Published in final edited form as:

Acad Pediatr. 2009 ; 9(3): 179–184. doi:10.1016/j.acap.2009.02.002.

Antibiotic Selection for Purulent Skin and Soft-Tissue Infections in Ambulatory Care: A Decision-Analytic Approach

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Abstract

Background—Community-associated methicillin-resistant *Staphylococcus aureus* (CAMRSA) has caused an nationwide epidemic of skin and soft-tissue infections (SSTIs) in ambulatory pediatrics. Antibiotic treatment recommendations suggest incorporating local epidemiology for the prevalence of CA-MRSA. We sought to identify the antibiotic strategy with the highest probability of activity and to identify threshold values for epidemiologic variables including bacterial prevalence and antibiotic resistance.

Methods—We used decision analysis to evaluate three empiric antibiotic strategies: (1) clindamycin, (2) trimethoprim/sulfamethoxazole (T/S) and (3) cephalexin. We calculated the probability of activity against the bacteria causing the infection (CA-MRSA, methicillin-sensitive *S. aureus* and group A *Streptococcus*) by incorporating estimates of prevalence and antibiotic resistance to determine the optimal strategy. Sensitivity analysis was used to identify thresholds for prevalence and antibiotic resistance where two strategies were equal.

Results—Clindamycin (0.95) and T/S (0.89) had substantially higher probability of activity than cephalexin (0.28) using baseline estimates for bacterial prevalence and antibiotic resistance. Cephalexin was the optimal antibiotic only when CA-MRSA prevalence was <10%. The probability of activity for clindamycin and T/S was highly sensitive to changes in the values for bacterial prevalence (both CA-MRSA and group A *Streptococcus*) and CA-MRSA resistance to clindamycin.

Conclusions—Empiric treatment of SSTIs with either clindamycin or T/S maximizes the probability that the antibiotic will be active when CA-MRSA prevalence is >10%. Deciding between T/S and clindamycin requires consideration of antibiotic resistance and prevalence of group A *Streptococcus*. This model can be customized to local communities and illustrates the importance of ongoing epidemiologic surveillance in primary care settings.

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Disclosures: None

Keywords

Methicillin-resistant *Staphylococcus aureus*; Decision analysis

Introduction

The emergence of community-associated methicillin-resistant *Staphylococcus aureus* (CA-MRSA) has caused an epidemic of skin and soft-tissue infections (SSTIs) in primary care settings that is disproportionately affecting children.[1] The prevalence of CA-MRSA among purulent SSTIs is >60% in some communities.[2] Other important causes of SSTIs include methicillin-sensitive *Staphylococcus aureus* (MSSA) and group A *Streptococcus* (GAS).[3]

Although cephalexin, which does not treat CA-MRSA, is the most commonly prescribed antibiotic for SSTIs, there has been increased use of antibiotics with CA-MRSA activity, such as trimethoprim/sulfamethoxazole (T/S) and clindamycin.[1] There are trade-offs between these alternatives. Clindamycin can be used to treat GAS whereas T/S is not effective for this organism. On the other hand, some communities have high rates of CA-MRSA resistance to clindamycin,[4, 5] which is not currently the case for T/S. Both the Centers for Disease Control[6] and the American Academy of Pediatrics[7] recommend that clinicians consider CA-MRSA when treating purulent skin infections. However, guidance regarding the specific antibiotic choice is not clear. Some experts have suggested that antibiotic treatment should target CA-MRSA when the community prevalence is 10% or greater.[8] This threshold is much lower than the prevalence in most US communities.

With the exception of patients who have had documented recurrent infections, whether or not the infection is caused by CA-MRSA is usually unknown at the initial point of care. Antibiotic selection is therefore empiric for most patients but should account for factors including the community prevalence of CA-MRSA and clinical characteristics of the infection (e.g. GAS is a common cause of cellulitis while *S. aureus* is a more common cause of abscess).

Our primary research objective was to determine which antibiotic is most likely to be active against bacteria causing purulent SSTIs by accounting for community prevalence and resistance patterns. Second, we sought to identify probability thresholds for bacterial prevalence and antibiotic resistance in order to help guide antibiotic selection. Key thresholds for this evaluation include CA-MRSA prevalence, where 10% has been suggested, and CA-MRSA resistance to clindamycin.

Methods

To address these objectives, we used decision analysis because this method allows the explicit weighting of trade-offs between alternative treatments. Decision analysis facilitates modeling clinical decision making by incorporating probabilities to account for uncertainties in disease states and assigning weights to each decision according to disease probabilities and the harms or benefits of associated treatments. The expected value of each clinical

decision incorporates the probability of each possible outcome and its assigned weight and thus enables a comparison between alternative treatments. In the case of clinical decision making for SSTIs, physicians must account for the probability of each organism (e.g. CA-MRSA, MSSA or GAS) and the possibility of antibiotic resistance for the particular antibiotic that the physician selects.

We developed a decision model to evaluate the choice between three empiric antibiotic strategies for SSTIs: (1) clindamycin; (2) T/S and (3) cephalexin. The endpoint for each strategy is the probability of antibiotic activity against the organism causing the infection. The optimal strategy is the one that maximizes the overall probability of activity. The decision model is displayed in Figure 1 which illustrates how each antibiotic strategy will be evaluated. The first set of branches reflects the prevalence for each bacteria causing SSTIs and the second set of branches reflects the probability that the antibiotic is active against the bacteria.

Model Assumptions

This model applies to pediatric patients <18 years old presenting to ambulatory care settings with purulent SSTIs. Patients are treated with an oral antibiotic and have no signs of systemic illness. The patients are assumed to have no relevant drug allergies and compliance with treatment is ensured. We assumed that an antibiotic was prescribed independent of whether or not incision and drainage (I&D) was performed. In terms of antibiotic susceptibilities, we assumed that all GAS were susceptible to clindamycin and cephalexin, all MSSA were susceptible to cephalexin and all CA-MRSA were resistant to cephalexin.

Model Variables

A list of model variables is shown in the Table. The initial values shown in the table are referred to as the base case. Model variables include the probability that the infection is caused by either *S. aureus* (defined as the sum of the probability of CA-MRSA and MSSA), GAS and other bacteria, and the probability of in vitro activity for each antibiotic/bacteria pairing. In order to estimate these probabilities, we used a report from our microbiology department for patients <18 years old presenting to the pediatric ambulatory care clinics at the University of California, San Francisco in 2007 where the specimen was described as an “abscess,” “boil,” “pus” or “pustule” (N=81). Since some patients may have multiple cultures with a single infection or may have recurrent infections, we only included the first culture for unique patients. From this report, we tallied the frequencies for each organism and the specific antibiotic susceptibilities to serve as estimates for our local epidemiology. After excluding cultures that were polymicrobial or with organisms likely to represent skin contamination, >99% were caused by *S. aureus* or GAS and so only these organisms are included in the model. The susceptibility profiles for all of the MRSA isolates were consistent with USA300, which is the predominant community –associated strain in San Francisco[9] and most of the United States.[10]

Model Analysis

The base case estimates were used for the first step in the model analysis where we identify the antibiotic strategy with the highest probability of activity. Because the base case analysis

relies on estimates for epidemiologic data which may be subject to error or bias, may change over time and may not apply to other communities, in the second step we performed one and two-way sensitivity analyses on these values to assess the stability of the model results and to identify thresholds where two strategies are equal. The prevalence of CA-MRSA, GAS and the probability of CA-MRSA resistance to clindamycin were varied in these analyses. For one-way sensitivity analysis, the base case value for a single variable is swept through a range of possible values while all other values are held constant. A threshold is identified when a change in the optimal strategy occurs within this range of values. For two-way sensitivity analysis, the base case values for two model variables are swept through a range of possible values simultaneously while the others are held constant. In this case, a threshold region is identified, corresponding to simultaneous values for each variable indicating where each strategy is preferred. Performing two-way sensitivity analysis is important because the thresholds identified in one-way sensitivity analysis may change if the values of more than one variable are changed.

We used TreeAge Pro (Williamstown, MA) software to conduct the analysis.

Results

Base Case

Using the base case model estimates, empiric clindamycin has the highest probability of activity at 0.95. This is followed by T/S at 0.89. The probability of activity for empiric use of cephalexin is substantially lower, at 0.28. We explored the stability of these findings through multiple sensitivity analyses.

One-Way Sensitivity Analysis

Probability of CA-MRSA—We sought to determine how low the CA-MRSA prevalence would need to be for cephalexin to be the preferred antibiotic strategy. To identify this threshold, one-way sensitivity analysis was performed on the prevalence of CA-MRSA among *S. aureus* infections by ranging from the base case value of 0.80 to an extreme low value of 0.00. As shown in Figure 2, the threshold occurs at 0.10, where the probability of activity for cephalexin and clindamycin are equal. Cephalexin has the highest probability of activity only when the CA-MRSA prevalence is below this threshold, whereas clindamycin has the highest activity above this value.

CA-MRSA resistance to clindamycin—Because geographic variation exists in CA-MRSA resistance to clindamycin and there is concern about further promotion of resistance with increased clindamycin use, one-way sensitivity analysis was performed on this variable. We sought to identify the threshold where the probability of activity between empiric clindamycin and T/S were equal. As shown in Figure 3, we ranged this value from 0.00 to 0.30 and identified a threshold probability at 0.13. For values below 0.13, clindamycin has higher probability of activity than T/S, whereas above this threshold, T/S has a higher probability of activity than clindamycin.

Two-Way Sensitivity Analysis

GAS prevalence and CA-MRSA resistance to clindamycin—Building on the one-way analyses, we explored the trade-offs between clindamycin and T/S which relate to treatment of GAS and CA-MRSA resistance. We sought to determine how changes in the GAS prevalence influence the threshold for CA-MRSA resistance to clindamycin. We addressed this using two-way sensitivity analysis where we varied the value of GAS prevalence and CA-MRSA resistance to clindamycin from 0.00 to 0.30 simultaneously. In Figure 4, two regions are identified corresponding to values where clindamycin and T/S each have the highest probability of activity. The curve separating the regions represents the threshold for CA-MRSA resistance to clindamycin across a range of GAS prevalence values. Figure 4 illustrates that this threshold decreases as the prevalence of GAS decreases and vice versa. For instance, if the GAS prevalence is lowered from the base case value of 0.10 to 0.05, the threshold decreases from 0.13 to 0.06 (Figure 4).

CA-MRSA prevalence and CA-MRSA resistance to clindamycin—A similar analysis explored the relationship between CA-MRSA prevalence and CA-MRSA resistance to clindamycin and the impact of changes in these values on important thresholds. To account for a wide variety of conditions we varied the CA-MRSA prevalence from 0.00 to 1.0 while simultaneously ranging CA-MRSA resistance to clindamycin from 0.00 to 0.30, shown in Figure 5. There are two key curves representing epidemiologic thresholds displayed in this figure.

Figure 5 shows that the threshold for CA-MRSA prevalence where cephalexin and clindamycin have equal probability of activity (identified as 0.10 in the base case) is only minimally affected by changes in CA-MRSA resistance to clindamycin. The curve separating these two regions is nearly vertical and shows that this threshold would range only from 0.09 to 0.12 while CA-MRSA resistance to clindamycin is ranged from 0.00 to 0.30.

On the other hand, when the CA-MRSA prevalence is greater than 0.12, the probability of CA-MRSA resistance to clindamycin has a substantial impact on the preferred antibiotic strategy. The curve separating the region where clindamycin is favored from the region where T/S is favored represents the threshold for CA-MRSA resistance to clindamycin. This threshold was identified in the base case as 0.13 using one-way sensitivity analysis. When the CA-MRSA prevalence is >0.50 , the threshold for CA-MRSA resistance to clindamycin is highly stable, changing minimally from 0.12 to 0.15. However, this threshold is highly sensitive to changes in the CA-MRSA prevalence for values between 0.12 and 0.50 where the threshold increases from 0.15 to 0.27.

Discussion

We used decision analysis to compare three commonly used antibiotic strategies for treating purulent SSTIs in ambulatory pediatrics. Our analysis shows that empiric treatment of purulent skin infections using either clindamycin or T/S has a higher probability of activity than treatment with cephalexin when the CA-MRSA prevalence is 10% or greater. This is the same level that has been suggested based on expert opinion and our model therefore

supports this recommendation. Although cephalexin remains widely prescribed for SSTIs, because the CA-MRSA prevalence is >10% in most US communities, using empiric clindamycin or T/S instead may improve patient outcomes. In terms of the choice between clindamycin or T/S when the prevalence is above 10%, our results show that the acceptable level for clindamycin resistance to CA-MRSA depends on both the prevalence of CA-MRSA and GAS. Using the base case model estimates, we identified a threshold of 0.13, however this value changes significantly based on variations in local epidemiologic patterns. Pediatricians can therefore customize the results of this model to account for trends in their community.

Decision analysis is well suited to evaluating antibiotic treatment strategies and identifying thresholds for antibiotic resistance and prevalence. To our knowledge, this is the first study to explicitly identify thresholds for CA-MRSA prevalence and CA-MRSA resistance to clindamycin that can be used to guide empiric antibiotic selection for purulent SSTIs. A recent evaluation of cellulitis treatment used decision analysis to highlight how changes in the estimates for CA-MRSA and GAS prevalence influence the optimal empiric antibiotic strategy.[11] However, because this analysis focused on cellulitis where the prevalence of GAS is substantially higher than among purulent SSTIs, these results have limited applicability to purulent SSTIs, which is the most common clinical manifestation of CA-MRSA. Other clinical examples where decision analysis has been used to evaluate antibiotic resistance thresholds include community-acquired pneumonia and urinary tract infections. [12, 13]

Our analysis highlights the importance of incorporating accurate estimates for epidemiologic data into treatment decisions. Prior studies using computerized decision-support for this purpose show improvement in the quality of empiric antibiotic prescribing for infectious diseases including maximizing the probability of prescribing active treatment.[14, 15] When antibiotic treatment guidelines are tailored to reflect local epidemiologic data significant modifications to guideline recommendations may occur.[16] Recent work by our group showed that primary care pediatricians do not have access to local and regularly updated epidemiologic data about antibiotic resistance patterns (unpublished data, currently under review). Although hospital antibiograms (cumulative reports of antibiotic susceptibility to bacteria) may provide some of this information, they can also be misleading because of the aggregate nature of the data. For instance, they do not distinguish between inpatient and outpatient cultures or by specimen source (e.g. bloodstream and abscess) and therefore any differences in resistance patterns within these subgroups may not be detected. Decision making about infectious diseases such as SSTIs in office settings could be enhanced by greater awareness of susceptibility patterns relevant to ambulatory patients.

There are several limitations to our analysis. First, the endpoint we used, the probability of antibiotic activity, is a microbiologic not a clinical endpoint. Therefore the results of our analysis do not directly reflect a clinical endpoint. Our model does not account for the fact that some physicians could choose to prescribe two antibiotics simultaneously (e.g. cephalexin and T/S), to address the limitations of each antibiotic individually. Additionally, we did not explicitly account for whether or not an incision and drainage was performed. Some patients with purulent SSTIs will resolve spontaneously or without antibiotic therapy

if an adequate I&D is performed, which may limit the importance of antibiotic therapy in these cases. However antibiotic selection is important because use of I&D among children is low[17, 18] and some studies suggest that even when I&D is performed, outcomes are improved when patients receive empiric therapy that is active against the bacteria.[19, 20] Another potential limitation is the validity of the epidemiologic data used in our analysis. Not all patients with purulent abscesses will be cultured which could bias the data from cumulative susceptibility reports. Additionally, the data we incorporated are from a high-volume, urban academic medical center where the prevalence of CA-MRSA may be different than other settings. We addressed this issue by varying these model variables using sensitivity analysis. Some physicians in smaller practice settings may not have direct access to representative data about culture results for SSTIs which could limit the application of this model to their practice. However, this only strengthens the argument for improving the collection and dissemination of ambulatory culture results to primary care physicians. We did not include variables to account for cost or patient compliance in the decision model, factors that could potentially impact the optimal treatment decision or outcome.

Notwithstanding these limitations, this decision analysis has clinical implications. It highlights the importance of continuous surveillance of both prevalence and antibiotic susceptibility rates because moderate changes in these values can greatly affect the optimal antibiotic strategy. Disseminating this information to primary care physicians may help them make informed treatment decisions about antibiotic use, including monitoring the appropriateness of a treatment strategy and signaling when changes should be considered. Stratifying antibiogram data according to patient setting (e.g. inpatient versus outpatient) and specimen source (e.g. abscess versus bloodstream) may further enhance the practical value of these data. This decision model can be customized to reflect the epidemiology of an individual community and can serve to assist in developing local guidelines for the empiric treatment of SSTIs. Additionally, this model has the potential to be applied to other infections caused by *S. aureus* and GAS where empiric antibiotic selection is common, including osteomyelitis and septic arthritis.

Acknowledgement

Dr. Hersh was supported by Grant T32HD044331 from the National Institute of Child Health and Human Development.

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Figure 1.
Schematic of decision tree for each antibiotic strategy.

Figure 2. One-way sensitivity analysis for the prevalence of CA-MRSA and the probability of antibiotic activity for cephalexin, clindamycin and trimethoprim/sulfamethoxazole (T/S).

Figure 3. One-way sensitivity analysis for the probability of CA-MRSA resistance to clindamycin and the probability of antibiotic activity for clindamycin and trimethoprim/sulfamethoxazole (T/S).

Figure 4.

Two-way sensitivity analysis for the prevalence of GAS and the probability of CA-MRSA resistance to clindamycin for treating with clindamycin or trimethoprim/sulfamethoxazole (T/S). Shaded areas reflect which antibiotic has the highest probability of activity.

Figure 4.

Two-way sensitivity analysis for the prevalence of CA-MRSA and the probability of CA-MRSA resistance to clindamycin for treating with clindamycin or trimethoprim/sulfamethoxazole (T/S). Shaded areas reflect which antibiotic has the highest probability of activity.

Table

Model variables and base case estimates.

Model Parameter	Base-Case Estimate
Bacterial Prevalence	
<i>S. aureus</i>	0.90
CA-MRSA among <i>S. aureus</i>	0.80
MSSA among <i>S. aureus</i>	0.20
GAS	0.10
Antibiotic Resistance Probability	
CA-MRSA to clindamycin	0.05
MSSA to clindamycin	0.10
GAS to clindamycin	0.00
CA-MRSA to T/S	0.01
MSSA to T/S	0.01
GAS to T/S	1.00
MRSA to cephalexin	1.00
MSSA to cephalexin	0.00
GAS to cephalexin	0.00

CA-MRSA, community-acquired methicillin-resistant *Staphylococcus aureus*MSSA, methicillin-sensitive *Staphylococcus aureus*GAS, group A *Streptococcus*

T/S, trimethoprim/sulfamethoxazole