Predicting MSSA in Acute Hematogenous Osteomyelitis in a Setting With MRSA Prevalence

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Background: Increased severity of illness in patient with acute hematogenous osteomyelitis (AHO) with methicillin-resistant *Staphylococcus aureus* (MRSA) necessitates prompt intervention, but overtreatment of methicillin-sensitive *S. aureus* (MSSA) may contribute to antibiotic resistance. Therefore, predicting methicillin sensitivity in suspected AHO is desirable. A previously published prediction algorithm has not performed well in settings with high prevalence of MRSA. We sought to develop a predictive equation using presenting factors to predict MRSA in our patient population with a predominance of MRSA.

Methods: A retrospective chart review was performed. Consecutive cases of AHO with positive blood or bone cultures were identified at a single children's hospital. Presenting features were recorded including duration of symptoms, weight-bearing, prior antibiotic use, vital signs, complete blood count, erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP). Univariate comparison was made between the groups with MRSA and MSSA. Continuous variables were compared with *t* tests and discrete variables were compared using the Fischer exact test. Logistic regression was performed using a forward stepwise regression to develop a model to predict MRSA.

Results: A total of 68 patients formed the study group, and 60% had MRSA (41 MRSA, 27 MSSA). Temperature, respiratory rate, heart rate, white blood cell count, absolute neutrophil count (ANC), ESR), and CRP were significantly higher in MRSA cases, whereas platelets were lower. Logistic regression resulted in a model utilizing temperature, ANC, and CRP. This model correctly predicted 87% of cases (92% of MRSA and 79% of MSSA) with an area under the curve of 0.919 ± 0.035 with a 95% confidence interval of 0.851, 0.987.

Conclusion: A logistic regression model incorporating temperature, ANC, and CRP correctly predicts methicillin resistance of *S. aureus* in 87% of cases. The model differs from one developed at an institution with a low rate of MRSA. Prediction of MRSA could help direct antibiotic management, whereas prediction of MSSA could help prevent overuse of antibiotics directed against MRSA.

Level of Evidence: Diagnostic study level IV.

Key Words: pediatric, infection, osteomyelitis, MSSA, MRSA

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The incidence of acute hematogenous osteomyelitis (AHO) in pediatric patients has increased in the last 2 to 5 decades.[1] Although there is growing evidence that the trend is international,[1,2] tertiary care centers in the United States have demonstrated a nearly 3-fold increase in the incidence of osteomyelitis compared with 20-year historical data.[3] The hospital admission rate for pediatric patients with AHO rose from 2.6 to 6 per 1000 patients between 2000 and 2004.[4] This increase coincides with the appearance of community-acquired methicillin-resistant *Staphylococcus aureus* (MRSA) and growing concern regarding poorer clinical outcomes in patients with osteomyelitis.[3,5–8] This epidemiological data suggests not only an increase in prevalence of AHO, but also in severity of osteoarticular infections over the last decade.

S. aureus is the most common causative organism in pediatric musculoskeletal infections including osteomyelitis.[3,5,6,9,10] Since 2001, the emergence and increasing prevalence of community-acquired MRSA has influenced the initial practice guidelines used to treat pediatric patients with musculoskeletal infections.[4,5,7,11,12] Specifically, the use of empiric antibiotic coverage for MRSA in pediatric patients with AHO is increasingly common. MRSA has been associated with increased severity of illness and worse clinical outcomes compared with patients with methicillin-sensitive *S. aureus* (MSSA).[4–7] Sequelae of *Staphylococcal* AHO include DVT, septic pulmonary emboli, multisystem organ failure, and death. Long-term sequelae include chronic osteomyelitis, segmental bone loss, and growth disturbances. Long-term complications of MRSA osteomyelitis have been reported in up to 33% of pediatric patients.[7] The virulence of MRSA necessitates accurate and timely treatment to limit the morbidity in patients with *Staphylococcal* AHO. However, there is growing concern in the medical community that empiric antibiotic coverage may contribute to antibiotic resistance in the long term.[11,12]

Recently, a diagnostic algorithm was proposed to help predict MRSA versus MSSA in pediatric patients

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with AHO. The investigators identified 4 independent variables predictive of MRSA osteomyelitis [temperature, hematocrit, white blood cell count, and C-reactive protein (CRP)].[13] However, the study population had a very low prevalence of MRSA and the remaining 91% were MSSA. A follow-up study in a setting with a higher rate of MRSA[14] found that the algorithm performed poorly in their population. In our setting, MRSA predominates (54%). The purpose of our study was to evaluate the utility of clinical predictors for MSSA in a setting where the majority, rather than the minority, of cases of AHO are caused by MRSA. We hypothesize that clinical predictors would allow identification of patients who are likely NOT to have MRSA (ie, likely to have MSSA), and that these would likely differ from the previously published criteria. We performed a retrospective chart review to evaluate presenting features of patients at our institution with AHO.

METHODS

IRB approval was obtained. Pediatric patients with AHO at a single children's hospital were identified based on discharge diagnosis codes and surgical procedure coding. Retrospective chart review of consecutive patients between 1 and 18 years of age with culture-proven *S. aureus* AHO was completed. Initial clinical and laboratory parameters were recorded for each patient with surgically verified *Staphylococcal* osteomyelitis. Data for 21 variables were collected at initial presentation to the emergency department or orthopaedic clinic. These variables were age at onset, duration of symptoms, history of prior hospitalization, antibiotic use at presentation, weight, weight-bearing status, affected site, subjective history of fever, temperature, respiratory rate, heart rate, systolic and diastolic blood pressure, white blood cell count, absolute neutrophil count (ANC), hematocrit and hemoglobin levels, platelet count, erythrocyte sedimentation rate (ESR), CRP, and oxygen saturation when recorded. Patients were excluded for the following reasons (number of patients): inadequate medical record (14 patients); under 1 year of age and over 18 years of age (8 patients); duration of symptoms at presentation >30 days (24 patients); with culture-negative data (17 patients); infection following trauma or surgery (21 patients); immunocompromised status (5 patients); bacteria other than *Staphylococcus* (4 patients); and treated nonsurgically (no surgical cultures available) (21 patients). Between 2006 and 2012, 68 patients met criteria for inclusion, whereas 114 patients were excluded.

Univariate comparisons were used to evaluate each variable between the MRSA and MSSA AHO groups. Comparisons between the 2 groups used t tests for continuous variables and Fisher exact test for discrete variables.

Logistic regression was performed using a forward stepwise regression to determine a model for predicting MSSA osteomyelitis based on initial clinical and laboratory parameters.

RESULTS

Of the 68 patients included in the study, 41 (60%) had confirmed MRSA osteomyelitis. This is compatible with current antibiogram data from our hospital indicating that for all community-acquired *S. aureus* isolates, 54% were MRSA. Clindamycin resistance was found in 7 isolates (3 MRSA and 4 MSSA).

There were 44 male and 24 female patients. Only 1 patient with MSSA osteomyelitis had a history of prior hospitalization within 6 months (unrelated to AHO), and no patient in the MRSA group had been recently hospitalized. Antibiotic use at presentation was noted in 44% of the MRSA group and 26% of the MSSA group, although this did not reach significance ($P = 0.199$). The lower extremity was involved in 79% of patients, with the tibia being the most frequent site of presentation. In addition, 34% of patients with *S. aureus* AHO received a secondary diagnosis of septic arthritis. Of the patients with associated septic arthritis, 2/3 of cases were in patients with MRSA osteomyelitis and 1/3 were associated with MSSA. Figure 1 demonstrates the anatomic sites of involvement at initial presentation.

Table 1 lists the univariate comparison of variables between MSSA and MRSA groups. Patients with MRSA osteomyelitis presented with significantly higher temperature, respiratory rate, and heart rate. With respect to laboratory studies, the MRSA group had on presentation a statistically significant elevation in white blood cell count and ANC, ESR, and CRP, and lower platelet counts. Although differences in weight and age were not significant, the MRSA group had an overall higher weight-to-age ratio. In other words, the MRSA group exhibited a higher mean weight despite a lower mean age of the study population. Non–weight-bearing was present in 81% of all patients with *Staphylococcal* AHO. History of fever was reported by 64 patients (94%).

Multivariate regression analysis was performed to determine a set of variables that may predict MRSA versus MSSA osteomyelitis in our patient population. There were 3 variables that were identified as copredictors of MRSA including temperature, CRP, and ANC. Greater elevations of these variables suggested MRSA (Table 2). These 3 variables were incorporated into a logistic regression equation to predict the probability of MSSA. Using this equation, probability of ≥ 0.5 ($z > 0$) indicates likelihood of MSSA osteomyelitis, whereas a probability of ≤ 0.5 ($z < 0$) indicates likelihood of MRSA osteomyelitis. Application to our sample population correctly predicted 87% of cases (79% MSSA and 92% MRSA):

$$\text{Probability (MSSA)} = \frac{e^z}{(1+e^z)}$$

$$z = 47.407 - 0.434\,(\text{temperature } (^\circ\text{F})) - 0.146\,(\text{CRP (mg/L)}) - 0.253\,(\text{ANC})$$

The corresponding receiver operating characteristic (ROC curve) for the z-value illustrates the performance of our prediction model (Fig. 2). The area under the curve is

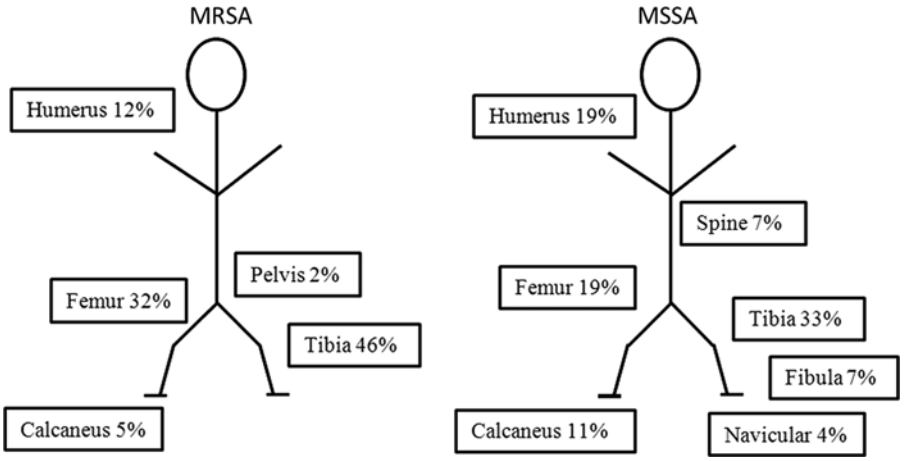

FIGURE 1. Incidence and anatomic sites of involvement of patients with MRSA versus MSSA osteomyelitis. The tibia and femur are the most frequent sites of involvement accounting for 78% of MRSA and 52% of MSSA cases. The humerus is the most commonly affected bone in the upper extremity. MRSA indicates methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-sensitive *Staphylococcus aureus.*

0.919 ± 0.035 with a 95% confidence interval of 0.851, 0.987. This is significantly better than chance ($P < 0.001$).

We also applied the criteria previously described by Ju et al[13] (temperature $>38^{\circ}$C, hematocrit $<34\%$, WBC $>$ 12,000, and CRP >13 mg/L) to our patient population. Although the majority of patients with MRSA osteomyelitis in the former study had all 4 clinical predictors, this study demonstrates that only 2.4% of MRSA patients met all 4 criteria and that 71% of the MRSA patients met ≤ 2 of the previously reported criteria. Using the cutoff of at least 2 clinical predictors to predict MRSA involvement, our population demonstrated a sensitivity of 0.71 and specificity of 0.81 in predicting MRSA. Figure 3 illustrates the percentage of patients in our MRSA and MSSA groups that have 0 to 4 clinical predictors as described by Ju and colleagues. Thus, use of the previously published parameters to determine empiric therapy in our setting to exclude the possibility of MRSA would result in undertreatment.

DISCUSSION

In our setting with MRSA predominance, we found that MRSA AHO presented with increased temperature, heart rate, respiratory rate, white blood cell, ANC, ESR, and CRP compared with patients with MSSA. A predictive equation using temperature, CRP, and ANC predicts MSSA with AUC 0.919.

The growing prevalence of MRSA in the community setting in many areas of the United States increases the

TABLE 1. Univariate Comparison of Clinical and Laboratory Parameters Between MRSA and MSSA Osteomyelitis Groups

Variables	MRSA (N = 41)	MSSA (N = 27)	*P*
Age	8.7 ± 4.5	10.1 ± 4.4	0.213
Duration of symptoms (d)	5.1 ± 3.4	8.4 ± 7.4	0.037
Prior hospitalization: no [n (%)]	41 (100)	26 (96)	0.397
Antibiotic use at presentation: no [n (%)]	23 (56)	20 (74)	0.199
Weight	39.1 ± 22.4	35.1 ± 15.2	0.386
Non–weight-bearing: yes [n (%)]	4/39 (10)	5/25 (20)	0.296
Fever-yes [n (%)]	40 (98)	24 (89)	0.293
Temperature (°F)	100.7 ± 2.2	99.2 ± 1.6	0.003
Respiratory rate	29 ± 11	23 ± 4	0.004
Heart rate (bpm)	129 ± 32	104 ± 22	0.001
Systolic BP (mm Hg)	118 ± 15	114 ± 13	0.333
Diastolic BP (mm Hg)	69 ± 13	69 ± 9	0.734
White blood cell count	13.32 ± 5.86	10.22 ± 4.48	0.023
Neutrophil count	10.18 ± 4.85	7.17	0.012
Hematocrit	33.6 ± 3.7	34.9 ± 2.6	0.093
Hemoglobin	11.6 ± 1.5	12.1 ± 1.2	0.139
Platelet count	280 ± 120	355 ± 190	0.049
ESR	67.4 ± 25.0	52.2 ± 31.1	0.038
C-reactive protein	24.2 ± 12.7	9.6 ± 7.8	< 0.001
O_2 saturation	95.8 ± 4.6 (n = 16)	97.7 ± 1.9 (n = 7)	0.297

ESR indicates erythrocyte sedimentation rate; MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-sensitive *Staphylococcus aureus.*

TABLE 2. Multivariate Forward Stepwise Regression Indicating the Most Significant Clinical Parameters That Help Differentiate MRSA Versus MSSA Acute Hematogenous Osteomyelitis in Our Patient Population

Variables	Odds Ratio	95% CI	*P*
Temperature	0.648	0.423, 0.993	0.046
C-reactive protein	0.865	0.796, 0.939	0.007
Absolute neutrophil count	0.776	0.645, 0.935	0.007

Odds ratios <1 indicate that higher clinical values predict MRSA.
CI indicates confidence interval; MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-sensitive *Staphylococcus aureus*.

risk for systemic illness and complications.[4,5,15,16] In our setting, empiric therapy directed to cover MRSA is indicated, but concerns exist that overuse of empiric antibiotics in suspected *Staphylococcal* AHO may lead to further antibiotic resistance and multidrug-resistant organisms in the future. Furthermore, 1 antibiotic frequently used for suspected MRSA, vancomycin, requires additional laboratory surveillance, may lead to more severe adverse reactions including nephrotoxicity and ototoxicity, and may be less effective against MSSA for bone and joint infections than oxacillin.[16,17] Hence, better targeting for initial empiric therapy is desirable.

Our results were similar to those of Ju and colleagues, in that factors indicating more pronounced physiological response were predictors. Specifically, the presentation of increased heart and respiratory rate coupled with elevated temperature fulfill documented criteria for the diagnosis of systemic inflammatory response syndrome, or in the setting of suspected infection, sepsis.[18] These findings suggest that patients with MRSA osteomyelitis present with more severe illness than those with MSSA. In addition, the finding of decreased platelet counts may be indicative of a more global decrease in serum reticuloendothelial components that accompanies systemic illness, disseminated intravascular coagulation, and systemic inflammatory response syndrome.[19,20] In contrast to the previous study, the trend of decreased hemoglobin and hematocrit in the MRSA group did not reach statistical significance. In addition, the finding of refusal to bear weight on the involved extremity was so common in both groups that it did not help differentiate MRSA vs. MSSA osteomyelitis. Interestingly, the average duration of symptoms before presentation was over 3 days shorter in the MRSA group. This was statistically significant, and may represent accelerated symptoms or severity of systemic illness associated with MRSA, influencing patients and families to seek treatment more quickly.

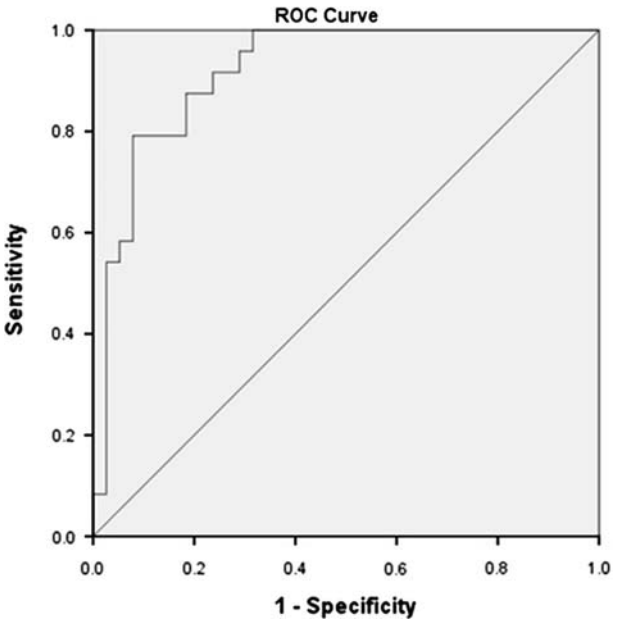

FIGURE 2. Receiver operating characteristic for *z*-value and logistic regression model for predicting MSSA versus MRSA osteomyelitis using heart rate, platelet count, and ESR. AUC = 0.919 (±0.035), demonstrating good to excellent accuracy of the prediction model. ESR indicates erythrocyte sedimentation rate; MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-sensitive *Staphylococcus aureus.*

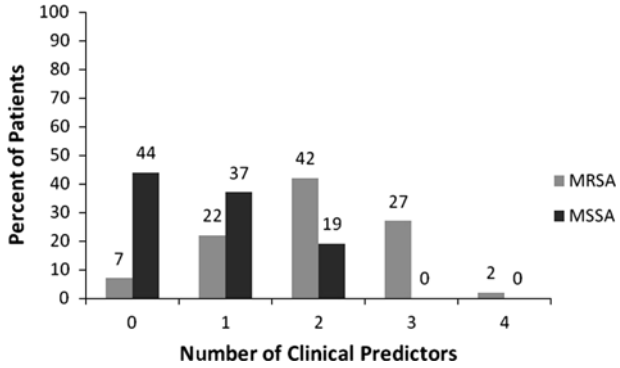

FIGURE 3. Percentage of patients in the MRSA and MSSA osteomyelitis groups in our patient population that possessed 0 to 4 of the clinical predictors as described by Ju et al.[13] MRSA indicates methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-sensitive *Staphylococcus aureus.*

We were able to develop a formula that incorporates patients' temperature, ANC, and CRP to predict MSSA in suspected *S. aureus* osteomyelitis. To understand the utility of a predictive equation, it may be helpful to consider the results in terms of undertreatment of MRSA (potentially very serious), versus overtreatment of MSSA (undesirable but not usually life threatening). For example, if we used a probability of MSSA > 50% to guide initial antibiotic treatment, that would correctly predict 93% of patients. Two cases of MRSA would be incorrectly predicted, which could lead to undertreatment, whereas 6 patients with MSSA would be overtreated. If 75% probability of MSSA was used as a cutoff, however, only 1 MRSA case would have been undertreated, but 10 MSSA cases would be overtreated. The absolute value of the probability would of course be tempered by clinical judgment taking into account the patient's clinical condition.

In contrast, using the previously published criteria with a cutoff of ≥ 2 predictors for MRSA would result in undertreatment of 12 of 41 patients and overtreatment of 5 of 27 MSSA patients. Another recent publication has applied the criteria of Ju and colleagues to their patient population with 24% MRSA and found that it did not perform satisfactorily, but their study did not offer an alternate strategy.[14]

There are several limitations to our study. Many patients were excluded, as detailed above, in part due to following previously published inclusion criteria in an effort to be consistent with prior studies. The number of patients in the study limits the power of our analysis. It is possible that with a greater number of patients, other observed trends may have reached significance. However, it is unlikely to negate the current significant findings with regard to heart rate, ESR, platelet count, CRP, temperature, and respiratory rate. In addition, collecting clinical parameters retrospectively may allow confounders. For instance, patients may or may not have received an antipyretic before obtaining initial vital signs at the hospital, potentially altering temperature at presentation. With respect to application, the use of an equation, rather than easily remembered criteria is more cumbersome. However, the result of the equation is a percentage likelihood of MSSA which may be more useful than simple yes/no prediction. We have published a calculator on our residency Web site where values could be input for informational purposes (http://www.uab.edu/medicine/surgery/orthopaedics/research/mrsa-vs-mssa). Alternately, one could input the 3 variables and calculate z using the listed equation and use a cutoff of 0 as a predictor, with positive values predicting methicillin sensitivity. The information should be used cautiously, however, as the equation has not been prospectively validated. Finally, the discordant findings of the current study with 2 previously published studies on the topic suggest that infection is subject to geographic variation and that results in other institutions would also differ. Knowledge of local presentation patterns and your institution's antibiogram is important. At our institution, patients with suspicion for osteomyelitis are empirically treated with antibiotics targeting MRSA in the absence of evidence of methicillin sensitivity.

Our study also has strengths. It is the first to propose an algorithm for use in a setting with a predominance of MRSA, and the largest number of MRSA cases evaluated to date.

Clearly, a prediction algorithm is only a single tool in the diagnostic armamentarium, and is highly influenced by the local patient and bacterial populations. Probability must be interpreted in light of the overall patient condition, especially in cases where patients present acutely ill. Additional factors also play a role in initial antibiotic selection including clindamycin resistance, which was too uncommon in our population to generate specific statistical analysis or guidance. More definitive early predictors such as PCR testing may be of benefit, but are not currently routinely available in our institution.

In conclusion, in our clinical practice setting where MRSA predominates in cases of AHO, a prediction algorithm can be used to correctly predict methicillin sensitivity and resistance with 87% accuracy when applied to our cohort retrospectively. This could be useful to guide empiric therapy, which at our institution typically is selected to treat MRSA. Validation of the prediction model in a prospective study is indicated.

REFERENCES

1. Christiansen P, Frederiksen B, Glazowski J, et al. Epidemiologic, bacteriologic and long-term follow-up data of children with acute hematogenous osteomyelitis and septic arthritis: a ten-year review. *J Pediatr Orthop B*. 1999;8:302–305.
2. Malcius D, Trumpulyte G, Barauskas V, et al. Two decades of acute hematogenous osteomyelitis in children: are there any changes? *Pediatr Surg Int*. 2005;21:356–359.
3. Gafur BA, Copley L, Hollmig T, et al. The impact of current epidemiology of pediatric musculoskeletal infection on evaluation and treatment guidelines. *J Pediatr Orthop*. 2008;28:777–785.
4. Arnold SR, Elias D, Buckingham SC, et al. Changing patterns of acute hematogenous osteomyelitis and septic arthritis: emergence of community-associated methicillin-resistant *Staphylococcus aureus*. *J Pediatr Orthop*. 2006;26:703–708.
5. Saavedra-Lozano J, Mejias A, Ahmad N, et al. Changing trends in acute osteomyelitis in children; impact of methicillin-resistant *Staphylococcus aureus* infections. *J Pediatr Orthop*. 2008;28:569–575.
6. Hawkshead J III, Patel N, Steele R, et al. Comparative severity of pediatric osteomyelitis attributable to methicillin-resistant versus methicillin-sensitive *Staphylococcus aureus*. *J Pediatr Orthop*. 2009;29:85–90.
7. Vander Have KL, Karmazyn B, Verma M, et al. Community-associated methicillin-resistant *Staphylococcus aureus* in acute musculoskeletal infection in children; a game changer. *J Pediatr Orthop*. 2009;29:927–931.
8. Wang JL, Chen SY, Wang JT, et al. Comparison of both clinical features and mortality risk associated with bacteremia due to community-acquired methicillin-resistant *Staphylococcus aureus* and methicillin-susceptible *S. aureus*. *Clin Infect Dis*. 2008;46:799–806.
9. Meller I, Manor Y, Bar-ziv J, et al. Pediatric update #8. Acute hematogenous osteomyelitis in children. Long-term results of surgical treatment. *Orthop Rev*. 1989;18:824–831.
10. Gerber JS, Coffin SE, Smathers SA, et al. Trends in the incidence of methicillin-resistant *Staphylococcus aureus* infection in children's hospitals in the United States. *Clin Infect Dis*. 2009;49:65–71.
11. Fergie J, Purcell K. The treatment of community-acquired methicillin-resistant *Staphylococcus aureus* infections. *Pediatr Infect Dis J*. 2008;27:67–68.
12. Sandora TJ, Goldmann DA. Preventing lethal hospital outbreaks of antibiotic-resistant bacteria. *N Eng J Med*. 2012;367:2168–2171.
13. Ju KL, Zurakowski D, Kocher MS. Differentiating between methicillin-resistant and methicillin-sensitive *Staphylococcus aureus* osteomyelitis in children. *JBJS*. 2011;93:1693–1701.
14. Wade Shrader M, Nowlin M, Segal LS. Independent analysis of a clinical predictive algorithm to identify methicillin-resistant *Staphylococcus aureus* osteomyelitis in children. *J Pediatr Orthop*. 2013;33:759–762.
15. Scott RJ, Christofersen MR, Robertson WW Jr, et al. Acute osteomyelitis in children: a review of 116 cases. *J Pediatr Orthop*. 1990;10:649–652.
16. Davis JS. Management of bone and joint infections due to *Staphylococcus aureus*. *Intern Med J*. 2005;35:S79–S96.
17. Tice AD, Hoaglund PA, Shoultz DA. Outcomes of osteomyelitis among patients treated with outpatient parenteral antimicrobial therapy. *Am J Med*. 2003;114:723–728.
18. Van der Poll T, Joost CMM. Systemic inflammatory response syndrome and compensatory anti-inflammatory response syndrome in sepsis. *J Innate Immun*. 2010;2:379–380.
19. Kraemer B, Campbell RE, Schwertz H, et al. Bacteria differentially induce degradation of Bcl-xL, a survival protein, by human platelets. *Blood*. 2012;120:5014–5020.
20. Ogura H, Satoshi G, Toshiaki I, et al. SIRS-associated coagulopathy and organ dysfunction in critically ill patients with thrombocytopenia. *Shock*. 2007;28:411–417.