International Journal of Infectious Diseases 16 (2012) e453–e456

Contents lists available at SciVerse ScienceDirect

International Journal of Infectious Diseases

journal homepage: www.elsevier.com/locate/ijid

Predictors of septic shock in patients with methicillin-resistant *Staphylococcus aureus* bacteremia

Simon W. Lam *, Seth R. Bauer, Elizabeth A. Neuner

Cleveland Clinic Health System, Department of Pharmacy, 9500 Euclid Avenue, Mail Code: Hb-105, Cleveland, OH 44195, USA

ARTICLE INFO

Article history:
Received 14 September 2011
Accepted 2 February 2012

Corresponding Editor: William Cameron, Ottawa, Canada

Keywords:
Methicillin-resistant *Staphylococcus aureus*
Bacteremia
Septic shock

SUMMARY

Objectives: Risk factors for septic shock associated with methicillin-resistant *Staphylococcus aureus* (MRSA) bacteremia are not well described. We designed this study to assess the independent predictors of septic shock in patients with MRSA bacteremia.

Methods: This retrospective chart review included 234 patients with MRSA bacteremia admitted to a tertiary care academic medical center. Cases of septic shock and non-septic shock MRSA bacteremia were compared in terms of patient baseline characteristics and co-morbidities, modes of acquisition, and MRSA genotyping. Independent risk factors were determined by multivariable analysis.

Results: On univariate analysis the presence of chronic kidney disease, respiratory failure, acute renal failure, staphylococcal cassette chromosome (SCC*mec*) type II, and higher APACHE II scores were significantly correlated with the presence of septic shock. On multivariate analysis, baseline APACHE II score (adjusted odds ratio (AOR) for 1-point increase 1.13, 95% confidence interval (CI) 1.04–1.22, $p = 0.005$), acute renal failure (AOR 2.57, 95% CI 1.02–6.48, $p = 0.045$), and SCC*mec* type II (AOR 2.60, 95% CI 1.01–6.75, $p = 0.049$) were independently associated with MRSA bacteremic septic shock.

Conclusions: The development of septic shock associated with MRSA bacteremia was independently correlated with baseline severity of illness, presence of acute renal failure, and an MRSA genotyping consistent with nosocomially acquired MRSA infection.

1. Introduction

Bloodstream infections (BSIs) are associated with substantial mortality and morbidity. *Staphylococcus aureus* is the second leading pathogen associated with BSIs, and the rate of methicillin resistance is rising.[1] In the most recent National Nosocomial Infections Surveillance report, the proportion of *S. aureus* isolates that showed resistance to methicillin was almost 60% among intensive care units (ICUs) in the USA. This represents an 11% increase when compared to resistance rates for 1998–2002.[2] This increase is methicillin resistance among *S. aureus* is mirrored across the world. An even more worrisome detail is that methicillin resistance may be an independent risk factor for adverse patient outcome.[3–6]

S. aureus causes a wide range of infections.[7,8] Among ICU patients, it is the most common cause of sepsis.[9] Several studies have determined that the development of complications, including septic shock, from *S. aureus* infections is correlated with increased mortality.[10,11] Gomez and colleagues, in a prospective, observational study of all methicillin-resistant *S. aureus* (MRSA) bacteremia at their institution from 2000 to 2004, found that baseline severity of illness, inadequate empiric treatment, and the development of complications (septic shock, acute renal failure, disseminated intravascular coagulopathy) were independent predictors of mortality.[10] Furthermore, Guilarde and colleagues found severe sepsis and septic shock to be independent risk factors for mortality among patients with *S. aureus* bacteremia.[11]

Despite the prevalence of MRSA infections, the wide spectrum of disease presentation, and the relationship between septic complications and worsened outcomes, there is a paucity of data for identifying significant risk factors for the development of septic shock among patients with MRSA BSI. Identifying such risk factors may further help clinicians on the triage of patients and in the identification of high-risk groups for further investigation.

The aim of the present study was to determine the independent pathogen and patient risk factors for the development of septic shock in patients with MRSA bacteremia. Since the development of shock in an infected patient can be affected by the initial treatment course, including the selection of antibiotics and adequate resuscitation, for the purposes of this study only shock that was present at the time the first positive blood culture was drawn was considered. This was done in order to reduce the number of

* Corresponding author. Tel.: +1 216 444 8913; fax: +1 216 444 9150.
E-mail address: lams@ccf.org (S.W. Lam).

1201-9712/$36.00 – see front matter © 2012 International Society for Infectious Diseases. Published by Elsevier Ltd. All rights reserved.
doi:10.1016/j.ijid.2012.02.007

confounders associated with treatment of infection and focus on the native pathogen and patient risk factors.

2. Methods

2.1. Patient selection

The study was conducted at a large, academic, tertiary medical care center. This was a retrospective case-controlled study of patients with MRSA bacteremia from January 2004 to October 2006. All patients with MRSA bacteremia who received treatment and had a hospital length of stay of at least 5 days were eligible for inclusion. Patients with polymicrobial blood cultures and those treated for <72 h were excluded. Only the first episode of MRSA bacteremia for each patient was included in the study. A computerized list of potentially eligible patients with MRSA bacteremia was generated by the medical informatics department through query of the microbiology laboratory database. Data, including demographics, clinical characteristics, and treatment, were collected retrospectively from the patient medical records and the pharmacy and microbiology databases. This study was approved by the local investigational review board.

2.2. Definitions

MRSA bacteremia was defined according to the Centers for Disease Control and Prevention criteria.[12] Bacteremia was defined as community-acquired, healthcare-associated, or hospital-acquired according to standard definitions.[13] The source of bacteremia was identified based on the presence of local signs and symptoms that were temporally related (<48–72 h), in conjunction with isolation of MRSA from the implicated source before or after MRSA blood cultures, without any other identifiable source.[14] Potential sources of infection included intravenous catheter, endocarditis, endovascular, respiratory, soft tissue, joints, urinary tract, or peritoneal. Uncomplicated bacteremia was defined as isolation of MRSA from blood cultures in patients without endocarditis and without evidence of hematogenous spread. Complicated bacteremia was defined as the presence of spread of infection, or infection involving a prosthesis that was not removed within 4 days.[15] Septic shock was defined as hemodynamic instability with two systemic inflammatory response syndrome (SIRS) criteria.[16] For the purpose of identifying independent risk factors and to avoid interference from clinician management of severe infections, only septic shock at presentation (at the time the culture was drawn) was considered.

2.3. Microbiological data

The local microbiology laboratory obtained vancomycin minimum inhibitor concentrations (MICs) using the E-test method in accordance with the guidelines established by the Clinical and Laboratory Standards Institute. The staphylococcal cassette chromosome (SCC*mec*) type was identified by a multiplex PCR with four primer-pairs as previously described.[17] Characterization of Panton–Valentine leukocidin (PVL) production by *S. aureus* was performed as previously described.[18] The presence of PVL toxin was evaluated in patients with SCC*mec* type IV MRSA bacteremia.

2.4. Statistical analysis

All comparisons were unpaired, and all tests of significance were two-tailed. Continuous variables were compared using the Student's *t*-test for normally distributed variables and the Mann–Whitney *U*-test for non-normally distributed variables. The Chi-square test or Fisher's exact test was used to compare categorical variables. A multiple logistic regression analysis was performed incorporating potential risk factors based on statistical findings ($p < 0.1$) found in the univariate analysis with plausible clinical significance. Statistical covariates were removed from the final model. A statistical software program (SPSS, version 15.0 for Windows; SPSS, Inc., Chicago, IL, USA) was used to perform all analyses.

3. Results

3.1. Patient characteristics

Of 357 total evaluated patients, 234 were eligible and included in the analysis. At the time the positive blood culture was drawn 38 patients (16%) were in septic shock.

The majority of the bacteremia cases were either healthcare-associated or nosocomially acquired (83%). No difference was found in mode of acquisition between septic shock patients and non-septic shock patients. Patients with septic shock were more likely to have a respiratory infection as the source of the MRSA bacteremia, but this difference was not statistically significant. In addition, patients with septic shock had a higher baseline APACHE II score and were more likely to have baseline class III–V chronic kidney disease (CKD). Aside from the differences listed above, the patients were matched in other evaluated areas, including age, gender, and baseline co-morbidities (Table 1).

Interestingly, the proportion of MRSA bacteremia that caused septic shock decreased in a step-wise fashion from 2004 to 2006, although this trend did not reach statistical significance (Figure 1).

3.2. Pathogen characteristics

The median E-test MIC of vancomycin for these MRSA isolates was 1.5 mg/l. No correlation was found between vancomycin MIC and the development of septic shock in these patients. The

Table 1
Baseline characteristics

	Septic shock ($n = 38$)	Non-septic shock ($n = 196$)	*p*-Value
Male, *n* (%)	19 (50)	124 (63)	0.13
Age, years, mean ± SD	59.7 ± 15.1	57.3 ± 16.2	0.39
APACHE II, mean ± SD	16.1 ± 5.9	12.1 ± 5.1	<0.001
Mode of acquisition, *n* (%)			0.20
Community	3 (8)	37 (19)	
Nosocomial	16 (42)	63 (32)	
Healthcare-associated	19 (50)	96 (49)	
Co-morbidities, *n* (%)			
Diabetes	18 (47)	82 (42)	0.53
CHF	9 (24)	44 (22)	0.87
Class III–V CKD	13 (34)	38 (19)	0.04
Immunosuppression	5 (13)	47 (24)	0.20
Source, *n* (%)			
Respiratory	8 (21)	21 (11)	0.07
Catheter-related	11 (29)	60 (31)	0.84
Unknown	10 (26)	32 (16)	0.14
Other/mixed	9 (24)	83 (42)	
MRSA genotype, *n* (%)			
SCC*mec* type II	30 (79)	69 (35)	0.04
SCC*mec* type IV	7 (18)	123 (63)	0.04
Other	1 (3)	4 (2)	
Vancomycin MIC, *n* (%)			
1.0 mg/l	2 (5)	9 (5)	0.70
1.5 mg/l	19 (50)	108 (55)	0.56
2.0 mg/l	17 (45)	79 (40)	0.61
Additional complications, *n* (%)			
Acute renal failure	12 (32)	20 (10)	<0.001
Respiratory failure	13 (34)	27 (14)	0.002

APACHE, acute physiology and chronic health evaluation; CHF, congestive heart failure; CKD, chronic kidney disease; MIC, minimum inhibitory concentration; MRSA, methicillin-resistant *Staphylococcus aureus*; SCC*mec*, staphylococcal cassette chromosome; SD, standard deviation.

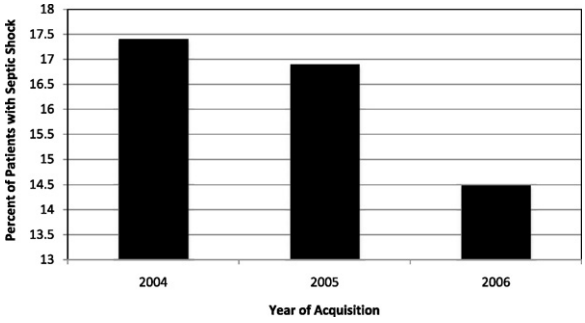

Figure 1. Proportion of MRSA-induced septic shock according to year of acquisition.

presence of PVL cytotoxin was tested in 76 patients with SCC*mec* type IV MRSA, of whom 56 (74%) tested positive. Among those with PVL-positive MRSA, only five (9%) presented with septic shock, and no significant association was found.

Genotyping of the MRSA species revealed that the majority contained either SCC*mec* type II or type IV. A significantly higher proportion of patients with SCC*mec* type II MRSA developed septic shock (Table 1). More of SCC*mec* type II isolates (92%) were either nosocomially acquired or healthcare-associated when compared to SCC*mec* type IV ($p < 0.001$). Eight patients who did not have SCC*mec* type II developed septic shock, and of these cases seven (88%) were either nosocomially acquired or healthcare-associated.

3.3. Outcomes

Not surprisingly, patients who presented with septic shock at the time the first positive culture was obtained had significantly higher hospital mortality (44.7% vs. 12.2%, $p < 0.001$). Patients with septic shock were also more likely to have additional organ dysfunction, including acute renal failure and respiratory failure requiring mechanical ventilation.

3.4. Independent risk factors for septic shock

On multivariate analysis, which included all factors that met statistical criteria and were clinically relevant, three independent risk factors for the development of septic shock in patients with MRSA bacteremia were found; these were increased APACHE II score, accompanying acute renal failure, and SCC*mec* type II (Table 2).

4. Discussion

This study found that higher baseline APACHE II scores, acute renal failure, and SCC*mec* type II containing MRSA were significant predictors of septic shock in patients with MRSA bacteremia. Aside from septic shock being a significant predictor of worsening mortality,[10,19] there were several other reasons why this outcome measure was chosen. The majority of the studies in this area have focused on using patient and pathogen characteristics to predict patient outcome measures.[10,11,19] However, patient outcomes may be affected by many extraneous factors, such as institutional standards for the management of septic shock and local antimicrobial utilization, dosing, and monitoring practices. Using septic shock at the time the first positive culture was drawn circumvents any treatment-related biases that may otherwise be introduced. This may partly explain why our study, unlike other investigations,[20–22] did not find a correlation between vancomycin MIC and outcomes. The findings of increased APACHE II score and acute renal failure as predictors of septic shock are most likely correlated with the baseline severity of the infection.

Table 2
Multivariate analysis for risk of developing septic shock

Factor	AOR (95% CI)	*p*-Value
APACHE II (per point increase)	1.13 (1.04–1.22)	0.005
Acute renal failure	2.57 (1.02–6.48)	0.045
SCC*mec* type II	2.60 (1.01–6.75)	0.049

AOR, adjusted odds ratio; CI, confidence interval; APACHE, acute physiology and chronic health evaluation; SCC*mec*, staphylococcal cassette chromosome.

S. aureus causes a wide magnitude of infections. Many different host and pathogen factors have been implicated in the severity of *S. aureus* infections.[23] Our study found that among patients with MRSA bacteremia, those infected with SCC*mec* type II MRSA were more likely to have septic shock. Healthcare-associated MRSA infections are generally caused by MRSA isolates that contain SCC*mec* types I, II, and III, while community-associated MRSA isolates frequently carry SCC*mec* types IV or V.[24–26] An international trial that examined the distribution of resistance determinants in 117 community-acquired MRSA infections, found that all of the species had methicillin resistance by SCC*mec* type IV elements.[24] Studies within the past decade on the emergence of community-acquired MRSA infections have determined that the isolates are distinct from those that cause healthcare-associated infections.[27] Isolates from the community are susceptible to most non-beta-lactam antibiotics,[27] carry SCC*mec* type IV,[28] and frequently contain the PVL cytoxin.[18] In contrast, MRSA strains associated with healthcare-associated MRSA infections are usually multidrug-resistant and carry SCC*mec* type II.[27]

Our findings are consistent with other studies that have found worsened outcomes in patients with healthcare-acquired MRSA infections.[19,29] In a prospective observational study, Ganga and colleagues evaluated the relationship between SCC*mec* type and outcomes in patients with *S. aureus* bacteremia at their institution.[19] On multivariate analysis, they discovered that SCC*mec* type II was an independent predictor of mortality (odds ratio (OR) 3.73, 95% confidence interval (CI) 1.81–7.66, $p = 0.00$). The authors suggested that a possible explanation for the increased mortality was differences in virulence factors or antibiotic susceptibility. Since our study evaluated risk factors for septic shock at the time the culture was drawn, it is unlikely that antibiotic susceptibility would have been the contributing factor. This would suggest that there may be other virulence factors that are determinants of increased mortality with SCC*mec* type II infection.

Our study has a number of limitations. The epidemiological breakdown of various subtypes of MRSA is different in different geographical areas. Hence, the findings of SCC*mec* type being a significant predictor of septic shock may not be applicable in other areas. However, a recent epidemiological study of invasive MRSA infections in nine different metropolitan areas within the USA found similar MRSA infection trends as in the current study. In that study, 58.4% of the invasive MRSA infections were healthcare-associated, with 26.6% and 13.4% being hospital-acquired and community-associated, respectively.[30] These proportions were similar to those of the current study, suggesting that our local MRSA epidemiology is similar to national trends.

In our study, the PVL toxin was assessed only in patients with SCC*mec* type IV MRSA bacteremia, which precludes any conclusions about the potential virulence factors in patients with SCC*mec* type II infections. In addition, the retrospective nature of this study limited the number of potential variables that could be collected. It is conceivable that there are other confounding factors that were not elucidated from the current study design.

Despite the known limitations of this study, our findings suggest that there may be underlying pathogen-specific risk factors that may predict the severity of MRSA infection. Further research into the clinical utility of identifying pathogen risk factors for severe infection is needed.

In conclusion, this study found that increased APACHE II score, concomitant acute renal failure, and SCC*mec* type II genotyping were independent risk factors for the development of septic shock associated with MRSA bacteremia. Increased APACHE II score and acute renal failure are most likely correlated with the severity of baseline infection. The finding of the presence of SCC*mec* type II as an independent risk factor warrants further investigation to elucidate the potential virulence factors associated with this genotype.

Ethical considerations: This study was approved by the local investigational review board and complied with the principles laid down in the Declaration of Helsinki.

Conflict of interest: No competing interest declared for all authors.

References

1. Wisplinghoff H, Bischoff T, Tallent SM, Seifert H, Wenzel RP, Edmond MB. Nosocomial bloodstream infections in US hospitals: analysis of 24,179 cases from a prospective nationwide surveillance study. *Clin Infect Dis* 2004;**39**: 309–17.
2. National Nosocomial Infections Surveillance (NNIS) System Report, data summary from January 1992 through June 2004, issued October 2004. Am J Infect Control 2004;**32**:470–85.
3. Cosgrove SE, Sakoulas G, Perencevich EN, Schwaber MJ, Karchmer AW, Carmeli Y. Comparison of mortality associated with methicillin-resistant and methicillin-susceptible *Staphylococcus aureus* bacteremia: a meta-analysis. *Clin Infect Dis* 2003;**36**:53–9.
4. Blot SI, Vandewoude KH, Hoste EA, Colardyn FA. Outcome and attributable mortality in critically ill patients with bacteremia involving methicillin-susceptible and methicillin-resistant *Staphylococcus aureus*. *Arch Intern Med* 2002;**162**:2229–35.
5. Romero-Vivas J, Rubio M, Fernandez C, Picazo JJ. Mortality associated with nosocomial bacteremia due to methicillin-resistant *Staphylococcus aureus*. *Clin Infect Dis* 1995;**21**:1417–23.
6. Selvey LA, Whitby M, Johnson B. Nosocomial methicillin-resistant *Staphylococcus aureus* bacteremia: is it any worse than nosocomial methicillin-sensitive *Staphylococcus aureus* bacteremia? *Infect Control Hosp Epidemiol* 2000;**21**:645–8.
7. Davis SL, Rybak MJ, Amjad M, Kaatz GW, McKinnon PS. Characteristics of patients with healthcare-associated infection due to SCC*mec* type IV methicillin-resistant *Staphylococcus aureus*. *Infect Control Hosp Epidemiol* 2006;**27**:1025–31.
8. Moran GJ, Krishnadasan A, Gorwitz RJ, Fosheim GE, McDougal LK, Carey RB, et al. Methicillin-resistant *S. aureus* infections among patients in the emergency department. *N Engl J Med* 2006;**355**:666–74.
9. Vincent JL, Sakr Y, Sprung CL, Ranieri VM, Reinhart K, Gerlach H, et al. Sepsis in European intensive care units: results of the SOAP study. *Crit Care Med* 2006;**34**:344–53.
10. Gomez J, Garcia-Vazquez E, Banos R, Canteras M, Ruiz J, Banos V, et al. Predictors of mortality in patients with methicillin-resistant *Staphylococcus aureus* (MRSA) bacteraemia: the role of empiric antibiotic therapy. *Eur J Clin Microbiol Infect Dis* 2007;**26**:239–45.
11. Guilarde AO, Turchi MD, Martelli CM, Primo MG. *Staphylococcus aureus* bacteraemia: incidence, risk factors and predictors for death in a Brazilian teaching hospital. *J Hosp Infect* 2006;**63**:330–6.
12. Garner JS, Jarvis WR, Emori TG, Horan TC, Hughes JM. CDC definitions for nosocomial infections, 1988. *Am J Infect Control* 1988;**16**:128–40.
13. Friedman ND, Kaye KS, Stout JE, McGarry SA, Trivette SL, Briggs JP, et al. Health care-associated bloodstream infections in adults: a reason to change the accepted definition of community-acquired infections. *Ann Intern Med* 2002;**137**:791–7.
14. Johnson LB, Almoujahed MO, Ilg K, Maolood L, Khatib R. *Staphylococcus aureus* bacteremia: compliance with standard treatment, long-term outcome and predictors of relapse. *Scand J Infect Dis* 2003;**35**:782–9.
15. Fowler Jr VG, Boucher HW, Corey GR, Abrutyn E, Karchmer AW, Rupp ME, et al. Daptomycin versus standard therapy for bacteremia and endocarditis caused by *Staphylococcus aureus*. *N Engl J Med* 2006;**355**:653–65.
16. Bone RC, Balk RA, Cerra FB, Dellinger RP, Fein AM, Knaus WA, et al. Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. The ACCP/SCCM Consensus Conference Committee. American College of Chest Physicians/Society of Critical Care Medicine. *Chest* 1992;**101**: 1644–55.
17. Boye K, Bartels MD, Andersen IS, Moller JA, Westh H. A new multiplex PCR for easy screening of methicillin-resistant *Staphylococcus aureus* SCC*mec* types I–V. *Clin Microbiol Infect* 2007;**13**:725–7.
18. Lina G, Piemont Y, Godail-Gamot F, Bes M, Peter MO, Gauduchon V, et al. Involvement of Panton–Valentine leukocidin-producing *Staphylococcus aureus* in primary skin infections and pneumonia. *Clin Infect Dis* 1999;**29**:1128–32.
19. Ganga R, Riederer K, Sharma M, Fakih MG, Johnson LB, Shemes S, et al. Role of SCC*mec* type in outcome of *Staphylococcus aureus* bacteremia in a single medical center. *J Clin Microbiol* 2009;**47**:590–5.
20. Hidayat LK, Hsu DI, Quist R, Shriner KA, Wong-Beringer A. High-dose vancomycin therapy for methicillin-resistant *Staphylococcus aureus* infections: efficacy and toxicity. *Arch Intern Med* 2006;**166**:2138–44.
21. Sakoulas G, Moise-Broder PA, Schentag J, Forrest A, Moellering Jr RC, Eliopoulos GM. Relationship of MIC and bactericidal activity to efficacy of vancomycin for treatment of methicillin-resistant *Staphylococcus aureus* bacteremia. *J Clin Microbiol* 2004;**42**:2398–402.
22. Soriano A, Marco F, Martinez JA, Pisos E, Almela M, Dimova VP, et al. Influence of vancomycin minimum inhibitory concentration on the treatment of methicillin-resistant *Staphylococcus aureus* bacteremia. *Clin Infect Dis* 2008;**46**:193–200.
23. Lowy FD. *Staphylococcus aureus* infections. *N Engl J Med* 1998;**339**:520–32.
24. Vandenesch F, Naimi T, Enright MC, Lina G, Nimmo GR, Heffernan H, et al. Community-acquired methicillin-resistant *Staphylococcus aureus* carrying Panton–Valentine leukocidin genes: worldwide emergence. *Emerg Infect Dis* 2003;**9**:978–84.
25. Huang H, Flynn NM, King JH, Monchaud C, Morita M, Cohen SH. Comparisons of community-associated methicillin-resistant *Staphylococcus aureus* (MRSA) and hospital-associated MSRA infections in Sacramento, California. *J Clin Microbiol* 2006;**44**:2423–7.
26. Berglund C, Molling P, Sjoberg L, Soderquist B. Predominance of staphylococcal cassette chromosome *mec* (SCC*mec*) type IV among methicillin-resistant *Staphylococcus aureus* (MRSA) in a Swedish county and presence of unknown SCC*mec* types with Panton–Valentine leukocidin genes. *Clin Microbiol Infect* 2005;**11**: 447–56.
27. Naimi TS, LeDell KH, Como-Sabetti K, Borchardt SM, Boxrud DJ, Etienne J, et al. Comparison of community- and health care-associated methicillin-resistant *Staphylococcus aureus* infection. *JAMA* 2003;**290**:2976–84.
28. Ma XX, Ito T, Tiensasitorn C, Jamklang M, Chongtrakool P, Boyle-Vavra S, et al. Novel type of staphylococcal cassette chromosome *mec* identified in community-acquired methicillin-resistant *Staphylococcus aureus* strains. *Antimicrob Agents Chemother* 2002;**46**:1147–52.
29. Klevens RM, Morrison MA, Fridkin SK, Reingold A, Petit S, Gershman K, et al. Community-associated methicillin-resistant *Staphylococcus aureus* and healthcare risk factors. *Emerg Infect Dis* 2006;**12**:1991–3.
30. Klevens RM, Morrison MA, Nadle J, Petit S, Gershman K, Ray S, et al. Invasive methicillin-resistant *Staphylococcus aureus* infections in the United States. *JAMA* 2007;**298**:1763–71.