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ABSTRACT

Purpose: Skin and soft tissue infections (SSTIs) cause about 15 million cases of infection that result in more than 869,000 annual hospitalizations in the United States. Cellulitis accounted for 63% of all patients hospitalized with SSTIs between 2009 and 2011. The primary objective of this study was to evaluate physician adherence rates to evidence-based practice guidelines. Secondary objectives included evaluating antibiotic selection preferences and duration of therapy. The goal of the project was to generate data to inform the development of a hospital-based protocol for nonnecrotizing SSTI treatment.

Methods: This study was a single-center, retrospective, electronic chart review of patients admitted to the hospital for nonnecrotizing SSTI. We reviewed charts of patients who were admitted with a diagnosis of cellulitis and abscess infection from August 2014 to August 2015.

Results: Vancomycin, piperacillin/tazobactam, and clindamycin were the initial empiric antibiotics used most frequently. The adherence rates to guideline-recommended empiric antibiotic therapy and duration of treatment were about 40% and 70%, respectively. The median duration of antibiotic therapy was 12 days. Male gender and presence of purulent discharge as independent variables led to poor adherence to guideline-recommended empiric antibiotic therapy (male versus female gender, 35% versus 50.8%; $P = 0.045$; purulent discharge [yes versus no], 23.9% versus 60.4%; $P < 0.0001$).

Conclusions: The results showed substantial noncompliance with guideline recommendations on empiric antibiotic selection for the treatment of nonnecrotizing SSTIs. There is a substantial opportunity for clinical pharmacist intervention in ensuring the efficient utilization of hospital resources to improve guideline compliance; promote appropriate antibiotic selection; reduce unnecessary antibiotic exposure; and reduce cost of hospitalization.

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INTRODUCTION

The increasing incidence of skin and soft tissue infections (SSTIs), with a corresponding rise in hospital admissions, poses a public health dilemma that requires a more tailored clinical pharmacotherapy intervention. Increasing incidence is evident in about 15 million annual cases of SSTIs[1] and more than 869,000 annual hospital admissions in the United States.[2] This common clinical condition can have mild to life-threatening complications.

Cellulitis is a subtype of SSTI that is among the most frequent in hospitalized patients. Among 471,550 patients with SSTIs hospitalized between 2009 and 2011, cellulitis accounted for 63% (298,036).[3] Cellulitis is a serious SSTI due to its acute infectious process and its propensity to spread through lymphatic tissue and the bloodstream.[4] In the recent terminology of the Food and Drug Administration's Center for Drug Evaluation and Research, cellulitis is classified as an acute bacterial skin and skin structure infection (ABSSSI).[5]

Hospitalized patients with SSTIs tend to have a longer hospital stay than patients without SSTIs. A matched cohort study by Hatoum et al. found that hospitalized patients with SSTIs spent, on average, an additional 3.81 days in the hospital with an increased hospitalization cost of $14,974 compared with patients without SSTIs.[6] A prospective, multicenter, observational study by Lipsky et al. found that patients with ABSSSIs had an average hospital stay of 7.1 days.[7]

Current practices that could contribute to such patient outcomes include paucity of a consensus on optimal pharmacotherapy protocol, prolonged use of broad-spectrum antibiotics, or treatment course. This was highlighted in a multicenter retrospective study by Jenkins et al. in which the use of broad gram-negative antibiotics or a treatment course longer than 10 days were common among hospitalized patients with ABSSSIs.[8] Such clinical practices and the lack of a consensus on drug treatment offer the clinical pharmacist a substantial opportunity for a protocol-based pharmacotherapy intervention with a goal of reducing unnecessary antibiotic exposure, improving patient outcomes, and utilizing hospital resources more efficiently.

To generate data for the development of a hospital-based protocol for nonnecrotizing SSTI treatment, this research

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sought to evaluate physician prescribing patterns and duration for antibiotics in the treatment of these infections. We hypothesized that there is a substantial opportunity for antimicrobial stewardship practice and clinical pharmacist interventions. The study also assessed the impact of the institution's current antibiotic treatment of nonnecrotizing SSTIs on hospital length of stay, readmission rate, and hospitalization cost.

METHODS

Study Design

This study was a single-center, retrospective electronic chart review of patients admitted to the hospital for cellulitis and abscess based on *International Classification of Diseases, Ninth Revision* (ICD-9) codes of 680–682.9. The presence of cellulitis and abscess was confirmed by the history and physical examination (H&P) description provided by the admitting physician, documentation of the patient H&P, and subsequent progress notes. Similarly, the presence of purulence was documented, together with an incision and drainage procedure as described by the physician in the patient chart. The study was approved by both the Xavier University of Louisiana and Louisiana State University institutional review boards.

Study Setting

This study was done at the University Medical Center New Orleans, a tertiary academic teaching hospital and level 1 trauma center. Patients have access to care at the same location via the emergency department, the 283-bed hospital, and specialty ambulatory clinics. The medical center caters mostly to an indigent and uninsured population.

Study Population

All patients 18 years of age and older with ICD-9 codes of 680–682.9 for cellulitis and abscesses at the time of admission were eligible for this study. ICD-9 codes were used to determine both admitting and discharge diagnoses. Patients younger than 18 years of age and patients without ICD-9 codes of 680–682.9 were excluded.

Data Collection

The following data were collected from eligible charts: age, gender, race, site of infection, microbiological culture results, length of stay, antibiotics, length of therapy, cost of hospitalization, readmission rates (14 days and 30 days), causative pathogen, primary service at admission, and penicillin allergy.

The following comorbidity data were also collected: diabetes, intravenous (IV) drug use, prior methicillin-resistant *Staphylococcus aureus* (MRSA) infection, recent surgery (defined as surgery within the last month), prior history of cellulitis, peripheral artery disease, peripheral vascular disease, and diagnosed alcoholism. The cost of hospitalization was determined by documenting the total bill for the specific encounter.

Outcomes

The primary and secondary outcomes were specified before the study began. The primary outcome was the physician adherence rate to the 2014 Infectious Diseases Society of America (IDSA) guideline recommendation on empiric antibiotic selection.[8] The secondary outcomes included physicians' antibiotic selection, duration of treatment, readmission rate (defined as readmission within 30 days after hospital discharge), and cost of hospitalization.

To assess the primary and some secondary outcomes, current physician practice patterns in regard to selection of empiric antibiotics and duration of therapy were compared to the 2014 IDSA clinical guideline recommendations. Physicians' choices of empiric antibiotics for nonnecrotizing SSTIs were compared to guideline-recommended empiric antibiotics.

Statistical Analysis

Descriptive data analysis was performed for demographic characteristics, *chi*-square for comparison of categorical data, and logistic regression analysis for impact of independent variables on adherence to guidelines. A P value of less than 0.05 was considered statistically significant. SAS statistical software (version 9.4) was used for the data analysis.

RESULTS

Baseline Demographics

Two hundred and twenty-two patients with ICD-9 codes for cellulitis and abscess admission between August 2014 and August 2015 were screened for eligibility. Fourteen patients were excluded during the screening process because they left against medical advice after admission. In total, 208 patient charts were reviewed for data collection and results analysis (Figure 1). The time frame of August 2014 to August 2015 was selected for data collection on eligible patients because the 2014 IDSA guideline was published in June 2014. The mean age of the study population was 43 years, 65 (31%) were female, and 89 (43%) were white (Table 1). Almost 50% of the patients were admitted into the internal medicine unit, and 10% of the patients had penicillin allergy (Table 2).

Baseline Comorbidity and Site of Infection

IV drug use and diabetes were the most common baseline active comorbid conditions at the time of patient admission (Table 3); prior history of cellulitis and alcoholism were also

Figure 1 Patient Chart Screening

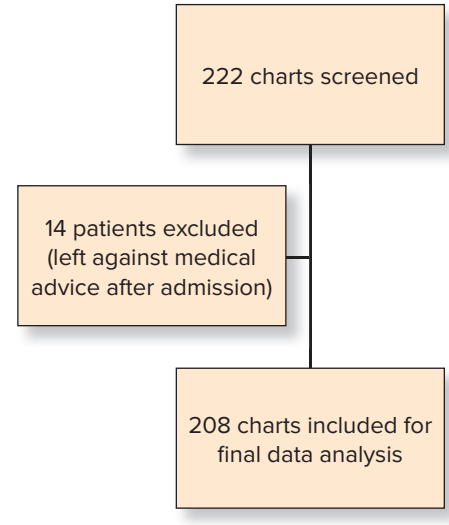

Table 1 Baseline Characteristics (N = 208)	
Age in years, mean (range)	43 (18–80)
Female, n (%)	65 (31)
Male, n (%)	143 (69)
Race, n (%)	
White	89 (43)
Black	110 (53)
Other	9 (4)
Penicillin allergy, n (%)	20 (10)

Table 2 Service Unit at Admission, n (%)	
Infectious disease	1 (0.5)
Surgical intensive care unit	1 (0.5)
Urology	1 (0.5)
Medical intensive care unit	2 (0.9)
Otolaryngology/ENT	6 (2.9)
Acute care surgery	6 (2.9)
Trauma	12 (5.8)
Plastic surgery	16 (7.7)
Surgery	17 (8.2)
Orthopedics	20 (9.7)
Oral and maxillofacial	25 (12.1)
Internal medicine	100 (48.3)

ENT = ear, nose, and throat.

Table 3 Comorbid Conditions, n (%)	
Intravenous drug user	48 (26)
Diabetes	45 (25)
History of cellulitis	37 (20)
Alcoholism	22 (12)
Methicillin-resistant *Staphylococcus aureus*	16 (9)
Peripheral venous disease	11 (6)
Recent surgery (≤ 30 days prior to admission)	3 (2)
Peripheral artery disease	0 (0)

Table 4 Site of Infection, n (%)	
Upper extremities	87 (42)
Arm	44 (21)
Hand	43 (21)
Lower extremities	58 (28)
Leg	48 (23)
Foot	10 (5)
Face/neck	35 (17)
Face	32 (15)
Neck	3 (1)
Trunk	14 (7)
Buttock	14 (7)

among the comorbid conditions. Upper extremities were the most common site of infection, occurring in about 42% of patients at admission (Table 4).

Causative Pathogen and Nonpharmacological Intervention

Among patients for whom a culture was done, 39% had a positive result, and gram-positive microbes were the main causative pathogens. MRSA was the most common isolated pathogen (Table 5). There was a 97% adherence rate to incision and drainage recommendations under the IDSA guidelines, reflecting 113 of the 117 cases in which purulence was reported.

Primary Outcome

There was a 40% adherence rate to the IDSA guideline recommendations on empiric antibiotic selection. Vancomycin was the most frequent empiric antibiotic selected for nonnecrotizing SSTI treatment (Table 6); piperacillin/tazobactam plus vancomycin was the top choice among empiric antibiotic combinations (Table 7). On discharge, clindamycin was the most commonly prescribed antibiotic (Table 8).

Secondary Outcomes

The median duration of therapy was 12 days, with a 70% adherence rate to guideline recommendations (Table 9). Guideline adherence was 60% for nonpurulent infections and 24% for purulent infections (Table 10). The average length of hospital stay was 3.5 days. There were eight readmissions: two within 14 days after discharge and six 30 days after discharge.

Both logistic regression and *chi*-square analysis of the data showed that gender and presence of purulence had a statistically significant effect on guideline adherence rate (Table 11). Adherence to guideline-recommended antibiotics by gender was 35% for men versus 50.8% for women ($P = 0.045$). Adherence to guideline-recommended antibiotics was 23.9% if purulence was reported and 60.4% if it was not ($P < 0.0001$).

DISCUSSION

Cellulitis and abscesses are among the most common subtypes of skin and skin structure infections leading to hospitalization. There has been a lack of consensus on optimal pharmacotherapy management, but the IDSA has recently published guidelines for the management of these infections.[8] Despite these guidelines, we hypothesized that, in an academic teaching institution such as ours, there would be substantial variation in pharmacotherapy strategies used for nonnecrotizing SSTIs. This study was initiated to assess current antibiotic prescribing practices for nonnecrotizing SSTI management, while generating data to guide the development of a standardized antibiotic selection pathway protocol for their management.

Gram-positive bacteria were the primary causative pathogens for cellulitis as shown by the culture results of our study. *S. aureus* was the most common isolated pathogen, with MRSA as the most frequent isolate. This outcome is similar to the result of a retrospective epidemiologic study by Ray et al.[3] In our study, vancomycin was the most common monotherapy initiated. When combination therapy was used, piperacillin/tazobactam plus vancomycin or clindamycin plus vancomycin were most commonly initiated.

The high use of vancomycin as monotherapy likely reflects heightened concern about community-onset MRSA as the cause for cellulitis. Several studies, including Jenkins et al.,[9] have reported that MRSA is the major cause of SSTI. Our study also demonstrated that MRSA was a common pathogen in these infections. Furthermore, a prospective multicenter study by Lipsky and colleagues reported that vancomycin was the most common empiric antibiotic used in the management of complicated skin and soft tissue infections.[7]

The frequent use of piperacillin/tazobactam and vancomycin as an initial combination pharmacotherapy is likely

Table 5 Culture and Isolated Pathogen

	Culture, n (%)	Purulent, n (%)	Nonpurulent, n (%)
Positive	82 (39.4)	64 (55)	18 (20)
Negative	92 (44.2)	42 (36)	50 (55)
None	34 (16.3)	11 (9)	23 (25)
Isolated Pathogens (N = 82)			
MRSA	33 (40)	24 (73)	9 (27)
MSSA	19 (23)	17 (89)	2 (11)
Streptococcus species	13 (16)	8 (62)	5 (38)
Gram-negative rods	17 (21)	15 (88)	2 (12)

MRSA = methicillin-resistant *Staphylococcus aureus;*
MSSA = methicillin-susceptible *S. aureus.*

Table 6 Empiric Antibiotic Selection

Initial Empiric Antibiotics	N (%)	% Adherence
Vancomycin	128 (61.5)	39/128 = 30.5
Piperacillin/tazobactam	111 (53.4)	31/111 = 28
Clindamycin	68 (32.7)	38/68 = 55.9
Ampicillin/sulbactam	14 (6.7)	5/14 = 35.7
Ciprofloxacin	10 (4.8)	0
Metronidazole	5 (2.4)	0
Cefazolin	3 (1.4)	2/3 = 66.7
Amoxicillin/clavulanate	1 (0.5)	0
Ceftriaxone	2 (0.96)	0
Nafcillin	2 (0.96)	0
Sulfamethoxazole/trimethoprim	3 (1.4)	1/3 = 33.3
Doxycycline	1 (0.5)	0
Aztreonam	3 (1.4)	0
Linezolid	1 (0.5)	0
Penicillin G	1 (0.5)	0
Amoxicillin	1 (0.5)	0
Overall IDSA guideline adherence		83/208 = 39.9

IDSA = Infectious Diseases Society of America.

due to concern for broad coverage as a result of the baseline comorbidities of those admitted for cellulitis management. In our cohort, diabetes was one of the common comorbidities. In these patients, there is a perceived need to cover a broad spectrum of pathogens in cellulitis. The rationale for the combination of clindamycin and vancomycin could stem from the antitoxin properties of clindamycin.[10]

The upper extremities and lower extremities were the most common sites of infection in our study. This is in contrast to Lipsky et al., who reported the lower foot as the most common site at clinical presentation.[7] In our study, IV drug use and diabetes were the most common baseline comorbidities. Most cellulitis related to IV drug use occurs within the upper extremities, while diabetes-related skin infections occur mostly in the lower extremities.

We found a high degree of compliance with the IDSA guideline recommendation of incision and drainage (96.6%), but much lower adherence with recommended empiric antibiotic therapy (40%). The high adherence rate for nonpharmacological management of cellulitis infections likely reflects the widespread understanding about the importance of incision and drainage in abscesses.

The 40% adherence rate to recommended empiric antibiotic therapy seen in our study is also not surprising. The major factor in nonadherence was the frequent use of empiric antibiotic combination therapy when not appropriate. This was associated with evidence of purulence on presentation. Interestingly, male gender was also associated with poorer adherence to guidelines, but overall purulence was higher in men than in women (70% versus 30%).

Purulence as an independent predictor of adherence rate was associated with lower adherence. We hypothesize that purulence may be seen by house staff as a marker of severity that would more likely be associated with polymicrobial infection. Many of these patients may have had baseline comorbidities that were interpreted as increasing the risk for polymicrobial infection. The presence of purulence as an independent predictor for the use of broad antibiotics was also reported in the study by Jenkins et al.[9]

The frequent use of empiric antibiotic combinations for MRSA and gram-negative pathogen coverage also contributed to the poor adherence rate. The practice of initiating broad-spectrum coverage appears to be increasing over the years. Berger et al. reported that the use of antibiotics with antipseudomonal activity increased significantly from 16% to 28% between 2000 and 2009.[17] Similarly, the use of antibiotics against MRSA significantly increased from 30% to 71% in the same period. Such changes in antibiotic prescribing may stem from concern about the increasing emergence of antimicrobial resistance. However, other than MRSA, there is little evidence of increasing resistance for microbes typically associated with cellulitis. Moreover, numerous centers have noted decreasing rates of MRSA.[11]

As with many academic health centers, the house staff generates most of the orders for empiric antibiotics. Unfortunately, our antimicrobial stewardship program (ASP) has noted that the education of house staff and consistent monitoring of their antibiotic use is severely hampered by the nature of their medical training. House staff rotate through different services on a frequent basis (most commonly monthly) and through different hospitals. Consequently, provider-specific education and feedback become more difficult. Attempts to implement order sets at our institution have been difficult for similar reasons. Data generated by this study will serve as the basis for broad-based education for all house staff.

The median duration of therapy for cellulitis infection was 12 days in our study. This resulted in a 70% adherence rate to guideline-recommended duration of treatment. The IDSA guidelines recommend that the duration of antibiotics should be five days, but antibiotic treatment should be extended to more than five days if clinical improvement is poor. Severity and possible complications during hospitalization could have contributed to the variation in inpatient therapy duration in

Table 7 Empiric Antibiotic Combinations

Common Initial Antibiotic Combination	N	Adherence, n (%)
Piperacillin/tazobactam and vancomycin	83	31 (37.3)
Clindamycin and vancomycin	14	0 (0)
Piperacillin/tazobactam and vancomycin and clindamycin	7	0 (0)
Piperacillin/tazobactam and vancomycin and ciprofloxacin	2	0 (0)
Clindamycin and ciprofloxacin	2	0 (0)
Vancomycin and ciprofloxacin	2	0 (0)
Piperacillin/tazobactam and metronidazole	2	0 (0)
Ciprofloxacin and metronidazole	2	0 (0)

Table 8 Prescribed Discharge Antibiotics, n (%)

Clindamycin	76 (37)
Sulfamethoxazole/trimethoprim	63 (30)
Amoxicillin/clavulanate	30 (14)
Ciprofloxacin	12 (6)
Cephalexin	9 (4)
Doxycycline	4 (2)
Penicillin V	2 (1)
Amoxicillin	2 (1)
Metronidazole	2 (1)
Linezolid	1 (0.5)
None	12 (6)

Table 9 Duration of Antibiotic Therapy and Cost of Hospitalization

Days of Antibiotics	Median (range)
Total days of antibiotic therapy	12 (1–48)
Days of inpatient antibiotics	2 (1–18)
Days of outpatient antibiotics	10 (0–30)
Adherence to IDSA guideline	70.2%
Average cost of hospitalization	$16,618.14

IDSA = Infectious Diseases Society of America.

Table 9. Extended duration of prescribed discharge antibiotics, also shown in Table 9, was another contributing factor to the overall duration of therapy.

Our study showed variation in empiric antibiotic strategies for the management of cellulitis and substantial noncompliance to evidence-based clinical guideline recommendations. It also highlights an ample need for the development of standardized antibiotic selection protocols in the management of cellulitis. Pasquale et al. reported that interventions made by an ASP resulted in significant reductions in length of stay and 30-day all-cause readmission rates in patients with SSTIs.[12]

This study has several limitations. The results from this single-center study may not be generalizable to other institutions. Our study was a retrospective chart review, and the diagnosis of nonnecrotizing SSTIs was based on prior chart documentation without prospective criteria for diagnosis and severity classification. In our study, we observed that the treatment approach was always reflective of a severe infection. The rationale behind treating all admitted patients as having severe nonnecrotizing SSTI could be attributed to prescribers following the old 2005 SSTI guideline (which did not clearly distinguish SSTIs as mild, moderate, or severe) or presence of comorbidities (diabetes, IV drug use, recent surgery, prior history of cellulitis, and MRSA infection) and systemic signs of infection and purulent drainage.

An additional limitation is the documentation of readmission rates. The readmission rates reported from the chart review may not be a true representation of treatment failure. Some patients who may have experienced treatment failure could have visited a different hospital for the relapse. For those patients readmitted within 14 days post-discharge, a common observation was that they were hospitalized for an average of about one day. These patients may have received only one or two doses of IV antibiotics prior to discharge the next day. In addition, these patients presented with comorbidities, such as diabetes and previous history of cellulitis infection. Similar observations were present in those readmitted 15 to 30 days post-discharge. Such patients were only hospitalized for about two days and presented with comorbidities of diabetes, peripheral venous disease, and previous history of cellulitis infection. These patients could have benefited from the identification and treatment of predisposing conditions for recurrent cellulitis and prescription of prophylactic antibiotics as recommended by the IDSA guideline. Furthermore, the degree of patient adherence to the prescribed discharge antibiotics could have contributed to readmission.

The study focuses on patients coded with cellulitis at discharge. We did not check the accuracy of the coding prospectively. However, chart review did confirm the presence of a skin and soft tissue condition that was consistent with cellulitis or other nonnecrotizing SSTI. Also, given that our study was conducted within two to 14 months after the publication of the 2014 IDSA guideline on SSTI, another limitation of the study is the expectation that prescribers will change their practice within two to 14 months of a guideline release.[8] The literature on adoption of clinical practice guidelines often cites an estimated 17-year time lag in putting new clinical guideline recommendations into practice or translating basic science into patient benefit.[19]

Finally, the possibility of misdiagnosis among patients reviewed in this study is a potential limitation. Misdiagnosis of cellulitis is a practice gap that needs to be closed with improved diagnostic approach, detailed history and physical examination, more dermatologist consults, and less rush for empiric antibiotic coverage for a potential "infection." According to a single-center retrospective study by Weng et al., about one-third of patients diagnosed with lower extremity cellulitis at admission were later found to be misdiagnosed either during discharge or during a 30-day follow-up period.[18] In that study, patients with complicating factors such as recent surgery, trauma, or diabetic ulcer were excluded. Our study evaluated

Table 10 Empiric Antibiotic Adherence to IDSA Guideline Recommendation in the Presence of Purulent Infection

Guideline Adherence	Purulent (n = 117)	Nonpurulent (n = 91)
No	89	36
Yes	28	55
Adherence	24%	60%

IDSA = Infectious Diseases Society of America.

Table 11 Effects of Variables on Adherence to IDSA Guideline Recommendations

Independent Variables	Odds Ratio	95% CI	*P* value
Age	1.013	0.989–1.037	0.2902
Gender (male vs. female)	0.495	0.259–0.944	0.0329
Purulence (yes vs. no)	0.203	0.110–0.37	< 0.0001

CI = confidence interval; IDSA = Infectious Diseases Society of America.

patients diagnosed with cellulitis in both upper and lower extremities and included patients with complicating factors such as recent surgery.

Incidence of misdiagnosis by clinicians could be attributed to the practice of "defensive medicine" (a tendency to administer antibiotics for a potential infection when faced with uncertain diagnosis of possible cellulitis). Such practice leads to unnecessary antibiotic use and patient exposure to both the therapeutic and potential adverse effects of antibiotics. Unnecessary patient exposure to antibiotics could contribute to the increasing problem of antibiotic resistance. In addition, misdiagnosis could result in unnecessary hospital stays, inefficient utilization of hospital resources, and increased costs.

CONCLUSION

There is a need for the development and implementation of protocols to promote change in the prescribing patterns of antibiotics in our academic teaching institution. Such an initiative might target antibiotic selection, de-escalation opportunities, and treatment duration in the management of cellulitis. The initiative could also develop easily accessible, standardized educational modules for rotating house staff based on IDSA guidelines. Specific antibiotic selection protocols (perhaps through order sets) could be promoted as well. Ultimately, the ASP should develop tools for antibiotic-use monitoring and feedback to house staff and attending staff on a frequent basis to encourage guideline adherence. Based on the results of our study, the IDSA guidelines have been incorporated into the hospital's mobile clinical companion application. We have developed both an antibiotic selection pathway and an order set for the management of nonnecrotizing SSTIs. This antibiotic selection pathway has been incorporated into the hospital's antimicrobial stewardship kit in the mobile clinical companion application. Implementation of such initiatives may improve patient care outcomes and promote better utilization of hospital resources. The impact of the antibiotic selection pathway and an order set on better adherence to IDSA guidelines could be evaluated in future studies.

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