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Duration of therapy recommended for bacteraemic illness varies widely amongst clinicians

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ABSTRACT

The optimum duration of antimicrobial therapy would eradicate infection whilst minimising potential adverse drug effects to the patient. Australian and New Zealand infectious diseases (ID) and ICU specialists were surveyed regarding their recommended duration of antibiotic treatment for five common bacteraemic syndromes. A total of 239 clinicians responded to the survey (15.5% ICU and 84.5% ID). Overall, the most common reported durations were 7 (33.7%), 10 (25.9%) and 14 (26.0%) days, with 46% of responses recommending ≤7 days. Most respondents (>75% for each characteristic) would not modify duration based on host characteristics such as patient age or co-morbidities. ID physicians recommended longer durations than ICU physicians for all five syndromes (ID, median 10, IQR 7–14, range 1–28 days; ICU, median 7, IQR 5–10, range 2–21 days). Across all respondents, the median (IQR) duration for each syndrome was: CVC-BSI, 7 (7–10) days; bacteraemic pneumonia, 7 (7–10) days; bacteraemic UTI, 10 (7–14) days; bacteraemic IAI, 7 (7–12) days; and bacteraemic SSTI, 10 (7–14) days. Marked variation exists amongst clinicians' recommended duration of antibiotic treatment for BSI. A proportion of clinicians recommend therapy of ≤7 days at present (33.3–59.7% across scenarios). Patient characteristics are not strongly considered in the decision on therapy duration. This survey was undertaken as preparatory work for initiation of the BALANCE study, an ongoing randomised trial comparing 7 days with 14 days of therapy for BSI, providing an evidence base to inform best clinical treatment for this patient population.

1. Introduction

Bacteraemia is a leading cause of morbidity and mortality in critically ill patients [1]. Antimicrobial resistance is emerging as the most important health-related threat to humanity of the 21st century, with antibiotic overuse being the key driver [2]. One of the most common causes of unnecessary antibiotic use is an excessive treatment duration [3,4]. Several studies have shown similarities in effectiveness when comparing shorter courses with longer courses of therapy for common community-acquired and nosocomial infections [5–7]. However, few large multicentre randomised control trials currently exist to guide the treatment duration for critically ill bacteraemic patients [7,8].

We have conducted a nationwide survey of Australian and New Zealand infectious diseases (ID) and intensive care unit (ICU) specialists to understand current practice in duration of antibiotic therapy and self-reported treatment durations for common bacteraemic conditions in critically ill patients as well as to ascertain whether participants' responses suggest collective equipoise for a randomised trial in Australia and New Zealand to compare different durations of antibiotic therapy for bacteraemic patients. This survey was conducted in collaboration with the authors of a similar Canadian-based national survey [9] as a follow-up study to assess the responses in Australia and New Zealand.

2. Materials and methods

2.1. Study setting and population

A national practice survey was conducted amongst Australian and New Zealand ID and ICU specialists regarding their

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recommended treatment durations for critically ill patients with bacteraemia. This study was in collaboration with the University of Toronto (Toronto, Ontario, Canada) for permission to use and adapt their original survey. Approval for the survey was granted by the Human Research Ethics Committee at Monash Health, Australia.

2.2. Survey design

The survey was based on the tool used previously in the Canadian study [9]. Key modifications were the inclusion of specific antimicrobial regimens in the scenario text (as we believe this facilitated clinicians answering the question), adaption for Australian nomenclature and spelling, and omission of some questions to reduce the overall survey length. The survey outlined five common clinical scenarios encountered in the ICU that included blood-culture positive confirmed bacteraemia: central venous catheter (CVC)-related bloodstream infection (BSI); pneumonia; urinary tract infection (UTI); skin and soft-tissue infection (SSTI); and intra-abdominal infection (IAI). In all five scenarios, patients had already received adequate source control and were responding to initial therapy at the time of bacteraemia confirmation. Clinicians were asked 'What total duration of antibiotics (intravenous and oral) would you usually recommend for this patient?', with choices ranging from 0 days to >28 days in daily increments. Further questions examined whether treatment duration was influenced by patient characteristics, pathogen and specific patient conditions. Concluding questions asked clinician about their perspective on the appropriateness of prevailing treatment durations. The survey was piloted locally on five specialists to determine flow and phrasing and to ensure that the survey could be completed within 10 min (Supplementary material). The primary outcome was self-reported duration of antibiotic treatment for bacteraemia in critically ill patients. Secondary outcomes included effect of patient co-morbidities and pathogen on the recommended duration of antimicrobial therapy.

2.3. Survey administration

ID and ICU physicians were surveyed anonymously during December 2017 in a self-administered manner using a secure web-based survey data collection interface. Australian and New Zealand ID physicians received three electronic mail-outs via the Australasian Society of Infectious Diseases 'Ozbug' e-mail group. Australian and New Zealand ICU physicians received three electronic mail-outs via the Australian and New Zealand Intensive Care Society Clinical Trials Group (ANZICS-CTG). Both groups received the initial invitation to participate and two subsequent e-mail reminders 2 weeks and 4 weeks later.

2.4. Statistical analysis

Continuous variables were presented as the median and interquartile range (IQR). Comparisons were made using a Wilcoxon rank-sum, Wilcoxon signed-rank or Friedman test as appropriate. *P*-values of <0.05 were considered statistically significant. Discrete variables were compared using the χ^2 of Fisher's exact test as appropriate. All analysis was undertaken using STATA v.13.1 (StataCorp LP, College Station, TX).

3. Results

3.1. Characteristics of survey respondents

A total of 239 clinicians responded, including 202 (84.5%) ID specialists and 37 (15.5%) ICU specialists, offering recommendations on 1075 responses across five clinical scenarios in total (Supplementary material). The membership of Ozbug includes approximately 700 practicing clinicians; hence, the response rate for ID physicians was approximately 29%. Included amongst the ID clinicians were 42 ID fellows as well as 160 fully qualified specialists including 86 who had dual training in ID and clinical microbiology. The clinicians reported a wide range of clinical experience: 0–5 years (26.7%); 6–10 years (21.5%); 11–15 (17.8%); and >15 years (34.0%). There were clinicians from most states of Australia (Victoria, 29%; New South Wales, 26%; Queensland, 17%; Western Australia, 9%; South Australia, 7%; and Northern Territory, 1%) as well as New Zealand (11%). No responses were received from Tasmania.

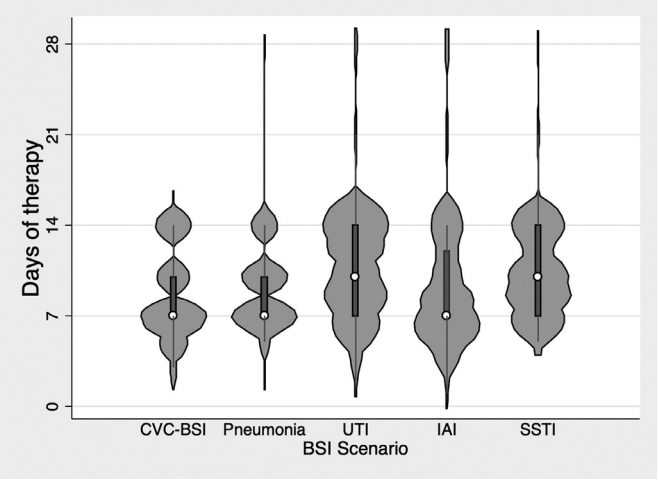

Fig. 1. Violin plot distribution of recommended treatment durations for five bacteraemia infection scenarios amongst all respondents. The dot represents the median, the box shows the interquartile range and the line represents 95% of responses. The shaded area represents the density (frequency) of answers for the duration. BSI, bloodstream infection; CVC, central venous catheter; UTI, urinary tract infection; IAI, intra-abdominal infection; SSTI, skin and soft-tissue infection.

3.2. Appropriateness of prevailing treatment durations

When asked explicitly whether prevailing antibiotic treatment courses are appropriate, the majority of clinicians responded that courses were too long (133/205; 65%). An additional 26 respondents (13%) answered that they did not know. Only a minority of respondents answered that prevailing treatment durations were either appropriate (42/205; 20%) or too short (4/205; 2%).

3.3. Recommended durations of antibiotic treatment for bacteraemic syndromes

The usual recommended antibiotic treatment durations for the common bacteraemic syndromes in critically ill patients exhibited a discrete distribution, with nearly all respondents recommending either 14 days ($n = 280$; 26.0%), 10 days ($n = 278$; 25.9%), 7 days ($n = 362$; 33.7%) or 5 days ($n = 101$; 9.4%) of treatment (Fig. 1). The median (IQR) recommended durations were numerically similar for the five syndromes, including CVC-BSI [7 (7–10) days], bacteraemic pneumonia [7 (7–10) days], bacteraemic UTI [10 (7–14) days], bacteraemic IAI [7 (7–10) days] and bacteraemic SSTI [10 (7–14) days], although the distributions varied significantly ($P < 0.001$) (Fig. 1). The mean and standard deviation are presented in Table 1 as they better reflect the overall number of days of antibiotics used in the hypothetical patient population.

The most commonly recommended duration overall was 7 days ($n = 362$; 33.7%). The proportion of clinicians offering a recommendation of ≤7 days varied significantly between the five syndromes: CVC-BSI ($n = 134$; 59.7%); bacteraemic pneumonia ($n = 110$; 51%);

Table 1
Mean recommended antibiotic treatment durations for bacteraemic patients according to Australian infectious diseases (ID) and intensive care unit (ICU) physicians.

Bacteraemic syndrome	Overall median (IQR)	Overall mean ± S.D. ($n=239$)	ID physicians mean ± S.D. ($n=202$)	ICU physicians mean ± S.D. ($n=37$)	*P*-value (ICU vs. ID)*
CVC-BSI	7 (7–10)	8.6 ± 3.6	9.1 ± 3.5	6.4 ± 2.5	<0.001
Bacteraemic pneumonia	7 (7–10)	9.2 ± 3.3	9.5 ± 3.8	7.8 ± 2.2	0.011
Bacteraemic UTI	10 (7–14)	10.7 ± 4.5	11.4 ± 4.4	6.5 ± 1.8	<0.001
Bacteraemic IAI	7 (7–10)	9.2 ± 4.5	9.5 ± 5.8	8.2 ± 3.5	0.178
Bacteraemic SSTI	10 (7–14)	10.3 ± 3.4	10.5 ± 3.7	9.5 ± 2.9	0.118

IQR, interquartile range; S.D., standard deviation; CVC-BSI, central venous catheter-related bloodstream infection; UTI, urinary tract infection; IAI, intra-abdominal infection; SSTI, skin and soft-tissue infection.
* Wilcoxon rank-sum test.

Table 2
Median recommended durations of Australia and New Zealand respondents when asked about different pathogens causing central venous catheter-related bloodstream infection.

Pathogen	Median (IQR) duration recommended (days)	*P*-value*
Escherichia coli	10 (7–14)	Comparator
Klebsiella pneumoniae	7 (7–10)	0.37
Enterococcus faecalis	10 (7–14)	<0.001
Pseudomonas aeruginosa	10 (7–14)	<0.001
Acinetobacter baumannii	10 (7–14)	<0.001
Staphylococcus aureus	14 (14–14)	<0.001
Enterobacter cloacae	7 (7–10)	0.001
CoNS	5 (3–7)	<0.001

IQR, interquartile range; CoNS, coagulase-negative staphylococci.
* Wilcoxon rank-sum test.

bacteraemic UTI ($n=68$; 31.7%); bacteraemic IAI ($n=117$; 55.4%); and bacteraemic SSTI ($n=67$; 33.3%) ($P < 0.001$).

3.4. Influence of pathogen on treatment duration

For the scenario of CVC-BSI, respondents were asked to re-state their recommended duration of treatment for different pathogens. Compared with the recommended median treatment duration for *Escherichia coli* (Table 2), the only pathogen without a significantly different recommendation of duration was *Klebsiella pneumoniae* [7 (7–10) days; $P=0.37$]. Whilst the median duration recommended [10 (7–14) days for each pathogen] did not change for *Enterococcus faecalis, Pseudomonas aeruginosa* and *Acinetobacter baumannii*, the distributions showed significant differences ($P < 0.001$ for each pathogen versus *E. coli*). The median (IQR) duration was extended for *Staphylococcus aureus* [14 (14–14) days; $P < 0.001$]. Conversely, the median (IQR) recommended durations were reduced for *Enterobacter cloacae* [7 (7–10) days; $P=0.001$] and coagulase-negative staphylococci (CoNS) [5 (3–7) days; $P < 0.001$], including 28 respondents (12.5%) who recommended only 1 day of antibiotics after removal of the CVC.

3.5. Influence of host factors and clinical response on treatment duration

A majority of respondents reported that they would not alter treatment duration based on baseline host characteristics, including age >65 years ($n=220$; 92%), liver cirrhosis ($n=184$; 77%), chronic kidney disease ($n=203$; 85%) or active malignancy ($n=182$; 76%). With regard to the clinical response, most respondents would not change the duration of treatment if the patient was still ventilator dependent on the planned cessation day of their original treatment duration ($n=181$; 76%). However, a majority would increase the antibiotic treatment duration if the patient was still febrile ($n=165$; 69%) or if the patient still required vasopressors ($n=143$; 60%) on the final day of the originally planned duration. Most respondents (130/204; 64%) would not require repeat abdominal imaging prior to discontinuing antibiotic therapy for an intra-abdominal abscess that had been drained. The median (IQR) duration was higher for intra-abdominal abscesses that were non-drainable or only partially drainable [14 (14–28) days; $P < 0.001$].

3.6. Influence of physician specialty

On average, ID physicians recommended longer treatment durations than ICU physicians for all five bacteraemic syndromes (Table 1). More ID physicians recommended prolonged therapy (>10 days) for each syndrome, including CVC-BSI (24% ID vs. 6% ICU; $P=0.013$), bacteraemic pneumonia (23% ID vs. 3% ICU; $P=0.044$), bacteraemic UTI (49% ID vs. 0% ICU; $P < 0.001$), bacteraemic IAI (27% ID vs. 12% ICU; $P=0.227$) and bacteraemic SSTI (34% ID vs. 22% ICU; $P=0.569$). There was wide variation amongst the ID clinicians' answers, with 42% of all ID responses recommending durations of ≤7 days and 31% recommending treatment regimens >10 days.

3.7. Comparison with Canadian respondents

This study was based on a similar Canadian survey but revealed significant differences between Canadian and Australian/New Zealand respondents. Compared with Canadian clinicians, the Australian/New Zealand respondents in the current study recommended shorter median durations for all scenarios with the exception of bacteraemic UTI (Table 3). These differences are most apparent when comparing prolonged therapy recommendations (>10 days) between Australian/New Zealand clinicians and their Canadian colleagues. Australian/New Zealand respondents were less likely to recommend prolonged duration compared with their Canadian colleagues for all syndromes (Table 3).

4. Discussion

This national survey of Australian and New Zealand ID and ICU physicians identified substantial variation in antibiotic duration recommendations for bacteraemia. The survey revealed which syndrome, pathogen, host and prescriber factors influence the self-reported duration of antimicrobial therapy.

Durations of 14, 10 and 7 days were distributed amongst all syndromes in this survey, with the median duration for each of the five syndromes being either 7 days or 10 days. There were few answers outside of 14, 10 or 7 days, suggesting a strong tradition of routine therapy durations. Use of a 7-day treatment course was more frequently reported in the current survey, in contrast to the Canadian survey that reported a most common duration of 14 days [9]. This may reflect a change in global temporal trend in treatment durations, however, as the Canadian survey was undertaken in 2011.

Table 3
Median recommended duration of Australia/New Zealand respondents (2017 survey) compared with Canadian respondents (2011 survey), and percentage of respondents from Australia/New Zealand and Canada recommending prolonged therapy (>10 days) for each syndrome.

Bacteraemic syndrome	Median recommended duration (days)		% recommending prolonged therapy	
	Australia/New Zealand	Canada	Australia/New Zealand ID	Canadian ID
CVC-BSI	7	10	24	49
Bacteraemic pneumonia	7	10	23	39
Bacteraemic UTI	10	10	49	59
Bacteraemic IAI	7	10	27	40
Bacteraemic SSTI	10	14	34	59

ID, infectious diseases; CVC-BSI, central venous catheter-related bloodstream infection; UTI, urinary tract infection; IAI, intra-abdominal infection; SSTI, skin and soft-tissue infection.

Overall, these data highlight the significant variation in the recommended durations of treatment amongst clinicians in treating the same syndrome. Despite this variation of recommended treatment durations, when asked a descriptive question about current treatment durations in patients with BSI (with options being 'usually too long', 'usually appropriate' and 'usually too short'), the majority of respondents stated that current treatment regimens for bacteraemic patients are 'usually too long'.

The source of bacteraemia appears to alter the antibiotic treatment duration recommendation. However, distributions were very similar for CVC-BSI, bacteraemic pneumonia, bacteraemic UTI, bacteraemic IAI and bacteraemic SSTI. The results showed two distinct patterns; CVC, pneumonia and IAI all had a median of 7 days with an IQR of 7–10 days, whilst the other two syndromes (UTI and SSTI) both had a median of 10 days with an IQR of 7–14 days. When comparing multiple pathogens in the CVC-BSI scenario, the causative bloodstream pathogen affected the duration of antibiotic treatment recommendations. Median durations remained at either 10 days or 7 days for all but two of the pathogens surveyed, albeit with a significantly different distribution. The two exceptions were CoNS (median 5 days) and *S. aureus* (median 14 days). CoNS are a common aetiology of CVC-BSI but have low virulence and usually require prosthetic material to cause ongoing infection. In contrast, *S. aureus* has a number of virulence factors that increase the likelihood of causing a more deep-seated metastatic infection. Observational studies have suggested a higher failure rate in treating *S. aureus* infections with treatment durations of <2 weeks [10,11], with Australian national guidelines reflecting this recommendation [12].

Host characteristics such as liver disease, chronic kidney disease, active malignancy and advanced age (>65 years) had no impact on the duration of recommended treatment in the vast majority of respondents in this survey. This may reflect the lack of supportive data to guide clinicians' use of such measures in determining duration. Measures of host response to treatment such as fever and ongoing vasopressor requirements resulted in an increased recommended duration of treatment by the majority of respondents, however ongoing ventilator dependence did not.

In each of the five bacteraemic syndromes included in this survey, ID physicians recommended longer durations of treatment than ICU physicians; this difference between specialties was also observed in the Canadian survey. The clinical reasoning or beliefs that drive this difference was not ascertained by the survey. Of note, this observation is a potential consideration when assessing the interplay of ID and ICU physicians, such as in an ICU antimicrobial stewardship programme.

This survey was limited by the overall low response rate from the ID and ICU societies, therefore it is difficult to be certain that the respondents are representative of the entire specialty body. In particular, there were few ICU respondents. As with all optional response surveys, an inherent bias is present because respondents to the survey may be non-representative of their specialties at large, thereby skewing the results. The ICU respondents in particular were members of the ANZICS-CTG, who are a select group of clinicians involved in clinical trials. It is also difficult to ascertain whether self-reported treatment recommendations are an accurate reflection of actual clinical practice These potential differences would be more accurately measured in observational studies of actual antimicrobial therapeutic practice.

5. Conclusion

Wide variations in the recommended durations of antimicrobial therapy prescribed for BSIs were identified among ID and ICU physician respondents to this survey. Clinicians' decision-making is influenced by the source of bacteraemia and the infecting pathogen but not by the patient's underlying medical co-morbidities.

This study adds to the current literature in several ways. It establishes evidence that there is significant variation in recommended treatment durations amongst clinicians who participated in the survey. This study also demonstrates that this variation has persisted at least from the aforementioned 2011 Canadian study [9] and that their findings were not limited to Canada alone, but suggests a potential international trend of inconsistence in clinician recommended treatment duration. Finally, this work supports the conduct of comparative effectiveness clinical trials of shorter courses of antibiotics (7 days) compared with longer/traditional courses (e.g. 14 days) in appropriate clinical scenarios [7]. These trials may also define patient and pathogen characteristics that will guide the selection of appropriate patients for a shorter duration of antimicrobial therapy. At present, more data are required before recommendations on a reduced duration of antimicrobial therapy can be incorporated into clinical treatment guidelines.

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Competing interests

None declared.

Ethical approval

Ethical approval was given by the Human Research Ethics Committee at Monash Health (Australia) [reference no. RES-17-0000-564L].

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijantimicag.2019.05.011.

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