When should DVT be suspected in children with osteomyelitis?

abstract

BACKGROUND: There is increasing recognition that deep venous thrombosis (DVT) is a complicating factor in some children with acute hematogenous osteomyelitis. The similarity in signs and symptoms of osteomyelitis and DVT make clinical recognition of this complicating condition difficult. It would be helpful to the clinician to identify by other means which children with osteomyelitis are at greatest risk for DVT.

We reviewed the available literature regarding osteomyelitis and DVT in children to identify potential characteristics of children with osteomyelitis that puts them at risk for concurrent DVT.

METHODS: We performed searches of the PubMed, Cochrane, CINAHL, and National Guideline Clearinghouse databases on the topic of osteomyelitis and thrombosis in children 0 to 18 years of age from 2001 to the present.

RESULTS: Four studies were included: 3 retrospective and 1 prospective. Studies varied in terms of clinical, laboratory, and imaging parameters evaluated. Overall they suggest trends toward increased incidence of DVT in children who were critically ill at presentation, had positive blood cultures, were infected with methicillin-resistant Staphylococcus aureus, had an elevated C-reactive protein, and had central venous catheters placed.

CONCLUSIONS: Strong consideration should be given to evaluating children with osteomyelitis for DVT if they are critically ill at presentation, particularly if they have pulmonary findings, are persistently bacteremic, especially with methicillin-resistant S aureus.
is believed that these children are at increased risk of disseminated infection, septic pulmonary emboli, respiratory failure, and other serious complications. It is, therefore, in the clinician’s interest to promptly identify those patients with osteomyelitis most at risk for DVT, so that therapy may be initiated when warranted and dangerous sequelae avoided. Our review sought to answer the question of when to suspect concurrent DVT in children with osteomyelitis.

METHODS
We performed searches of the PubMed, Cochrane, CINAHL, and National Guideline Clearinghouse databases by using the search terms osteomyelitis, bone infection, thrombosis, thrombus, DVT, and/or venous thrombosis. Inclusion criteria included English language studies published in the past 10 years. Case series with <5 patients were excluded, as were studies that evaluated the rate of DVT in patients with musculoskeletal infection, in general, where data from patients with osteomyelitis specifically was not available.

RESULTS
We included 4 studies in this review: 3 retrospective and 1 prospective. Table 1 provides the specific characteristics of the studies reviewed.

RETROSPECTIVE STUDIES
Gonzales et al retrospectively reviewed 180 patients from Houston, Texas, between 1999 and 2004 with acute S. aureus osteomyelitis; 9 (5%) were found to have concurrent venous thrombosis. One patient was identified before 2001, the remaining 8 after 2001. Of these 9 patients, 7 had MRSA, all of which were identified as belonging to the USA300 clonal group, the predominant community clone, and one that the same authors had previously identified as being particularly virulent. In addition, all of these 7 isolates carried the Panton-Valentine leukocidin (luk-S-PV and luk-F-PV) genes, also known to be associated with increased virulence. The remaining 2 infections were caused by methicillin-sensitive S. aureus (MSSA); the 1 isolate tested was Panton-Valentine leukocidin negative. All thromboses were adjacent to the site of infection, which included pyomyositis as well as osteomyelitis; 2 were also noted to be ipsilateral to the placement of a CVC. Most venous thromboses were diagnosed incidentally when imaging (MRI or computed tomography) was performed to evaluate for osteomyelitis; 1 was identified by Doppler ultrasound. Four patients developed septic pulmonary emboli, 1 developed bilateral airspace disease, and 1 developed pleural effusions. Three of the patients presented with chest radiographs suggestive of pulmonary emboli, rapidly requiring assisted ventilation and placement of intravascular filters. There were no deaths. Eight patients were evaluated for thrombotic disease: 3 patients had a positive lupus anticoagulant and 3 patients had low levels of proteins C and S; however, all of these findings normalized after resolution of the acute illness. Fibrinogen and D-dimer were elevated in 7 of 7 tested at presentation. All patients had positive blood cultures, for a mean duration of 5 days (range, 1–11).

Crary et al retrospectively reviewed 35 patients between 2003 and 2004 from Dallas, Texas, with osteomyelitis of the proximal upper and lower extremities, pelvis, and vertebra (a subgroup believed by the authors to be at highest risk of infection-related thrombosis because of the proximity to large veins). Seventeen patients with osteomyelitis of the ankle, foot, distal upper extremity, and cranium were excluded. Ten (29%) were found to have DVT. These patients were evaluated in detail and then compared with the group of patients with osteomyelitis without DVT. Seven patients had MRSA, 2 had MSSA, and 1 patient had a Candida tropicalis infection. Two of the thromboses were diagnosed 38 and 55 days after the diagnosis of osteomyelitis was made and were deemed to be CVC-related. Only 1 patient was clinically suspected of having a DVT (increasing leg swelling after admission) before confirmatory imaging; the rest were discovered incidentally on imaging done for diagnosis or follow-up of their infection. All patients had positive blood and wound cultures. Six patients had septic pulmonary emboli. There were no deaths. Only 7 of the 10 patients were evaluated for underlying thrombotic disease. One was a heterozygote for the Factor V Leiden mutation, 3 had elevated antiphospholipid antibody levels that normalized in 6 weeks, and 2 had elevated Factor VIII levels that resolved in 6 months. The authors compared the group of patients with osteomyelitis and DVT with the remaining 25 patients without DVT and found that there was no statistically significant difference in mean age, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), white blood cell (WBC) count, platelet count, or days to normal CRP, although there was a trend toward significant difference in CRP and days to normal CRP (mean CRP in DVT group, 22.6 mg/dL, vs 15.2 mg/dL in No DVT group, P = .06; mean days to normal CRP in DVT group, 52.9, vs 25.3 in No DVT group,
TABLE 1 Characteristics of the Studies Reviewed

<table>
<thead>
<tr>
<th>Study</th>
<th>Type</th>
<th>Inclusions</th>
<th>Exclusions</th>
<th>No. With DVT</th>
<th>Organisms</th>
<th>Clinical Findings</th>
<th>Blood Culture Positive</th>
<th>Mean CRP, mg/dL</th>
<th>Comparison with Patients Without DVT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gonzales8</td>
<td>Retrospective</td>
<td>180 patients with S aureus osteomyelitis</td>
<td>Not documented</td>
<td>9</td>
<td>7 MRSA, 2 MSSA</td>
<td>Septic pulmonary emboli (6), bilateral air space disease (1), pleural effusions (1)</td>
<td>9/9 (100%)</td>
<td>“elevated”</td>
<td>Not addressed</td>
</tr>
<tr>
<td>Crary11</td>
<td>Retrospective</td>
<td>35 patients with osteomyelitis of proximal upper &amp; lower extremities, pelvis, or vertebra</td>
<td>17 patients with excluded sites: ankle, foot, distal upper extremities, cranium</td>
<td>10</td>
<td>7 MRSA, 2 MSSA, 1 C tropicalis</td>
<td>Septic pulmonary emboli (6), 1 also had cerebral abscess and 1 also had endocarditis</td>
<td>10/10 (100%)</td>
<td>22.6</td>
<td>No difference in age, ESR, WBC, platelets; higher CRP values approached significant difference</td>
</tr>
<tr>
<td>Hollmig12</td>
<td>Retrospective</td>
<td>212 children with osteomyelitis of spine, pelvis, extremities</td>
<td>Not documented</td>
<td>11</td>
<td>8 MRSA, 3 MSSA</td>
<td>Septic pulmonary emboli (6), pleural effusions (1)</td>
<td>Not addressed</td>
<td>16.9</td>
<td>Older, shorter symptom duration before admission, higher temp, higher rates of S aureus infection</td>
</tr>
<tr>
<td>Bouchoucha13</td>
<td>Prospective</td>
<td>70 patients with osteomyelitis</td>
<td>Neonates, nosocomial, direct inoculation / infection</td>
<td>7</td>
<td>3 MRSA, 4 MSSA</td>
<td>Deteriorated health on admission (5), diffuse alveolar lesions (3)</td>
<td>6/7 (86%)</td>
<td>25.1</td>
<td>Higher ESR, higher blood culture positivity, more febrile days</td>
</tr>
</tbody>
</table>

* Findings listed are those for patients with DVT in comparison with those without DVT (when available).

There was a significant difference in the mean length of stay of patients with DVT: 33.5 vs 14.2 days ($P = .001$).

Expanding on the above work with a larger number of patients from the same institution, Hollmig et al12 performed a retrospective review of 212 children between 2002 and 2004 with osteomyelitis of the spine, pelvis, and extremities. Eleven (5%) were found to have DVT. Eight patients had MRSA and 3 had MSSA isolated. One patient had a DVT that was remote to the site of infection but near a CVC. And 1 patient had a DVT that was both adjacent to the site of infection and near the CVC. The remaining 9 patients all had thromboses adjacent to the site of infection. Six patients had pulmonary emboli, and 1 had bilateral pleural effusions. There were no deaths. Of the 9 patients tested for underlying thrombotic disease, 1 was found to be a heterozygote for the Factor V Leiden mutation, and 1 was found to be a heterozygote for the prothrombin 20210A mutation. The authors compared the group of children with and without DVT. At the time of presentation, children who developed DVT were older (mean age, 10.9 years vs 7.4 years, $P = .0065$), had a longer duration of symptoms (14.4 days vs 5.6 days, $P = .0007$), and had a higher mean body temperature (38.3°C vs 37.2°C, $P = .024$). They were also found to have a higher mean CRP (16.9 mg/dL vs 6.8 mg/dL, $P = .0044$). There was no significant difference between the groups in terms of WBC count or ESR. Seven (63%) of the 11 children with DVT were admitted to the ICU, versus 6 (3%) of the children with osteomyelitis without DVT. Children with DVT had a greater mean number of procedures per child than those without DVT, 2.6 vs 0.9 ($P = .0001$), and had a longer mean length of stay, 30.6 days vs 9.5 days ($P = .0004$).

PROSPECTIVE STUDY

Bouchoucha et al13 performed a descriptive prospective study evaluating...
children treated for acute hematogenous osteomyelitis at Tunis Children’s Hospital between 2007 and 2009. Doppler ultrasonography exploring for DVT was performed only in cases described as having “local clinical signs.” Neonates and patients with nosocomial or direct inoculation osteomyelitis were excluded. Of the 70 patients treated for acute hematogenous osteomyelitis, 7 (10%) were found to have DVT. It was unclear whether all 7 were found by Doppler ultrasonography done specifically to evaluate for DVT, or incidentally by other imaging performed to evaluate for osteomyelitis. Three of the patients had infection with MRSA, and 4 had infection with MSSA. All DVTs were adjacent or proximal to the site of infection; relationship to CVC was not addressed. Six patients had positive blood cultures. Five were described as having “deteriorated general health status” on admission and 3 went on to develop diffuse alveolar lesions and respiratory distress. There was 1 death. Predisposition to thrombotic disease was not addressed. The authors compared the group of patients with DVT with the remaining 63 patients without DVT. Patients with DVT had statistically significant higher mean CRP levels (25.1 mg/dL vs 10.9 mg/dL, \( P = .001 \)), ESR (84 mm/h vs 48 mm/h, \( P = .003 \)), and rate of blood culture positivity (86% vs 36.5%, \( P = .02 \)). Patients with DVT also had a higher mean number of febrile days (12 vs 3, \( P < .01 \)). Patients with DVT were more likely to have pulmonary infection (only 1 patient in the group without DVT had pulmonary infection, \( P = .002 \)), and to be infected with MRSA (only 3 cases of MRSA were isolated from the group without DVT, \( P = .04 \)). There was no statistically significant difference in age, gender ratio, temperature at presentation, WBC count, tissue culture positivity, or percentage of patients requiring surgical interventions.

**DISCUSSION**

The observation that most DVTs in the preceding studies were found incidentally on imaging done for other purposes suggests that most physicians have low or no suspicion for concurrent DVT in patients with osteomyelitis. Indeed, the overlap in clinical presentation of osteomyelitis and DVT (pain, erythema, and edema of the affected site) makes physical diagnosis challenging. Given the unreliability of physical examination for diagnosis of concurrent DVT in patients with osteomyelitis, identifying risk factors for DVT in this group of patients is of particular importance. These risk factors could help better direct diagnostic workup and imaging modality.

The limited evidence presented in this review suggests that children with osteomyelitis and DVT are at risk for a number of comorbidities, the most serious of which are septic pulmonary emboli, respiratory failure, and death. Early diagnosis of DVT may allow for initiation of therapy that may prevent such dangerous sequelae. Gonzales et al\(^8\) argue in their study that aggressive anticoagulant therapy should be considered in patients with MRSA and thrombosis, and certainly instituted once pulmonary emboli are identified. It is worth noting that none of the studies presented here evaluated the effectiveness of anticoagulation therapy on outcomes.

The literature reviewed here suggests a few trends that may help raise the suspicion for DVT in patients with osteomyelitis. Hollmig et al\(^12\) found that children with DVT tended to be older and have higher average body temperatures at presentation, although the prospective study by Bouchoucha et al\(^13\) found no difference. Hollmig also found that children with DVT had a longer mean duration of symptoms before diagnosis (14 days); these data were not examined elsewhere.

In all studies, the rate of blood culture positivity in children with osteomyelitis and DVT was high (86%–100%). These rates are higher than the most recently published rates of blood culture positivity in children with osteomyelitis (23%–52%).\(^14\)–\(^18\)

Of the 37 patients with osteomyelitis and DVT reviewed here, 36 (97%) had infection with \( S. aureus \). Of those with \( S. aureus \) infection, 25 (69%) had infection with MRSA. In the study by Gonzales et al\(^8\) 100% of the patients with MRSA were of the USA300 clone and carried the Panton-Valentine leukocidin (\( luk-S-PV \) and \( luk-F-PV \)) genes, genes which have previously been identified as conferring increased virulence.\(^5\)–\(^8\),\(^10\)

Three of the 4 studies reviewed here found that mean CRP levels were higher in children with DVT; however, mean values themselves varied between studies: mean CRP in the DVT groups ranged from 16.9 to 25.1 mg/dL, and mean CRP in the non-DVT groups ranged from 6.8 to 15.2 mg/dL. Bouchoucha et al\(^13\) found a significant difference in ESR between groups, but Cray et al\(^11\) and Hollmig et al\(^12\) did not. No study found a significant difference in WBC count.

Of the 23 patients evaluated for underlying thrombotic disorders, 3 were found to be heterozygotes for genetic mutations known to be prothrombotic; however, the clinical significance of
this is unclear. All other patients had normal findings or else had elevated prothrombotic factors that returned to normal once the acute illness resolved. Gonzales et al found that all 7 patients tested had elevated fibrinogen and D-dimer levels, raising the intriguing possibility of using these markers as a screening tool for DVT; however, no comparison was made with children with osteomyelitis without DVT, and unfortunately the only prospective study in this review did not address this issue. CVC use is a known independent risk factor for thrombosis. Two of the patients reviewed here were determined to have thrombosis related to their CVC, which occurred weeks after the diagnosis of osteomyelitis. An additional patient was suspected of having a CVC-related thrombosis as the thrombosis was distant to the site of infection but near the site of CVC placement.

Finally, children with osteomyelitis and DVT were generally found to be more critically ill than their counterparts without DVT. Of the 37 patients with DVT reviewed here, 19 presented with radiographic evidence of pulmonary disease (septic emboli or effusions), 17 required ICU admission, and at least 4 required mechanical ventilation. One patient died. The available comparison groups totaled 289 children with osteomyelitis without DVT. In this group, only 8 were identified as critically ill, requiring mechanical ventilation and/or ICU admission. Length of stay in children with DVT ranged from 30.6 to 33.5 days vs 9.5 to 14.2 days in children without DVT.

CONCLUSIONS/ RECOMMENDATIONS

• Clinicians should have a heightened suspicion for DVT in children with osteomyelitis who present with the following risk factors:
  • Critically ill at presentation
  • Pulmonary findings and/or admission to the ICU required. In some instances, pulmonary involvement may be the first or only sign of DVT in a patient with osteomyelitis
  • Osteomyelitis and positive blood cultures, particularly for those patients who are persistently bacteremic with MRSA
  • In patients with the above risk factors Doppler ultrasonography should be performed near the site of infection to evaluate for DVT.

Certain genes have been identified that may confer a higher risk of DVT and invasive infection, but testing for these genes is not widely available and therefore is currently of limited utility. In the future, genetic testing of pathogens may help identify children at risk. Future prospective studies to evaluate the utility of other parameters such as fibrinogen and D-dimer are needed.

Finally, given the higher incidence of DVT in children with osteomyelitis and the independent relationship of central venous access to thrombosis, efforts to decrease the widespread use of central venous catheters in these patients should be encouraged. Transition to oral antibiotics when patients are clinically improved could help minimize the added risk of thrombosis that central lines represent.

REFERENCES


