCT: procalcitonin, ESR: erythrocyte sedimentation rate.

to be more common in children who developed DVT than in children who did not develop DVT of pediatric osteomyelitis (42.9% vs. 4.7%, 72.7% vs. 24.4%, 89.3% vs. 21.2%) [2,5,7]. MRSA poses a severe threat to global health. It is frequently linked to significant morbidity, length of stay, and economic burden. The prevalence of MRSA differs by region. The rising incidence of MRSA osteomyelitis in USA has been reported in recent years [8]. At Texas Children's Hospital, CA-MRSA is responsible for more than 75% of infections [9]. In China, MRSA proportions have decreased significantly from 69% in 2005 to 30.2% in 2019 [10]. Blanca *et al.* investigated the molecular characterization of *S. aureus* from 9 patients with AHO and new onset DVT at Texas Children's Hospital [9]. Seven of the patients were infected with MRSA from the same clonal group (USA300) and all MRSA isolates carried the Panton-Valentine Leukocidin (PVL) genes. In the present study, both MRSA and MSSA infections accounted for a significant share of the cases. MSSA infection was found in 58% of AHO with DVT. MSSA also accounted for 65% of all AHO patients. We recommend more research to explore the molecular characteristics of *S. aureus* from AHO and DVT in China and other countries. DVT caused by MSSA infection should also be given more attention. Banani *et al.* reported that four consecutive children with *S. aureus* infection and DVT admitted to an ICU in India were all infected with MSSA [11]. It is also worth noting that some researchers have documented PVL carriage among MSSA in some regions [12].

The incidence of thrombosis in children follows a bimodal distribution, with the highest peak occurring in infants under the age of 1 month and the second peak occurring throughout adolescence [13]. The median age of diagnosis of DVT and staphylococcal osteomyelitis in our study was 9 years, and included 1 infant (5%, 1/19) and 5 teenagers (25%, 5/19). In line with earlier studies [6], our current findings revealed that children who were affected by DVT were older.

Suspected DVT can be diagnosed using several methods. We used compression and color ultrasound to confirm and rule out probable symptomatic DVT. Contrast venography is classically the gold standard to diagnose DVT. However, it is intrusive and expensive. CT and MRI also share some same limitations of venography. Doppler ultrasound, according to several articles, is a good choice that is both readily available and dependable in both the lower and upper extremities [14,15]. D-dimer levels were found to have poor discriminative and predictive power for DVT in one study [16]. However, due of its high diagnostic

sensitivity but limited specificity, a normal D-dimer is more beneficial in excluding DVT in children [17].

Several studies reported that patients with positive bacteremia and increased inflammation markers were linked to high risk factors of DVT [2,6,7]. This is supported by our findings. Multifocal infections were more common in children with AHO and DVT than in children without DVT [7]. As a result, it is hypothesized that some patients will develop disseminated *S. aureus* infections as a result of DVT acting as a source of septic thromboembolism. Prolonged antimicrobial therapy is proposed in cases where this problem occurs, with at least six weeks of intravenous medication followed by oral therapy until the thrombus disappears [3].

Pediatric DVT is a developing concern with few guidelines to steer treatment. In the majority of cases, pediatricians consult adult guidelines. Our patients were more likely to undergo thrombolytic treatment. In theory, earlier thrombolytic therapy could aid in symptom relief, pulmonary embolism prevention, and reestablishment of normal venous circulation. Common anticoagulation with LMWH, unfractionated heparin, and tissue plasminogen activator are common in pediatrics [18]. In the present study, patients were initially given LMWH. According to research in adults, LMWH has a more predictable dose response and requires less monitoring. In the case of provoked DVT in children where the principal provoking factor is no longer present, anticoagulation is generally recommended to be continued for 6 weeks to 3 months depending on characteristics of the DVT in children [19]. We found an early resolution of DVT in roughly 20% (4/19) of the patients after one week of LMWH treatment without recurrence, which is consistent with prior findings that showed that 25% of patients had thrombus dissolve within 7 to 10 days [20]. On the contrary, some studies suggest that anticoagulation therapy is not associated with better venous thromboembolism outcomes in pediatric trauma patients [21]. Prospective studies are needed to determine the duration of anticoagulation. One study compared DVT with or without AHO patients; children with DVT caused by osteomyelitis differ from children with DVT caused by other factors by the absence of comorbidities or post-thrombotic syndrome (PTS) [7]. Post-thrombotic syndrome is a clinical constellation of pain, swelling, visible collateral vein formation, and skin abnormalities ranging from hyperpigmentation and induration to stasis ulcers. In addition, just one PTS was observed among AHO patients in our study. Patients with AHO and DVT had an overall good outcome. There was no difference in age, inflammatory marker,

bacteremia rate, MRSA rate or ICU admission rate between patients whose DVT resolved in ≤ 3 weeks versus those that resolved in longer time.

Conclusions

We documented 19 cases of DVT associated with AHO caused by *S. aureus* in a Chinese pediatric population. DVT developed in more than 20% of AHO patients. The majority of DVT sites were in the lower extremity and all venous thrombus formed adjacent to the infection site. MSSA infection was found in more than half of the DVT patients. Patients with DVT had a higher level of inflammation marker, a higher likelihood of ICU admission, and a longer hospital stay. More than half of patients achieved DVT resolution in 3 weeks or less, and the 4 patients who had DVT clearance in 1 week underwent only 1-2 weeks of LMWH treatment and had no DVT recurrence.

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Authors' Contributions

All authors had access to the full dataset and take responsibility for the integrity of the data and the accuracy of the data analysis. LLL, GLY and LG conceived and designed the study. LLL, WZZ collected the data and designed the analysis. LG, LLL, GLY and ZJJ interpreted the data. LLL and GLY wrote the first draft of the paper. LG, GLY, CTM, WQ and LLL reviewed and approved the final report. The manuscript has been read and approved by all the authors. The requirements for authorship as stated earlier in this document have been met, and each author believes that the manuscript represents honest work, and that information is not provided in another form.

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