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Risk Factors for Mixed Complicated Skin and Skin Structure Infections To Help Tailor Appropriate Empiric Therapy

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Abstract

Background: Complicated skin and skin structure infections (cSSSIs) are a common reason for hospitalization. Inappropriate empiric therapy prolongs the hospital stay. Strategies that help clinicians target empiric therapy underlie antibiotic stewardship. We developed an algorithm to identify mixed (gram-positive + gram-negative organisms) cSSSI at hospital admission.

Methods: We performed a retrospective cohort study at a single academic medical center among patients hospitalized from April 2006 to December 2007 with a cSSSI. Inappropriate empiric therapy was defined as failure to deliver an antibiotic with in vitro activity against the offending pathogen(s) within 24 h of presentation. We derived a predictive rule to identify patients at risk for a mixed skin infection (MSI) and compared it with the "healthcare-associated" (HCA) definition.

Results: Among 717 patients hospitalized with a cSSSI, 68 (9.5%) had an MSI, with 38.2% of these receiving inappropriate empiric therapy. Intensive care unit admission (odds ratio [OR] 2.49; 95% confidence interval [CI] 1.12-5.52), infection other than an abscess (OR 2.01; 95% CI 1.06-3.81), and nursing home residence (OR 1.99; 95% CI 1.05-3.78) predicted MSI independently. The absence of all three factors identified non-MSI with 95.2% accuracy. The MSI rule improved the HCA classification accuracy for non-MSI by 21.9% without any loss in sensitivity.

Conclusions: Hospitalization with an MSI is a risk factor for inappropriate empiric therapy. Intensive care unit admission, infection other than an abscess, and nursing home residence help identify those patients with a higher MSI risk. Absence of all these factors reliably identified patients not needing empiric MSI coverage. Relative to the HCA definition, the MSI rule resulted in the potential to prevent more than one in five additional patients from receiving unnecessarily broad empiric coverage.

Complicated skin and skin structure infections (cSSSI) are a common and growing cause of hospitalization. For example, *Staphylococcus aureus*-related cellulitis hospitalizations increased four-fold in a recent six-year period and now account for 90,000 discharges annually [1]. Resistant organisms particularly remain a burden in this syndrome, with methicillin-resistant *S. aureus* (MRSA) accounting for 15% of all cases of cellulitis [2]. At the same time, gram-negative organisms are increasingly prevalent in this condition. Antimicrobial resistance among some gram-negative organisms is extensive [3,4]. This pattern of extensive resistance has resulted in greater utilization of broad-spectrum agents. Although this practice may enhance the likelihood a patient is treated appropriately, overuse of such agents clearly contributes to greater rates of resistance generally.

Contributing to the prescription of broader-spectrum antibiotics is the observation that use of a narrow empiric antimicrobial treatment prior to the identification of the causative organism may result in the patient receiving inappropriate therapy initially. Inappropriate therapy can adversely affect the mortality rate while simultaneously prolonging hospitalization [5].

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In an effort to balance the need to ensure that a patient receives appropriate empiric coverage with the pressure to limit the use of broad-spectrum agents, physicians require tools to identify persons most likely to merit broad-spectrum therapy. Alternatively, early and accurate identification of those patients in whom coverage may be limited can preserve microbial susceptibility to current antibiotics. One risk-based approach is the concept of healthcare-associated (HCA) infection, which aims to have physicians treat broadly those patients who have been hospitalized or received antimicrobial therapy recently, who are residents of a nursing facility, or who are on chronic hemodialysis. Unfortunately, the majority of subjects (nearly three quarters) now admitted with cSSSI meet the definitional requirements for an HCA, but fewer than 50% actually are infected with resistant organisms [5]. Concurrently, however, we observed that subjects with mixed skin infections (MSI), defined as the presence in culture of both a gram-positive and a gram-negative organism, occurring in approximately 10% of all cSSSI patients, were at high risk for inappropriate empiric therapy. Therefore, we sought to identify variables associated with such mixed infections to aid physicians in more appropriate utilization of broad-spectrum agents, confining them to situations in which they are in fact needed.

Patients and Methods

Study design

We performed a single-center retrospective cohort study of patients with cSSSI admitted to the hospital through the emergency department (ED). All consecutive patients hospitalized between April 2006 and December 2007 meeting the inclusion criteria (see below) were enrolled. The study was approved by the Washington University School of Medicine Human Studies Committee, and informed consent was waived. This population has been described previously [5–7].

Patients

Consecutive patients admitted from the community through the ED between April 2006 and December 2007 at the Barnes-Jewish Hospital, a 1,200-bed university-affiliated, urban teaching hospital in St. Louis, MO, were included if they had a cSSSI (Appendix 1) [8], and there was a bacterial infection, defined as a positive culture within 24 h of hospital admission. We excluded patients if certain diagnoses and procedures were present (Appendix 2) [8]. Patients were also excluded if they represented a readmission for the same diagnosis within 30 days of the original hospitalization. All inclusions and exclusions were based on the International Classification of Diseases, version 9, Clinical Modification (ICD-9-CM) coding. Notably, such deep infections as necrotizing fasciitis and gangrene were excluded.

Definitions

An HCA cSSSI was defined as any cSSSI in a patient with recent hospitalization (within the previous year [6]), antibiotics in the 90 d prior to admission, transfer from a nursing home, or need for dialysis. An MSI represented an infection with both a gram-positive and a gram-negative organism. Inappropriate empiric therapy was said to have been given if there was a delay of ≥ 24 h in treatment with an agent exhibiting in vitro activity against the pathogen(s) isolated.

Data elements

The following demographic and clinical baseline characteristics were collected: Age, gender, race/ethnicity, comorbidities, the presence of risk factors for HCA cSSSI, the presence of bacteremia at admission, and the location of the admission (ward vs. intensive care unit [ICU]). Bacteriology data included information on the specific bacterium or bacteria recovered, the site of the culture (e.g., tissue, blood), antibiotic susceptibility patterns, and whether the infection was monomicrobial, polymicrobial, or mixed. Treatment data included information on the choice of antimicrobial therapy and the timing of its institution relative to the obtaining of the culture specimen. The occurrence of such procedures as incision and drainage or debridement was recorded.

Statistical analyses

We developed a risk stratification algorithm to allow clinicians to identify at admission the patient's risk for an MSI in order to target empiric therapy appropriately. We first examined descriptive comparisons between patients with and without MSI on the basis of their clinical, demographic, microbiologic, and treatment characteristics. All continuous variables were compared using the student *t*-test for parametric and the Mann-Whitney U test for nonparametric distributions. All categorical variables were compared using the χ^2 test when the number of observations was five or greater and the Fisher exact test when the number of observations was fewer than five. All variables differing at $\alpha < 0.2$, in addition to those meeting the criteria for clinical plausibility, were included in the multivariable logistic regression model to examine independent predictors of MSI. Differences were deemed significant at $\alpha < 0.05$. Model discrimination was measured with the c-statistic and calibration with the Hosmer Lemeshow goodness-of-fit test. Positive and negative predictive values (PPVs, NPVs, respectively), of the risk factors alone and in combination were computed. The MSI prediction rule's success in detecting MSI were compared with that of the HCA risk factors. All calculations were performed in Stata version 9.2 (Statacorp, College Station, TX).

Results

Among the 717 patients admitted to the hospital with a cSSSI, 68 (9.5%) had an MSI, of whom 38.2% received inappropriate empiric therapy. The most frequent sources of culture were blood (n = 372; 51.9%), wound (n = 137; 19.1%), and tissue (n = 57; 7.9%). At baseline, MSI patients were similar to their non-MSI counterparts with regard to demographic factors and the prevalence of comorbidities (Table 1). Additionally, MSIs were more likely to be classified as HCA (82.4%) than were non-MSIs (72.6%; $p = 0.085$). Two specific HCA risk factors occurred more often in the MSI cohort: Recent hospitalization (80.9% in MSI vs. 66.0% in non-MSI; $p = 0.014$) and nursing home residence (22.1% vs. 10.5%; $p = 0.005$); (Table 1). Whereas cellulitis and abscess were more prevalent infection types in the non-MSI group, decubitus and diabetic foot ulcers were more frequent in the setting of MSI (Table 1). With respect to bacteriology results, cultures from

Table 1. Patient Baseline Characteristics and Infection Types

	Mixed (n = *68*)	*Nonmixed* (n = *649*)	*p value*[a]
Age	53.5 ± 18.1	51.2 ± 17.4	0.315
Female (%)	35 (51.5)	330 (62.2)	0.905
Race (%)			
Caucasian	33 (48.5)	307 (47.3)	0.946
African American	33 (48.5)	326 (50.2)	
Other	2 (2.9)	16 (2.5)	
Comorbidities (%)			
Diabetes mellitus	22 (32.4)	189 (29.1)	0.578
Peripheral vascular disease	1 (1.5)	21 (3.2)	0.713
Liver disease	7 (10.3)	45 (6.9)	0.309
Malignant disease	15 (22.1)	99 (15.3)	0.144
Human immunodeficicency virus infection	1 (1.5)	20 (3.1)	0.711
Organ transplant	1 (1.5)	11 (1.7)	1.000
Autoimmune disease	2 (2.9)	13 (2.0)	0.645
End-stage renal disease	6 (8.8)	65 (10.0)	1.000
HCAI (%)	56 (82.4)	471 (72.6)	0.085
HCAI risk factors (%)			
Hospitalization	55 (80.9)	428 (66.0)	0.014
Antibiotics	13 (19.1)	103 (15.9)	0.489
Nursing home	15 (22.1)	68 (10.5)	0.005
Dialysis	5 (7.4)	53 (8.2)	0.812
Type of infection (%)[b]			
Cellulitis	23 (33.8)	326 (50.2)	0.010
Decubitus ulcer	16 (23.5)	71 (10.9)	0.002
Surgical site	8 (11.8)	106 (16.3)	0.327
Device-associated infection	17 (25.0)	165 (25.4)	0.939
Diabetic foot ulcer	8 (11.8)	34 (5.2)	0.029
Abscess	13 (19.1)	230 (35.4)	0.007
Other[c]	3 (4.4)	23 (3.5)	0.729

[a]P values derived using Student's *t*-test for continuous variables, χ^2 test for categorical variables with five or more values per cell, and the Fisher exact test for categorical variables with five or fewer values per cell.
[b]Numbers add up to more than 100% because of overlap in diagnoses.
[c]Other infection types: Pilonidal cyst (n = 3); skin and subcutaneous structures (n = 2); chronic ulcer (n = 13); stump infection (n = 9).
HCAI = healthcare-associated infection.

626 patients (96.5%) with non-MSI grew out either a gram-negative or a gram-positive organism, with 38 cultures (5.9%), 33 of which were blood cultures, yielding *Candida* spp. (Table 2). Whereas most types of organism were more prevalent in the MSI group, such frequent culprits as *S. aureus*, and specifically MRSA, were balanced evenly between the two groups (Table 2). Notably, the prevalence of gram-positive pathogens was 74.7% in the non-MSI group, whereas that of gram-negative organisms was 21.7%, with *Pseudomonas aeruginosa* occurring in only 6.2% of all non-MSIs (Table 2).

We explored the details of the missing coverage among the 28 MSI patients receiving inappropriate empiric therapy (Table 3). The most frequently missed gram-negative coverage was for *P. aeruginosa* (n = 6; 23.1%), whereas that for gram-positive organisms was for vancomycin-resistant enterococci (VRE; n = 9; 34.6%). Patients in the MSI group had a greater severity of illness, as evidenced by their being more than twice as likely to require ICU care than the non-MSI group (Table 4). Along with this, they were nearly twice as likely to receive inappropriate empiric therapy (Table 4). The hospital mortality rate and length of stay (LOS) were directionally higher among patients with MSIs than among those with non-MSIs, although these differences did not reach statistical significance (Table 4).

Table 2. Bacteriology Findings

	Mixed (n = *68*)	*Nonmixed* (n = *649*)	*p value*[a]
Gram-negative organisms (%)	68 (100)	141 (21.7)	< 0.001
Acinetobacter	6 (8.8)	6 (0.9)	< 0.001
Citrobacter	4 (5.8)	8 (1.2)	0.020
Enterobacter	9 (13.2)	14 (2.2)	< 0.001
Escherichia coli	12 (17.6)	35 (5.4)	0.001
Klebsiella	10 (14.7)	26 (4.0)	0.001
Morganella	3 (4.4)	3 (0.5)	0.013
Proteus	6 (8.8)	15 (2.3)	0.010
Pseudomonas	21 (30.9)	40 (6.2)	< 0.001
Serratia	1 (1.5)	9 (1.4)	1.000
Stenotrophomonas	1 (1.5)	5 (0.8)	0.451
Bacteroides	6 (8.8)	13 (2.0)	0.006
Gram-positive organisms (%)	68 (100)	485 (74.7)	< 0.001
VRE	10 (14.7)	18 (2.8)	< 0.001
Enterococcus faecalis	14 (20.6)	37 (5.7)	< 0.001
Enterococcus faecium	7 (10.3)	20 (3.1)	0.010
Staphylococcus aureus	37 (54.4)	346 (53.3)	0.899
MRSA	23 (33.8)	229 (35.3)	0.894
MSSA	14 (20.6)	119 (18.3)	0.625
Streptococcus spp.	6 (8.8)	40 (6.2)	0.430
Candida spp. (%)	6 (8.8)	38 (5.9)	0.019

[a]P values derived using Fisher exact test for categorical variables.
VRE = vancomycin-resistant *Enterococcus*; MRSA = methicillin-resistant *Staphylococcus aureus*; MSSA = methicillin-sensitive *S. aureus*.

Table 3. Type of Missing Empiric Coverage among Patients with Mixed Complicated Skin and Skin Structure Infections Receiving Inappropriate Empiric Therapy (n = 26)

Organism type	*No. (%)*
Any gram-negative organism, including *Psuedomonas aeruginosa*	18 (69.2)
P. aeruginosa	6 (23.1)
Gram-negative and not gram-positive	11 (42.3)
P. aeruginosa and not gram-positive	4 (15.4)
Any gram-positive organism (including MRSA and VRE)	15 (57.7)
MRSA	3 (11.5)
VRE	9 (34.6)
Gram-positive and not gram-negative	8 (30.8)
MRSA and not gram-negative	2 (7.7)
VRE and not gram-negative	6 (23.1)
Gram-negative and gram-positive	7 (26.9)

MRSA = methicillin-resistant *Staphylococcus aureus*; VRE = vancomycin-resistant *Enterococcus*.

Table 4. Processes of Care and Outcomes

	Mixed (n = *68*)	*Nonmixed* (n = *649*)	*p value*[a]
Inappropriate treatment (%)	26 (38.2)	132 (20.3)	0.002
ICU admission (%)	9 (13.2)	33 (5.1)	0.013
Debridement (%)	19 (27.9)	256 (39.5)	0.063
Hospital mortality rate (%)	6 (8.8)	31 (4.8)	0.151
Hospital LOS, days			
Mean (SD)	9.7 (13.5)	8.2 (12.7)	
Median (IQR)	6.2 (3.6, 10.7)	5 (2.6, 9.7)	0.065

[a]Mann-Whitney U test.

ICU = intensive care unit; LOS = length of stay; SD = standard deviation; IQR = interquartile range.

In a logistic regression with MSI as the dependent variable, three factors emerged as significantly associated with the risk of an MSI: Need for ICU admission, infection that was not an abscess, and previous residence in a nursing home (Table 5). Although the calibration of the model was adequate (Hosmer-Lemeshow goodness-of-fit p = 0.931), the discrimination was only fair (c statistic 0.63). As a screening test for the presence of an MSI, the PPV of having at least one of the identified risk factors was poor (11.66%). Alternatively, the NPV exceeded 95% (Table 5). Although increasing the number of risk factors improved the PPV for MSI slightly, it also resulted in a reduction in the NPV (data not shown).

The comparison of MSI algorithm's characteristics with the HCA risk factors at identifying or excluding the presence of MSI showed no differences in either calibration, along with slightly better discrimination for the MSI risk factors (Table 6). However, although the absence of HCA risk factors would disqualify 178 of 190 patients correctly from dual coverage against both gram-positive and gram-negative organisms, the MSI algorithm would exclude 217 of 228, resulting in an increase in classification accuracy of 20.5% of non-MSI without any loss in the sensitivity for MSI (Table 6).

Discussion

We demonstrate that in a broad cohort of patients admitted to a large urban academic medical center from the community and having a cSSSI, approximately 10% had an MSI. Compared with non-MSIs, patients with MSIs were more likely to be classified as having an HCA cSSSI and to receive inappropriate empiric therapy. Because the presence of an MSI is associated with inappropriate empiric therapy, it presents a potential novel target for early recognition to tailor appropriate therapy. To aid clinicians in this task, we developed a simple bedside decision rule, by which if, at hospitalization, the patient does not require ICU care, his or her infection is an abscess, and he or she is not a nursing home resident, the likelihood that the infection is not an MSI exceeds 95%. This rule may help physicians identify subjects who do not require drugs to cover both a gram-negative and a gram-positive organism. Whereas the absence of HCA risk factors also results in a nearly 95% exclusion of MSI, the absolute number of misclassifications favors using our MSI risk factors. Namely, the greater specificity and NPV of the MSI rules compared with the HCA definition could help shield an additional 20.5% of patients from unnecessarily broad-spectrum treatment without any loss in sensitivity for MSI.

Table 5. Predictors of Mixed Infection Present on Admission[a]

Risk factor	*Odds ratio*	*95% CI*	*P value*[b]
ICU admission	2.49	1.12-5.52	0.025
Infection type: Not abscess	2.01	1.06-3.81	0.032
Nursing home	1.99	1.05-3.78	0.036

[a]Factors entered in regression (at univariable $\alpha < 0.2$) but not retained at $p < 0.05$ were recent hospitalization, cancer, cellulitis, decubitus ulcer, diabetic foot infection; factors not entered because of co-linearity were healthcare-associated infection (colinear with recent hospitalization and nursing home residence) and diabetes mellitus (co-linear with diabetic foot infection).

[b]Calibration: Hosmer-Lemeshow goodness-of-fit χ^2 p = 0.931; discrimination: c-statistic = 0.63.

CI = confidence interval; ICU = intensive care unit.

Combating further emergence of antimicrobial resistance requires a thoughtful approach to choosing empiric therapy. At the same time, strong data indicate that inadequate coverage early in the course of the infection markedly worsens outcomes. For example, the mortality rates in pneumonia [9–14] and blood stream [15–22] and other [23] infections are elevated when inadequate empiric coverage is chosen, a rise that is not attenuated by antibiotic escalation in response to culture results [24]. To improve early decision making, the concept of HCA infection was developed. The idea was to bring into sharper relief the risk factors predisposing patients coming in from the community to infections with pathogens traditionally found to be responsible for nosocomial infections. Although these definitions have been incorporated into evidence-based practice guidelines [25], they have never been validated. Furthermore, emerging evidence suggests that the HCA definition's lack of specificity results in more permissive use of broad-spectrum antibiotics, thus heightening concerns about selective pressure to promote further resistance and even to worsen individual patient outcomes [26].

In the case of cSSSI, although inappropriate empiric therapy does not appear to elevate the risk of in-hospital death, it does alter hospital resource utilization [6]. In the same data set analyzed in the current study, in a generalized linear model with the log-transformed LOS as the dependent variable, adjusting for multiple potential confounders, inappropriate empiric therapy conferred an attributable incremental increase in the hospital LOS of 1.8 days (95% CI 1.4-2.3) [6]. Together with the concerns about resistance pressures stemming from unnecessarily broad empiric coverage, the concern about the most efficient use of healthcare resources is a compelling impetus for developing risk stratification algorithms to use at the bedside, which can help clinicians develop appropriate coverage decisions that align with the goals of both best clinical care and antibiotic stewardship. Our identification of MSI as a risk group for inappropriate empiric therapy and the development of a simple decision rule to limit the probability of an MSI is consonant with this philosophy.

There is a bewildering lack of mention of the probability of a cSSSI being caused by both a gram-positive and a gram-negative organism in the most recent evidence-based practice guidelines from the Infectious Diseases Society of America [27]. Their guideline committee focused mostly on such

Table 6. Mixed Skin Infection (MSI) and Healthcare-Associated Infection (HCAI) Test Characteristics for MSI Identification and Exclusion

	Sensitivity[a]	*Specificity*[a]	*PPV*[a]	*NPV*[a]	*Calibration*	*Discrimination*
MSI	83.8	33.4	11.7	95.2	0.931	0.63
HCAI	82.4	27.4	10.6	93.7	0.955	0.61

[a]Given as percent.

gram-positive pathogens as *S. aureus* and *S. pyogenes*. Although acknowledging resistance emergence in both, little attention is afforded to gram-negative culprits, either singly or in combination with gram-positive bacteria. The fact that our study, conducted subsequent to the publication of the above guideline in 2005, has discovered a 10% prevalence of MSI among patients hospitalized with cSSSI likely attests to the continuing shifts in the bacteriology of infectious disease in general and cSSSI in particular. However, given the single-center nature of our study, the data require confirmation in a larger, preferably multicenter, study.

Along these lines, our data suggest that the risk of having a gram-negative cSSSI in the setting of a non-MSI is substantially lower (21.7%) than that of a gram-positive infection (74.7%). The fact that roughly one in five patients without MSI risk factors may still be infected with a gram-negative pathogen is worrisome and suggests that additional risk stratification algorithms to identify these patients early are required to tailor appropriate coverage. However, it is helpful to recognize that *P. aeruginosa* is indeed a rare culprit in non-MSI, and this can have immediate implications for narrowing empiric coverage away from antipseudomonal agents. It is important to note that in our data, the prevalence of gram-negative infection is higher than in a recently reported cohort from another academic medical center [28], implying that local bacteriology patterns should remain the primary drivers of empiric treatment decisions.

Our study has a number of limitations. First, as a retrospective cohort study, it is prone to various forms of bias, most notably selection bias. To minimize the possibility of such, we established a priori case definitions and enrolled consecutive patients over a specific period of time. Second, as in any observational study, confounding is an issue. Although we developed regression models to account for factors that impact the risk of MSI, residual confounding remains a concern. Third, we identified only a small number of MSIs, and this necessarily limited our ability to validate the predictive model. Validation in a large multicenter cohort is necessary to improve the generalizability of our results.

In summary, an MSI is present in 10% of all patients admitted from the community with a cSSSI. These patients are more likely than those without an MSI to receive initially inappropriate empiric antibiotic therapy. To balance the benefit of tailored appropriately broad coverage for these patients with the concerns about promoting antimicrobial resistance, our simple bedside rule can identify with 95% reliability those patients who are at low risk for an MSI, and thus limit the use of broad-spectrum antimicrobial drugs.

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Appendix 1. Inclusion Criteria According to International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) Code

Principal diagnosis code	*Description*
680	Carbuncle and furuncle
681	Cellulitis and abscess of finger and toe
682	Other cellulitis and abscess
683	Acute lymphadenitis
685	Pilonidal cyst with abscess
686	Other local infections of skin and subcutaneous tissue
707	Decubitus ulcer
707.1	Ulcers of lower limbs, except decubitus ulcer
707.8	Chronic ulcer of other specified sites
707.9	Chronic ulcer of unspecified site
958.3	Posttraumatic wound infection, not elsewhere classified
996.62	Infection attributable to other vascular device, implant, and graft
997.62	Infection (chronic) of amputation stump
998.5	Postoperative wound infection

Appendix 2. Excluded ICD-9-CM Codes

Diagnosis code	*Description*
728.86	Necrotizing fasciitis
785.4	Gangrene
686.09	Erethyma gangrenosum
730.00–730.2	Osteomyelitis
630–677	Complications of pregnancy, childbirth, and puerperium
288.0	Neutropenia
684	Impetigo
Procedure code	
39.95	Plasmapheresis
99.71	Hemoperfusion