International Journal of Antimicrobial Agents 54 (2019) 491–495

Contents lists available at ScienceDirect

International Journal of Antimicrobial Agents

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

Benzylpenicillin versus flucloxacillin for penicillin-susceptible *Staphylococcus aureus* bloodstream infections from a large retrospective cohort study

A. Henderson[a,b,c,*], P. Harris[a,b,d], G. Hartel[e,f], D. Paterson[b], J. Turnidge[g], J.S. Davis[h,i], S.Y.C. Tong[h,j,k]

[a] *Infection Management Services, Building 17, Princess Alexandra Hospital, Brisbane, QLD 4102, Australia*
[b] *Centre for Clinical Research, Faculty of Medicine, University of Queensland, Royal Brisbane and Women's Hospital, Brisbane, QLD 4006, Australia*
[c] *School of Chemistry and Molecular Sciences, University of Queensland, Brisbane, QLD 4072, Australia*
[d] *Pathology Queensland, Royal Brisbane and Women's Hospital, Brisbane, QLD 4006, Australia*
[e] *Department of Statistics, QIMR Berghofer Institute of Medical Research, Herston, QLD 4006, Australia*
[f] *School of Population Health, University of Queensland, Royal Brisbane and Women's Hospital, Herston, QLD 4006, Australia*
[g] *Adelaide Medical School, University of Adelaide, Adelaide, SA 5000, Australia*
[h] *Global and Tropical Health Division, Menzies School of Health Research, Darwin, NT 0811, Australia*
[i] *Department of Infectious Diseases, John Hunter Hospital, Newcastle, NSW 2305, Australia*
[j] *Victorian Infectious Disease Service, The Royal Melbourne Hospital, Melbourne, VIC 3050, Australia*
[k] *Doherty Department, University of Melbourne, at the Peter Doherty Institute for Infection and Immunity, 792 Elizabeth Street, Melbourne, VIC 3000, Australia*

ARTICLE INFO

Article history:
Received 7 March 2019
Accepted 25 May 2019

Editor: Jeffrey Lipman

Keywords:
Penicillin-susceptible *Staphylococcus aureus*
Benzylpenicillin
Flucloxacillin
Bloodstream infection
Bacteraemia

ABSTRACT

In clinical practice, differing opinions exists regarding the optimal management of patients with penicillin-susceptible *Staphylococcus aureus* (PSSA) bloodstream infection (BSI). The aim of this study was to compare the 30-day mortality of patients treated with benzylpenicillin or flucloxacillin for PSSA BSI from a large prospectively collected data set from Australia and New Zealand. A logistic regression model and propensity score treatment analysis using inverse probability of treatment weighting were used. A total of 915 patients were included in the study, with an overall mortality rate of 12.9% (118/915) [benzylpenicillin 10.5% (33/315) and flucloxacillin 14.2% (85/600)]. Endocarditis was associated with benzylpenicillin treatment choice, whereas skin and soft-tissue infection was associated with flucloxacillin treatment choice. In the multivariate analysis, increased 30-day mortality was associated with flucloxacillin compared with benzylpenicillin [odds ratio (OR) = 1.6, 95% confidence interval (CI) 1.0–2.5; $P = 0.05$). When adjusted for treatment choice in the propensity score analysis, flucloxacillin was again associated with increased 30-day mortality (OR = 1.06, 95% CI 1.01–1.1; $P = 0.03$). An increase in 30-day mortality associated with flucloxacillin use suggests a potential benefit for benzylpenicillin therapy in patients with PSSA BSI.

1. Introduction

Resistance to penicillin was observed in *Staphylococcus aureus* in the mid 1940s, soon after the introduction of penicillin as a therapeutic agent into clinical practice [1]. The emergence of penicillin-resistant *S. aureus* (PRSA) was widely encountered in hospitals thereafter, with some reports finding rates of PRSA rising from 14% to 38% in less than 1 year [2]. Two mechanisms are known to result in penicillin resistance in staphylococci. The most common, and earliest described, is the production of a serine β-lactamase known as penicillinase (PC1) that hydrolyses the β-lactam ring resulting in the product penicilloic acid [2]. The second mechanism leads to resistance to β-lactam agents, including penicillin, by production of an altered penicillin-binding protein, PBP2a, encoded by the *mecA* gene [3]. Following the emergence of PRSA, a new class of antistaphylococcal penicillins (ASPs) were developed that were resistant to hydrolysis of the β-lactam ring by penicillinase. The most commonly used of the ASPs is flucloxacillin in Australia and nafcillin in North America. These isoxazolyl penicillins, which are semisynthetic penicillin derivatives, are stable during exposure to

* Corresponding author. Infection Management Services, Building 17, Princess Alexandra Hospital, 199 Ipswich Road, Brisbane, QLD 4102, Australia.
E-mail address: andrew@hendonet.com (A. Henderson).

https://doi.org/10.1016/j.ijantimicag.2019.05.020
0924-8579/

penicillinase and are now the most commonly used agents for the treatment of *S. aureus* infections.

In current clinical practice, laboratories report penicillin-susceptible *S. aureus* (PSSA) strains based upon the phenotypic absence of penicillinase in addition to a minimum inhibitory concentration (MIC) below the breakpoint of 0.25 mg/L. However, despite widespread use of penicillin and ASPs in clinical practice for more than 50 years, the optimal therapy for patients with invasive PSSA remains controversial. This is particularly important, as a number of recent publications have reported an increasing proportion of PSSA among all *S. aureus* clinical isolates [4–6]. In Australia, PSSA bloodstream infection (BSI) rates are similar to those of methicillin-resistant *S. aureus* (MRSA) BSI rates, comprising 16% and 18% of all *S. aureus* BSIs, respectively [7].

The aim of this study was to compare the outcomes of patients with PSSA BSI treated with benzylpenicillin or flucloxacillin from a large prospectively collected data set of consecutive *S. aureus* bacteraemia (SAB) episodes from Australia and New Zealand. The hypothesis was that patients treated with benzylpenicillin for definitive therapy would have a lower 30-day mortality compared with those treated with flucloxacillin.

2. Materials and methods

Data from the Australia and New Zealand Co-operative Outcomes of Staphylococcal Sepsis (ANZCOSS) study, which collected data on all consecutive unique SAB episodes from 27 hospital-based or independent microbiology laboratories in Australia and New Zealand between January 2007 and September 2013, were used [8]. In the ANZCOSS study, the human research ethics committee or a local research governance office of each participating hospital or laboratory provided prospective approval. Individual participant consent was waived by the approving human research ethics committee.

Data collected in the ANZCOSS study included patient demographics, co-morbidities, treatment, and 7-day and 30-day mortality as primary outcome measures. As markers of infection severity were not included in the data collected, in the current study intensive care unit (ICU) admission within 48 h of the first positive blood culture was included as a surrogate for severe infection. The central data management team performed data checks for completeness at regular intervals, with queries sent to each participating laboratory.

For individuals with recurrent episodes of SAB, a separate episode was recorded if the blood culture was drawn >14 days after the previous episode. The 'definitive antibiotic agent' was defined as the intravenous agent chosen by the treating clinician after the susceptibility profile of the isolate was known. For the purpose of this analysis, only patients with PSSA bacteraemia who were treated with either benzylpenicillin or flucloxacillin were included. Antimicrobial susceptibility testing and reporting was performed by local site microbiology laboratories, with most participating laboratories using a combination of automated testing (VITEK®2; bioMérieux) and confirmatory phenotypic testing (nitrocefin hydrolysis method or penicillin disk test).

All statistical analysis was performed with *R: a language and environment for statistical computing* [9]. The χ^2 test, Fisher's exact test and Student's *t*-test were used for analysis of categorical and continuous variables, as appropriate. Univariate logistic regression was used to compare candidate variates as independent variables, with 30-day mortality included in the model as the outcome variable. A multivariable logistic regression model was then developed based upon backward stepwise elimination of covariates that differed between the benzylpenicillin and flucloxacillin treatment groups (Wald *P*-value <0.10). A goodness-of-fit analysis of the model was performed after each step in the model using Akaike's information criteria.

To calculate a propensity-adjusted comparison of 30-day mortality between benzylpenicillin and flucloxacillin, inverse probability of treatment weighting (IPTW) was performed to address imbalances between treatment covariates. To compute the average treatment effect, generalised boosted model (GBM) regression, which accounts for non-linear effects and interactions, was performed for estimating propensity scores before comparing outcome using IPTW. Only covariates that were clinically assessed to influence the definitive antibiotic agent choice, such as co-morbidities, risk factors and primary focus of infection, were included in the model. The propensity-adjusted model was performed using the Toolkit for Weighting and Analysis of Non-equivalent Groups (twang) package, and balance assessment between the benzylpenicillin and flucloxacillin groups was performed using the package [10]. In particular, standardised mean differences post balancing for all covariates were <0.1 (Supplementary Table S1).

3. Results

A total of 13 107 episodes of SAB were included in the ANZCOSS data set, of which 11 713 episodes were excluded based upon resistance phenotypes [2907 MRSA and 8806 penicillin-resistant methicillin-susceptible *S. aureus* (MSSA)]. Of the 1394 PSSA episodes, 415 were then excluded due to the definitive antibiotic treatment being antibiotics other than benzylpenicillin or flucloxacillin (cefazolin/cefalotin 108, vancomycin 84, not treated 62, other 161) and 64 were excluded from the final analysis owing to missing values for 30-day vital status, leaving 915 unique PSSA episodes in the data set. Although in the ANZCOSS data set a separate SAB episode was recorded if the blood culture was drawn >14 days after the previous episode, no participants with PSSA BSIs were identified as having a separate SAB episodes within 90 days of a previous episode.

Table 1 shows the demographics, risk factors, primary focus of infection and outcome variables of patients treated with benzylpenicillin compared with flucloxacillin. Patients treated with benzylpenicillin were more likely to have a primary focus of endocarditis. In contrast, patients treated with flucloxacillin were more likely to have a primary focus of skin and soft-tissue infection (SSTI) or a primary BSI. ICU admission and length of stay were similar among the two treatment groups. Crude 7-day mortality was significantly lower for benzylpenicillin (1.6% vs. 6.8%; $P < 0.001$), but the difference was not statistically significant for 30-day mortality (10.5% vs. 14.2%; $P = 0.11$).

The odds ratio (OR) for 30-day mortality (Table 2) for the flucloxacillin group compared with the benzylpenicillin group was 1.4 [95% confidence interval (CI) 0.9–2.2] in the univariate analysis and 1.6 (95% CI 1.0–2.5) in the multivariate model when adjusted for age, device-related infection, endocarditis, primary BSI, pneumonia and ICU admission.

Factors associated with choice of benzylpenicillin versus flucloxacillin were modelled using GBM regression. At baseline, the benzylpenicillin group had a higher mean of endocarditis and lower mean of primary BSI and SSTI (Supplementary Table 1). The maximum standardised difference and the maximum Kolmogorov–Smirnov statistic were 0.22 and 0.08 before IPTW and 0.03 and 0.02 after IPTW (Supplementary Table S1). In the propensity score model (Table 3), patients treated with flucloxacillin had a higher 30-day mortality (OR = 1.06, 95% CI 1.01–1.1) compared with those treated with benzylpenicillin.

Table 1
Comparison of variables for patients treated with benzylpenicillin compared with flucloxacillin[a]

Variable	Benzylpenicillin ($N=315$)	Flucloxacillin ($N=600$)	*P*-value
Male sex	212 (67.3)	396 (66.0)	0.74
Age			
Median age (years)	62	62	0.77
Age group[b]			0.47
Neonate ($n=23$)	6 (1.9)	17 (2.8)	
Child ($n=39$)	11 (3.5)	28 (4.7)	
Adult ($n=853$)	298 (94.6)	555 (92.5)	
Risk factors			
Dialysis	17 (5.4)	50 (8.3)	0.08[c]
IDU	23 (7.3)	35 (5.8)	0.57[d]
Device-related	88 (27.9)	182 (30.3)	0.39[e]
Primary focus			<0.001[f]
CNS infection ($n=29$)	12 (3.8)	17 (2.8)	0.43
Deep abscess ($n=17$)	9 (2.9)	8 (1.3)	0.12
Device-related infection ($n=196$)	62 (19.7)	134 (22.3)	0.40
Endocarditis ($n=81$)	43 (13.7)	38 (6.3)	<0.001
Osteoarticular infection ($n=176$)	69 (21.9)	107 (17.8)	0.16
Primary BSI ($n=230$)	67 (21.3)	163 (27.2)	0.05
Pneumonia ($n=35$)	13 (4.1)	22 (3.7)	0.72
SSTI ($n=151$)	40 (12.7)	111 (18.5)	0.02
Deep-seated[g]	133 (42.2)	170 (28.3)	<0.001
ICU admission			
ICU admission	47 (14.9)	73 (12.2)	0.28
ICU admission within 48 h of first positive blood culture	31 (9.8)	39 (6.5)	0.09
Outcomes			
Median LOS (days)	23	23	0.59
7-day mortality	5 (1.6)	41 (6.8)	<0.001
30-day mortality	33 (10.5)	85 (14.2)	0.11

IDU, intravenous drug use; CNS, central nervous system; BSI, bloodstream infection; SSTI, skin and soft-tissue infection; ICU, intensive care unit; LOS, length of stay.
[a] Data are *n* (%) unless otherwise stated.
[b] Neonate, ≤1 year; child, >1 to ≤16 years; and adult >16 years.
[c] Missing data for benzylpenicillin, $n = 26$; flucloxacillin, $n = 80$.
[d] Missing data for benzylpenicillin, $n = 38$; flucloxacillin, $n = 102$.
[e] Missing data for benzylpenicillin, $n = 13$; flucloxacillin, $n = 35$.
[f] χ^2 for 8×2 table.
[g] Includes endocarditis, CNS infection, deep abscess and bone/joint infection.

Table 2
Logistic regression analysis of variables associated with 30-day mortality in with penicillin-susceptible *Staphylococcus aureus* bloodstream infection (BSI) treated with benzylpenicillin or flucloxacillin

Variable	Unadjusted			Adjusted		
	OR	95% CI	*P*-value	OR	95% CI	*P*-value
Sex						
Female (ref.)	1.0	–	–			
Male	1.1	0.7–1.6	0.75			
Age[a]	1.03	1.02–1.05	<0.001	1.03	1.02–1.04	<0.001
Dialysis						
No	1.0	–	–			
Yes	1.02	0.4–2.1	0.96			
IDU						
No	1.0	–	–			
Yes	0.1	0.01–0.6	0.04			
Primary focus						
CNS infection	0.77	0.2–2.2				
Deep abscess	0.0	NA	0.98			
Device-related infection	0.4	0.2–0.7	0.004	0.7	0.4–1.05	0.09
Endocarditis	1.6	0.9–2.9	0.12	3.1	1.5–6.0	0.002
Osteoarticular infection	0.5	0.3–0.8	0.02			
Primary BSI	2.6	1.8–3.9	<0.001	2.7	1.7–4.3	<0.001
Pneumonia	2.1	0.9–4.5	0.20	2.8	1.1–6.7	0.2
SSTI	0.7	0.4–1.2	0.23			
ICU admission within 48 h of first positive blood culture						
No	1.0					
Yes	2.0	1.0–3.5	0.03	1.9	1.1–3.3	0.06
Treatment						
Benzylpenicillin	1.0					
Flucloxacillin	1.4	0.9–2.2	0.12	1.6	1.0–2.5	0.05

OR, odds ratio; CI, confidence interval; IDU, intravenous drug use; CNS, central nervous system; NA, not available; SSTI, skin and soft-tissue infection; ICU, intensive care unit.
[a] For each year increase.

Table 3
Propensity-score-adjusted analysis of 30-day mortality

Variable	OR (95% CI)	*P*-value
Treatment with flucloxacillin	1.06 (1.01–1.1)	0.03
Age	1.00 (1.00–1.00)	<0.001
Intravenous drug use	0.9 (0.88–0.97)	0.002
Endocarditis	1.1 (1.0–1.2)	0.04
Primary bloodstream infection	1.1 (1.04–1.2)	0.002
ICU admission within 48 h of first positive blood culture	1.1 (0.99–1.2)	0.08

OR, odds ratio; CI, confidence interval; ICU, intensive care unit.

4. Discussion

In this study, the 30-day mortality for PSSA BSIs in patients treated with benzylpenicillin and flucloxacillin was compared. In the multivariate model, increased mortality was seen in patients treated with flucloxacillin. When adjusted for treatment choice in the propensity score analysis, those patients treated with flucloxacillin were again more likely to die than those treated with benzylpenicillin by a factor of about 5%.

To our knowledge, this is the largest study to date in the medical literature directly comparing the outcomes of patients treated with flucloxacillin or benzylpenicillin for PSSA BSI. In the only other study to compare ASPs and benzylpenicillin, Nissen et al. found a non-significant reduction in 30-day mortality with dicloxacillin compared with benzylpenicillin (OR = 0.77, 95% CI 0.38–1.58) [11]. However, in that study, patients treated in the benzylpenicillin group had higher Pitt bacteraemia scores and greater rates of secondary manifestations such as endocarditis or osteomyelitis, and no difference in mortality was observed in their propensity score analysis of benzylpenicillin and dicloxacillin [11].

One of the potential reasons for limited comparative data may potentially be related to clinicians favouring ASPs over benzylpenicillin. First, the prevalence of PSSA infections is low, reported to be between 5–15% of MSSA isolates based on prevalence studies [5,6,12,13]. Therefore, as clinicians have become used to prescribing penicillinase-resistant β-lactams, such as flucloxacillin or cefazolin, for serious *S. aureus* infections, it is possible that benzylpenicillin is less likely to have been used for this indication despite laboratories reporting isolates as susceptible to penicillin [13]. Second, some clinicians and clinical groups, such as the American Heart Association (AHA), advocate treating both MSSA and PSSA BSIs the same, irrespective of whether or not penicillinase is detected [14]. This is typically based on concerns over laboratories detecting penicillinase, with approximately 10% of *S. aureus* isolates that test susceptible to penicillin still harbouring the *blaZ* gene. However, based upon several publications, the penicillin disk method recommended by the Clinical and Laboratory Standards Institute (CLSI) and the European Committee on Antimicrobial Susceptibility Testing (EUCAST) has adequate sensitivity to detect penicillinase [15–17].

Some experts, however, argue for the use of benzylpenicillin owing to a lower MIC distribution for penicillin compared with other β-lactam agents active against *S. aureus*, combined with the ability to achieve high levels of free non-protein-bound plasma drug concentrations [18]. Although the data to support this theoretical advantage are limited, many clinicians continue to use penicillin for therapy in this situation. This uncertainty is significant given that (i) *S. aureus* BSI is associated with high mortality and significant morbidity, (ii) *S. aureus* is one of the most common organisms isolated from blood cultures, (iii) *S. aureus* BSI is the most common reason for consultation with an infectious diseases specialist (which itself has been shown to improve outcomes) and (iv) a significant proportion of *S. aureus* bloodstream isolates worldwide will be reported as susceptible to penicillin [19].

The main limitation of this study is its observational nature, with the choice of treatment likely to be influenced by biases. Although a multivariate analysis and propensity-score-adjusted analysis were used to balance measured biases, it is possible that other unmeasured biases may have influenced the comparison. In particular, data collection was limited to easily accessible clinical data and therefore we were unable to analyse important variables such as severity of illness, source control or patient co-morbidities. In addition, we did not have specific data recorded for empirical antibiotic therapy, duration of therapy, whether treatment was monotherapy or combined, or dosing. It is possible that these factors might have influenced outcome. However, these factors are unlikely to be unevenly distributed between those whose definitive treatment was penicillin or flucloxacillin. Only a randomised controlled trial (RCT) would adequately be able to adjust for these potential confounders as well as unknown confounders. As only a small treatment difference was seen, we would suggest caution in interpreting the superiority of benzylpenicillin over flucloxacillin, as confounding variables such as severity of illness, patient co-morbidities and the specifics of antimicrobial therapy could not be included in the propensity score model.

Although specific dosing for antimicrobials was not recorded on an individual patient level, recommended doses for flucloxacillin and benzylpenicillin did not alter significantly during the period of the study, with national guidelines for dosing suggesting flucloxacillin 2 g every 4 h (q4h) and benzylpenicillin 2.4 g q4h for critical illness or deep-seated infections or flucloxacillin 2 g every 6 h and benzylpenicillin 1.8 g q4h for standard infections, with both drugs adjusted for renal function [20].

An interesting finding in this study was the association of 30-day mortality with episodes attributed to primary BSI. This may reflect that patients in this group were more likely to have a sepsis syndrome than in deep-seated infections or SSTIs, or potentially may have died before a focus became apparent. In addition, treatment duration and dosing may have differed for primary BSI than for other infections types and may have contributed to the higher association with mortality. Furthermore, a higher rate of endocarditis was noted in the benzylpenicillin group. This suggests that clinicians in the Australian and New Zealand region favour benzylpenicillin for endocarditis due to PSSA, which is contrary to the AHA guidelines [14]. Reasons for this are unknown, however given the uncertainty over treatment choice for PSSA BSIs, including endocarditis, further clinical studies are warranted to determine whether there is potential superiority of benzylpenicillin over flucloxacillin.

We were also unable to test isolates for the *blaZ* gene with gold-standard nucleic acid amplification tests. However, if isolates harbouring *blaZ* were included in the study, this would likely to have led to worse outcomes in the benzylpenicillin group compared with the flucloxacillin group and thus we would have underestimated any benefit from benzylpenicillin.

Based upon this observational study as well as the available evidence in the published literature, we believe there is sufficient evidence to support a RCT comparing benzylpenicillin and an (or multiple) ASPs. As the main argument for benzylpenicillin treatment over ASPs is the potential for improved outcomes owing to a lower MIC distribution, favourable pharmacokinetic/pharmacodynamic profile and fewer side effects, the study design should include assessment of efficacy for clinical outcomes as well as to compare significant side effects of therapy such as hepatotoxicity and nephrotoxicity.

5. Conclusion

In this large, observational cohort, a significant association between flucloxacillin use and all-cause mortality in PSSA BSI was

found, after adjusting for possible confounders, compared with benzylpenicillin. However, with the limitations of observational studies, this finding can only be assessed properly in an appropriately designed RCT. Additional observational studies may be potentially helpful in estimating a sample size for a definitive study.

Declaration of Competing Interest

None declared.

Acknowledgments

The authors would like to thank Despina Kotsanas (Monash Health, Australia) for managing the database and conducting data quality audits as well as each of the site investigators for collecting the data.

Funding

Support for ANZCOSS data collection was generously granted by the Australian Society for Antimicrobials (ASA). The ASA had no role in the design and conduct of the study; collection, management, analysis and interpretation of the data; preparation, review or approval of the manuscript; and decision to submit the manuscript for publication. JSD and SYCT received salary support from Australia's National Health and Medical Research Council [Career Development Fellowships #1083105 and #1065736, respectively].

Ethical approval

In the ANZCOSS study, the human research ethics committee or a local research governance office of each participating hospital or laboratory provided prospective approval. Individual participant consent was waived by the approving human research ethics committee.

Supplementary material

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijantimicag.2019.05.020.

References

[1] Kirby WM. Extraction of a highly potent penicillin inactivator from penicillin resistant staphylococci. Science 1944;99:452–3.
[2] Barber M. Staphylococcal infection due to penicillin-resistant strains. Br Med J 1947;2:863–5.
[3] Fuda CC, Fisher JF, Mobashery S. β-Lactam resistance in *Staphylococcus aureus*: the adaptive resistance of a plastic genome. Cell Mol Life Sci 2005;62:2617–33.
[4] Coombs GW, Nimmo GR, Daly DA, Le TT, Pearson JC, Tan HLAustralian Group on Antimicrobial Resistance. Australian *Staphylococcus aureus* Sepsis Outcome Programme annual report, 2013. Commun Dis Intell Q Rep 2014;38:E309–19.
[5] Resman F, Thegerstrom J, Mansson F, Ahl J, Tham J, Riesbeck K. The prevalence, population structure and screening test specificity of penicillin-susceptible *Staphylococcus aureus* bacteremia isolates in Malmö. Sweden. J Infect 2016;73:129–35. doi:10.1016/j.jinf.2016.05.011.
[6] Cheng MP, Rene P, Cheng AP, Lee TC. Back to the future: penicillin-susceptible *Staphylococcus aureus*. Am J Med 2016;129:1331–3. doi:10.1016/j.amjmed.2016.01.048.
[7] Coombs GW, Daley DA, Thin Lee Y, Pearson JC, Robinson JO, Nimmo GRAustralian Group on Antimicrobial Resistance. Australian *Staphylococcus aureus* Sepsis Outcome Programme annual report, 2014. Commun Dis Intell Q Rep 2016;40:E244–54.
[8] Turnidge JD, Kotsanas D, Munckhof W, Roberts S, Bennett CM, Nimmo GRAustralia New Zealand Cooperative on Outcomes in Staphylococcal Sepsis. *Staphylococcus aureus* bacteraemia: a major cause of mortality in Australia and New Zealand. Med J Aust 2009;191:368–73.
[9] R Core Team. *R: a language and environment for statistical computing*. Vienna, Austria: R Foundation for Statistical Computing. https://www.R-project.org/ [accessed 5 July 2019].
[10] Ridgeway G., McCaffrey D., Morral A., Griffin A., Burgette L. twang: toolkit for weighting and analysis of nonequivalent groups v.1.5. http://cran.r-project.org/web/packages/twang/index.html [accessed 5 July 2019].
[11] Nissen JL, Skov R, Knudsen JD, Ostergaard C, Schonheyder HC, Frimodt-Moller N, et al. Effectiveness of penicillin, dicloxacillin and cefuroxime for penicillin-susceptible *Staphylococcus aureus* bacteraemia: a retrospective, propensity-score-adjusted case–control and cohort analysis. J Antimicrob Chemother 2013;68:1894–900.
[12] Richter SS, Doern GV, Heilmann KP, Miner S, Tendolkar S, Riahi F, et al. Detection and prevalence of penicillin-susceptible *Staphylococcus aureus* in the United States in 2013. J Clin Microbiol 2016;54:812–14.
[13] Chabot MR, Stefan MS, Friderici J, Schimmel J, Larioza J. Reappearance and treatment of penicillin-susceptible *Staphylococcus aureus* in a tertiary medical centre. J Antimicrob Chemother 2015;70:3353–6.
[14] Baddour LM, Wilson WR, Bayer AS, Fowler VG Jr, Tleyjeh IM, Rybak MJAmerican Heart Association Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease of the Council on Cardiovascular Disease in the Young; Council on Clinical Cardiology; Council on Cardiovascular Surgery and Anesthesia; Stroke Council. Infective endocarditis in adults: diagnosis, antimicrobial therapy, and management of complications: a scientific statement for healthcare professionals from the American Heart Association. Circulation 2015;132:1435–86.
[15] Papanicolas LE, Bell JM, Bastian I. Performance of phenotypic tests for detection of penicillinase in *Staphylococcus aureus* isolates from Australia. J Clin Microbiol 2014;52:1136–8.
[16] Pereira LA, Harnett GB, Hodge MM, Cattell JA, Speers DJ. Real-time PCR assay for detection of *blaZ* genes in *Staphylococcus aureus* clinical isolates. J Clin Microbiol 2014;52:1259–61.
[17] Kaase M, Lenga S, Friedrich S, Szabados F, Sakinc T, Kleine B, et al. Comparison of phenotypic methods for penicillinase detection in *Staphylococcus aureus*. Clin Microbiol Infect 2008;14:614–16.
[18] Que Y-A, Moreillon P. *Staphylococcus aureus* (including staphylococcal toxic shock syndrome). *Mandell, Douglas and Bennett's principles and practice of infectious diseases*. Bennett JE, Dolin R, Blaser MJ, editors. 8th ed, Philadelphia, PA: WB Saunders; 2015. p. 2237–71.e5.
[19] Tong SY, Davis JS, Eichenberger E, Holland TL, Fowler VG Jr. *Staphylococcus aureus* infections: epidemiology, pathophysiology, clinical manifestations, and management. Clin Microbiol Rev 2015;28:603–61.
[20] eTG complete. Melbourne, VIC, Australia: Therapeutic Guidelines Limited; 2018. https://tgldcdp.tg.org.au/etgcomplete [accessed 20 April 2019].