Comparison of broad-spectrum antibiotics and narrow-spectrum antibiotics in the treatment of lower extremity cellulitis

Abdulaziz Saleh Almulhim[1,2]*, Fawaz M. Alotaibi[3]

[1]King Faisal University, College of Clinical Pharmacy, Al-Ahsa, Saudi Arabia,
[2]The University of Arizona, College of Pharmacy, Tucson, AZ, United States,
[c]Virginia Commonwealth University, School of Pharmacy, Richmond, Virginia

Address for correspondence:
Abdulaziz Saleh Almulhim, 3300 N Paseo De Los Rios, Tucson, Arizona, United States.
(Tel.): 520-2880444.
E-mail: almulhim@email.arizona.edu

ABSTRACT

Objective: Cellulitis is a commonly encountered medical illness and is most frequently caused by Group A β-hemolytic *Streptococcus* species and *Staphylococcus aureus*. The purpose of this study was to compare clinical outcomes of patients with lower extremity cellulitis treated with broad-spectrum and narrow-spectrum antibiotics.

Methods: This was a retrospective cohort study conducted in a community tertiary hospital between January 2016 and May 2016. Patients were included if they were diagnosed with uncomplicated non-purulent lower extremity cellulitis. Patients were divided into two groups: Individuals receiving narrow-spectrum antibiotics or receiving broad-spectrum antibiotics. Logistic regression analysis was used to estimate the odds ratio of repeat visit between the groups.

Results: A total of 599 patients with uncomplicated cellulitis were identified; of which 120 were included in the study (93 in narrow-spectrum arm and 27 in broad-spectrum arm). Repeat visit due to cellulitis was similar in both Groups 1 (4%) and 3 (3%) ($P = 0.89$) in the broad-spectrum arm and narrow-spectrum arm, respectively.

Conclusion: Broad-spectrum antibiotic use in uncomplicated cellulitis was common and unjustified given the results of our study. Implementation of clinical practice guidelines is recommended in limiting broad-spectrum antibiotics use in such population.

Keywords: Broad-spectrum antibiotics, cellulitis, infection, skin and soft tissue infections

Introduction

Skin and soft tissue infections (SSTIs) are classified based on the presence or absence of purulence; they are further divided based on severity and complexity.[1] Cellulitis is an infection of deep dermis and subcutaneous tissues characterized by swelling, erythema, pain, and tenderness.[2] A recent analysis of emergency department (ED) visits for SSTIs by the National Hospital Ambulatory Medical Care Survey for 1993–2005 concluded that there is nearly a 3-fold increase in the incidence of SSTIs.[3] Pathogens are typically skin flora with the most common causative pathogens being Group A β-hemolytic *Streptococcus* and *Staphylococcus aureus*.[2,4] Community-acquired methicillin-resistant *Staphylococcus aureus* (MRSA) has become increasingly prevalent such that it is included in the differential for causative pathogens.[5] Nevertheless, the current Infectious Diseases Society of America (IDSA) guidelines recommend that non-purulent cellulitis be treated with antibiotics active against methicillin-sensitive *Staphylococcus aureus* (MSSA) and β-hemolytic *Streptococci* only.[1] Broad-spectrum antibiotics are recommended only in

immunocompromised patients or patients with systemic signs of illness.[1] The guidelines define systemic signs of illness as the presence of two or more of the systemic inflammatory response syndrome (SIRS) criteria. However, broad-spectrum antibiotics continue to be administered for patients with uncomplicated SSTIs.[6-8] Antimicrobial resistance is considered a growing problem worldwide. The increased use of anti-pseudomonal antibiotics has been linked to increased risk of multidrug-resistant organisms.[9] It is also important to mention that the risk of MRSA infections is increased in IV drug users, prisoners, children and those with penetrating trauma, and purulent drainage.[3]

The recommended duration of the treatment for uncomplicated cellulitis is 5 days of antimicrobial therapy, which has been shown to be as effective as a 10-day course.[1,8,10] Several studies have found that cellulitis treatment failure was not different regardless of the spectrum of activity.[6,11] Data are robust that non-purulent cellulitis can be treated with non-MRSA antibiotics such as penicillin or first-generation cephalosporins.[1,6] The purpose of this study was to determine

the treatment failure rate of lower extremity cellulitis when treated with broad-spectrum antibiotics compared to narrow-spectrum antibiotics and to describe the inappropriate use of broad-spectrum antibiotics in lower extremity cellulitis.

Methods

Study design, data source, and data collection

A retrospective chart review of adult patients 18 years or older who were admitted to the hospital or visited the ED between January 2016 and May 2016 was conducted. Patients were identified using International Classification of Diseases, 10th revision. Patients were included only if they had a lower extremity cellulitis diagnosis (L03.115, L03.116, and L03.90). The primary author reviewed charts to select eligible patients for review of the electronic record. Patient's demographics, laboratory and microbiological results, and antibiotics administered during admission or prescribed were reviewed and recorded [Table 1]. Patients were excluded if they had one or more of the following: Upper extremity cellulitis; complicated SSTIs; animal bites; immunosuppression; purulent cellulitis; surgical site infections; IV drug use; pregnancy; separate or concomitant source of infection; and history of MRSA infection. Immunosuppression was defined as neutropenia and immunosuppressive therapy (e.g., chemotherapy in the past 4 weeks, cyclosporine, tacrolimus, azathioprine, 20 mg/day or more of prednisone, or its equivalent for more than 3 months).[12] Sample size was determined based on the findings of previous studies.[6-8,13] This study was deemed by Northwest Medical Center Institutional Review Board.

Definitions

Diagnosis of cellulitis was confirmed through chart review based on the provider's assessment and documentation for cellulitis.

Complicated SSTIs were defined as infections that extend deeper into tissues other than skin and subcutaneous tissues including necrotizing fasciitis and diabetic foot infections.[14] Due to the lack of consensus definition,[14] we defined broad spectrum as antibiotics with activity against *Pseudomonas aeruginosa* or a combination of two injectable antibiotics with different spectrum of activity.[6,8,11] Any antibiotic administered or prescribed for lower extremity cellulitis during the study was considered in the analysis. Treatment failure was defined as any repeat visit to the hospital due to cellulitis. ED visit only without admission also was included in this definition. Duration of therapy was defined as the cumulative number of calendar days during which antibiotics were administered and/or prescribed. Duration of therapy longer than 10 days was considered inappropriate.[6,11] Inappropriate antibiotic use was defined as the use of vancomycin in the absence of penicillin allergy, and the use of piperacillin-tazobactam (PTZ) in the absence of indication (i.e., SIRS criteria).[1] SIRS was defined as the presence of two of the following: Heart rate >90 beats/minutes, respiratory rate >20/min, white blood cell count (WBC) >12,000/mm^3, or <4,000/mm^3, or >10% bands, and body temperature >38°C or <36°C.

Outcomes assessment

Treatment failure in patients treated with narrow-spectrum antibiotics compared to broad-spectrum antibiotics was considered as the primary outcome. Cumulative duration of therapy, hospital length of stay, and inappropriate antibiotic use in hospitalized patients were considered secondary outcomes.

Means and standard deviation were calculated for continuous variables. Frequency and percentage were reported for the categorical variables. Chi-square and Student's *t*-test were used to evaluate the primary and secondary outcomes, respectively.

Table 1: Demographic characteristics for those who received (broad- and narrow-spectrum antibiotics)

Variable	Broad-spectrum antibiotics (*n*=27)	Narrow-spectrum antibiotics (*n*=93)	*P*-value
Age (mean, SD)	68 (19)	59 (23)	0.06
Hospital admission *n* (%)	27 (100)	18 (19.3)	0.05
Sex *n* (%)			0.068
Female	10 (37)	53 (56)	
Male	17 (62)	40 (43)	
BMI, Kg/m^2 (mean, SD)	31.2 (1)	30.5 (1)	0.69
Temperature, °F, (mean, SD)	99 (1)	98 (0.7)	0.001
WBC (mean, SD)	10.71 (5.8)	7.4 (2)	0.006
MRSA nasal			-
Positive	2	0	
Negative	7	4	
N/A	18	89	
Lactic acid ≥2 (*n*)*	4	0	0.001
SIRS+*n* (%)	6 (22)	1 (1)	-

SD: Standard deviation, BMI: Body mass index, WBC: White blood cell count 10⁹ cell/L, °F: Fahrenheit, MRSA: Methicillin-resistant *Staphylococcus aureus*, SIRS: Systemic inflammatory response syndrome, *Only four patients had lactic acid levels ≥2 in the broad-spectrum antibiotics

Independent risk factors for hospital repeat visit were identified by logistic regression analysis. Variables with $P = 0.05$ or less were included in multivariate logistic regression analysis. STATA 14.0 (Stata Corp, College Station, TX) software was used for data analysis.

Results

A total of 599 patients were identified with a diagnosis of cellulitis between January 2016 and May 2016, of which 479 (79.9%) were excluded from the analysis after applying our inclusion and exclusion criteria [Figure 1]. The final cohort included 120 patients with lower extremity cellulitis [Figure 1]. Among the 120 included patients, 93 (77.5%) have received narrow-spectrum antibiotics and 27 (22.5%) have received broad-spectrum antibiotics. Demographics, laboratory, and microbiological values are shown in Table 1. Only 18 (19.3%) of those who received narrow-spectrum antibiotics were hospitalized and received injectable antibiotics compared to 27 (100%) who received broad-spectrum antibiotics ($P = 0.05$). The WBC was significantly higher among those who received broad-spectrum antibiotics (10.7×10^9 cell/L ± 5.8) compared those who received narrow-spectrum arm (7.4×10^9 cell/L ± 2) ($P = 0.006$). 4 patients (14.8%) had elevated lactic acid (i.e., ≥ 2 mmol/L) levels in the broad-spectrum group, while none of the patients in the narrow-spectrum group had elevated lactic acid ($P = 0.001$). Of the four patients, two had other reasons for lactic acid elevation in addition to cellulitis (i.e., rhabdomyolysis and missing hemodialysis session). SIRS was present in 6 of 27 (22%) patients in the broad-spectrum group compared to 1 of 18 (1%) in the injectable narrow-spectrum group [Table 1]. The most commonly used antibiotic in the broad-spectrum arm was PTZ 17 of 27 (62.9%), among which only 1 of 17 (5.8%) patient met SIRS criteria [Table 2]. Vancomycin in combination with PTZ was used in 13 of 27 (48.1%) patients, among which only 1 of 27 (7.6%) was positive for MRSA [Table 2]. The most commonly used antibiotics in the narrow-spectrum arm were cephalexin 48 (51.6%), sulfamethoxazole-trimethoprim 23 (24.7%), clindamycin 21 (22.5%), vancomycin 8 (8.6%), and cefazolin 5 (5.3%). MRSA nasal screening was performed in only 4 (4.3%) patients in the narrow-spectrum arm and none tested positive [Table 2]. Only 1 of 27 (3.7%) patient had a positive blood culture in the broad-spectrum arm. Yet, only 15 of 27 (55.5%) had blood samples collected for culture. 13 (48%) patients in the broad-spectrum arm had an all-cause repeat visit compared to 19 (20%) in the narrow-spectrum arm (OR: 3.47, [95% CI: 1.36–8.8]). 1 patient (4%) in the broad-spectrum arm had hospital repeat visit due to cellulitis compared to 3 (3%) in the narrow-spectrum arm ($P = 0.89$) [Figure 2].

Univariate logistic regression analysis revealed that the length of stay (OR: 1.36, [95% CI: 1.15–1.62]) and body temperature (OR: 1.5, [95% CI: 1–2.38]) were statistically associated with repeat visit [Table 3]. However, after adjusting for
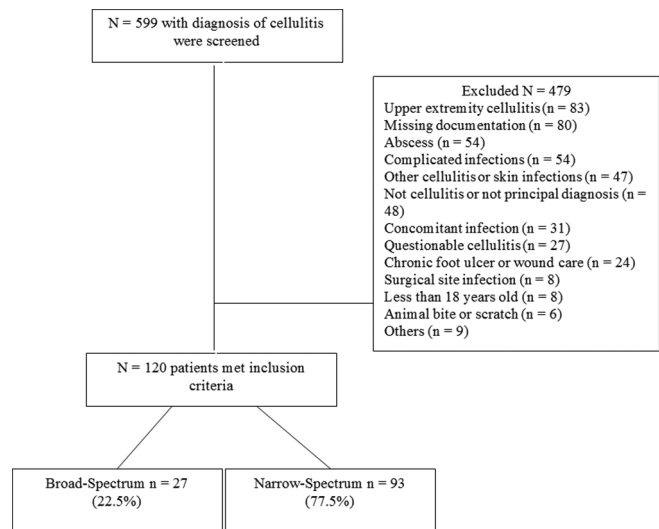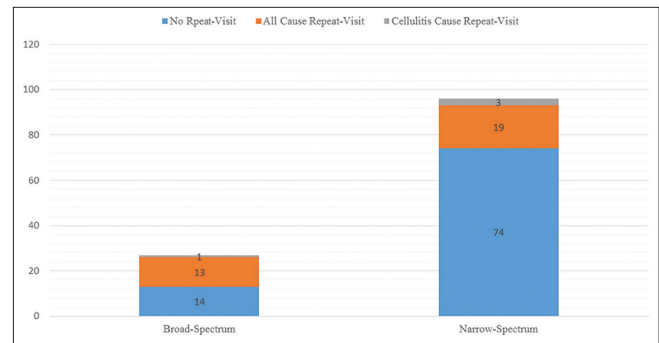

Figure 1: Patient selection flowchart

Figure 2: Primary outcome

Table 2: Injectable antibiotics used among patients who received broad- and narrow-spectrum antibiotics

Antibiotics, N[af]	SIRS, N	MRSA[a], N	Penicillin allergy, N
Vancomycin (30)	Positive (7)	Positive (1)	Positive (2)
PTZ (17)	Positive (1)	Positive (1)	-
Vancomycin+PTZ (13)	Positive (1)	Positive (1)	-
Meropenem (1)	Positive (1)	N/A	Positive (1)
Cefazolin (8)	Negative (8)	Negative[b] (3)	-
Ceftriaxone[c] (8)	Positive (1)	Positive[c] (1)	-
Cefoxitin[d] (3)	Positive (2)	Negative (2)	-
Levofloxacin (1)	Positive	N/A	Positive (1)
Ampicillin-sulbactam (1)[e]	Negative	Positive	-

[a]Only 13 patients had MRSA nasal screen done in both arms, N/A: Not available, [b]Only three patients had MRSA nasal screen done in both arms, [c]MRSA nasal screen was done in two patients, patient also was on vancomycin, [d]All received vancomycin as well, and MRSA nasal screen was done in two patients only, [e]Patient was also on clindamycin, [f]Patients could receive combination of antibiotics at the same time

confounders in the multivariate logistic regression Table 4, only the length of stay was associated with higher odds for repeat visit (OR: 1.32, [95% CI: 1–1.6]). The mean duration of therapy was not different between the groups: 9.3 ± 2 days in the broad-spectrum arm compared to 8.3 ± 2 days in the narrow-spectrum arm ($P = 0.19$). 27 patients received more

Table 3: Univariate regression analysis clinical associations for repeat visit

Variable	Odds ratio[a]	P value*	95% confidence interval
Age	1.00	0.31	0.99–1.0
Sex	0.43	0.05	0.18–0.99
BMI	1.00	0.10	0.99–1
Length of stay	1.36	<0.001	1.15–1.62
Temperature	1.5	0.02	1–2.38
SIRS	4.00	0.08	0.85–19
WBC	1.00	0.14	0.9–1.12

BMI: Body mass index, SIRS: Systemic inflammatory response syndrome, WBC: White blood cell count, a: Odds ratio greater than one was considered significant, *$P \geq 0.05$ was considered statistically significant

Table 4: Multivariate logistic regression model for repeat visits after adjusting for the other confounders

Variable	Odds ratio	P value	95% confidence interval
Length of stay	1.32	0.024	1–1.6

than 10 days of total antibiotic therapy 27 of 120 (22.5%) in both arms. The mean length of stay was similar between the broad-spectrum group and narrow-spectrum group (4.6 ± 2 vs. 4.1 ± 1 days, $P = 0.29$), respectively.

Discussion

Cellulitis is a commonly encountered SSTI. The total number of SSTIs related visits to ambulatory care physicians increased from 8.6 million in 1997 to 14.2 million in 2005.[11] Despite the availability of national guideline, uncomplicated cellulitis is commonly treated with broad-spectrum coverage.[7,8,15] Few patients had systemic signs of illness (i.e., SIRS) and the majority of patients in the broad-spectrum arm (77.8%) 21 of 27 did not need such broad coverage.[1] This is contradictory to the most recent IDSA guidelines and consistent with previous studies demonstrating that broad-spectrum antibiotics were overutilized in patients with uncomplicated SSTIs.[6,8,15] Havey et al. found thatthe PTZ use was deemed inappropriate for 86.7% of patients with cellulitis, 66.7% of patients with abscess.[13] In their retrospective study, Jenkins et al. included 533, of which 320 (60%) patients diagnosed with non-purulent cellulitis. Blood cultures were collected from 225 of 320 (70%) patients and only 15 (5%) had positive blood cultures. Not surprisingly, Gram-negative organisms were identified only in 1 (2%) patient. Nevertheless, 144 of 320 (45%) patients received broad-spectrum antibiotics.[6] This study shares some similarities with their studies in that the use of antipseudomonal antibiotics (i.e., PTZ in our study) was commonly administered 17 of 27 (62.9%) with only 6 patients (22%) meeting SIRS criteria [Table 2]. Jenkins et al. conducted another retrospective pre-intervention-post-intervention study.[7] They found that the exposure to antibiotics with antipseudomonal activity decreased from 28% to 18%. Based on their findings, the development of guidelines seems to be an attractive solution to decrease the inappropriate use of broad-spectrum antibiotics.

Walsh et al. reported the inappropriate use of antibiotics in SSTIs without complicating factors.[8] They reported that 21 of 163 (17.5%) received antipseudomonal coverage. Only 3 (6.4%) Gram-negative organisms were isolated from wound cultures.

Altogether, we think that our use of broad-spectrum antibiotics in non-purulent cellulitis is not justified given our clinical and laboratory findings. Because we excluded patients with complicated SSTIs, active IV drug users, patients with a history of MRSA infection, and purulent cellulitis, vancomycin use was considered inappropriate in 23 of 30 (76.6%), as only two patients had documented penicillin allergy and only nine had an MRSA nasal screening done of which two had SIRS on admission [Table 2]. In our institution, MRSA nasal screening is frequently done in the intensive care unit (ICU) only and will not be done for patients admitted to the medical floor unless ordered by the provider. MRSA nasal screening was done in 13 (10.8%) patients in both arms [Table 2]. Controversy exists with regard to the utility of MRSA surveillance in hospitalized patients.[13] One study found that MRSA colonization increases the risk of MRSA infection.[16] Safdar et al. conducted a systematic review to determine the relationship between MRSA or MSSA carriage status and subsequent infection.[17] They found that patients colonized with MRSA had 4-fold increased risk for MRSA infection compared to MSSA-colonized patients (OR: 4.08, [95% CI, 2.09–7.94]). In addition, IDSA guidelines recommend the addition of vancomycin or other antibiotics with activity against MRSA in patients colonized with MRSA.[1]

The mean duration of therapy in our study was similar in both arms (9.3 vs. 8.3 days) in the broad-spectrum arm and narrow-spectrum arm, respectively. Our study showed that the majority of our cellulitis patients 96 of 120 (80%) received treatment of 10 days or less, with only 24 of 120 (20%) receiving antibiotics of >10 days. This was surprising as our expectation was that the majority of patients will receive antibiotic therapy for 14 days or more as this was commonly reported in previous studies.[6,8] IDSA guidelines recommend duration with antimicrobial therapy for 5 days, but longer duration of therapy may be needed in patients who showed evidence of delayed response. Hepburn et al. conducted a randomized, double-blind placebo-controlled trial to determine if 5 days of therapy provided equal efficacy to 10 days of therapy.[10] They found that the resolution of signs of infection was similar between both groups. The authors of this study used Levofloxacin as the drug of choice of this study and generalizing results to different antibiotics may not be applicable. Jenkins et al. in his retrospective pre-intervention-post-intervention study also found that patients who received a short course of therapy were not more likely to experience clinical failure than those who received a longer course of therapy.[6]

This study has several limitations. First, this was a retrospective study and we could only control for confounders that we

collected. Second, also due to the retrospective nature and the absence of blinding, there could be a chance for reviewer bias; however, we tried to avoid bias during data collection through extensive chart review and excluding patients with questionable non-purulent cellulitis. Third, due to the retrospective nature of this study, we did not evaluate delayed response and the need for antibiotics for more than 5 days, or previous antibiotic use before admission or ED visits. This is important as the most recent IDSA guidelines recommend to broaden the antibiotic coverage in patients who fail oral therapy. Fourth, severity of illness may not have been captured well in patient's charts. Fifth, using repeat visit as the only criterion for treatment, failure may be insufficient and a closer follow-up and patient contact should have been implemented for better evaluation of the clinical outcomes. Sixth, the relatively small sample size in the broad-spectrum treatment arm could have affected the results of this study; however, it is comparable to the previous studies addressed the same problem. Last, we used SIRS criteria to determine the need for broad-spectrum antibiotics in patients with uncomplicated cellulitis. This is consistent with IDSA guidelines;[1] nevertheless, the task force of the Society of Critical Care Medicine considered SIRS criteria to be unhelpful in identifying sepsis.[17] This was supported by a study conducted in Australia and New Zealand that found one in eight patients admitted to ICUs with infection and organ failure did not fulfill the minimum two or more SIRS requisite to be labeled with sepsis diagnosis.[18]

In conclusion, the use of broad-spectrum antibiotics in patients with uncomplicated SSTIs is common and is not recommended based on the results of our study. We believe that implementation of clinical practice guidelines and providing frequent reminders to providers to adhere to national clinical guidelines will help in reducing the unnecessary use of broad-spectrum antibiotics.

Acknowledgments

References

1. Stevens DL, Bisno AL, Chambers HF, Dellinger EP, Goldstein SL, Hirschmann JV, *et al*. Practice guidelines for the diagnosis and management of skin and soft tissue infections: 2014 update by the infectious diseases society of America. Am Fam Physician 2014;89:80-189.

2. Stevens DL, Bryant AE. Impetigo, Erysipelas and Cellulitis. 2016 Feb 10. In: Ferretti JJ, Stevens DL, Fischetti VA, editors. Streptococcus pyogenes : Basic Biology to Clinical Manifestations [Internet].

Oklahoma City (OK): University of Oklahoma Health Sciences Center; 2016.

3. Pallin DJ, Egan DJ, Pelletier AJ, Espinola JA, Hooper DC, Camargo CA Jr., *et al*. Increased US emergency department visits for skin and soft tissue infections, and changes in antibiotic choices, during the emergence of community-associated methicillin-resistant *Staphylococcus aureus*. Ann Emerg Med 2008;51:291-8.

4. Stulberg DL, Penrod MA, Blatny RA. Common bacterial skin infections. Am Fam Physician 2002;66:119-24.

5. Pollack CV Jr., Amin A, Ford WT Jr., Finley R, Kaye KS, Nguyen HH, *et al*. Acute bacterial skin and skin structure infections (ABSSSI): Practice guidelines for management and care transitions in the emergency department and hospital. J Emerg Med 2015;48:508-19.

6. Jenkins TC, Sabel AL, Sarcone EE, Price CS, Mehler PS, Burman WJ, *et al*. Skin and soft-tissue infections requiring hospitalization at an academic medical center: Opportunities for antimicrobial stewardship. Clin Infect Dis 2010;51:895-903.

7. Jenkins TC, Knepper BC, Sabel AL, Sarcone EE, Long JA, Haukoos JS, *et al*. Decreased antibiotic utilization after implementation of a guideline for inpatient cellulitis and cutaneous abscess. Arch Intern Med 2011;171:1072-9.

8. Walsh TL, Chan L, Konopka CI, Burkitt MJ, Moffa MA, Bremmer DN, *et al*. Appropriateness of antibiotic management of uncomplicated skin and soft tissue infections in hospitalized adult patients. BMC Infect Dis 2016;16:721.

9. Ohmagari N, Hanna H, Graviss L, Hackett B, Perego C, Gonzalez V, *et al*. Risk factors for infections with multidrug-resistant *Pseudomonas aeruginosa* in patients with cancer. Cancer 2005;104:205-12.

10. Hepburn MJ, Dooley DP, Skidmore PJ, Ellis MW, Starnes WF, Hasewinkle WC, *et al*. Comparison of short-course (5 days) and standard (10 days) treatment for uncomplicated cellulitis. Arch Intern Med 2004;164:1669-74.

11. Hurley HJ, Knepper BC, Price CS, Mehler PS, Burman WJ, Jenkins TC, *et al*. Avoidable antibiotic exposure for uncomplicated skin and soft tissue infections in the ambulatory care setting. Am J Med 2013;126:1099-106.

12. Sepkowitz KA, Brown AE, Telzak EE, Gottlieb S, Armstrong D. *Pneumocystis carinii* pneumonia among patients without AIDS at a cancer hospital. JAMA 1992;267:832-7.

13. Havey TC, Hull MW, Romney MG, Leung V. Retrospective cohort study of inappropriate piperacillin-tazobactam use for lower respiratory tract and skin and soft tissue infections: Opportunities for antimicrobial stewardship. Am J Infect Control 2015;43:946-50.

14. Dryden MS. Complicated skin and soft tissue infection. J Antimicrob Chemother 2010;65:iii35-44.

15. Hersh AL, Chambers HF, Maselli JH, Gonzales R. National trends in ambulatory visits and antibiotic prescribing for skin and soft-tissue infections. Arch Intern Med 2008;168:1585-91.

16. Weber SG, Huang SS, Oriola S, Huskins WC, Noskin GA, Harriman K, *et al*. Legislative mandates for use of active surveillance cultures to screen for methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant enterococci: Position statement from the joint SHEA and APIC task force. Am J Infect Control 2007;35:73-85.

17. Safdar N, Bradley EA. The risk of infection after nasal colonization with *Staphylococcus aureus*. Am J Med 2008;121:310-5.

18. Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, *et al*. The third international consensus definitions for sepsis and septic shock (Sepsis-3). JAMA 2016;315:801-10.