Assessing the impact of a ‘bundle of care’ approach to Staphylococcus aureus bacteraemia in a tertiary hospital

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SUMMARY

Background: Staphylococcus aureus bacteraemia is associated with significant morbidity and mortality. There is evidence that standardised care bundle implementation may improve the rates of appropriate investigations and improve overall management. A S. aureus bacteraemia care bundle was introduced at Christchurch Hospital, New Zealand in early 2014. We assessed the impact of the intervention on the management and outcome of S. aureus bacteraemia.

Methods: A cohort study of cases of S. aureus bacteraemia was conducted following standardised care bundle introduction. Prospective enrolment of post-intervention patients occurred from 1st January 2014 to 30th June 2015, with retrospective review of pre-intervention cases from 1st January 2009 to 31st December 2013.

Results: In the pre-intervention period 447 patients had at least one episode of S. aureus bacteraemia compared to 151 patients in the post-intervention period. The two groups were similar by gender, ethnicity, and age. Significant increases in Infectious Diseases consultation rate (86.6% vs 94.8%; p = 0.009), echocardiography (76.3% vs 96.3%; p < 0.001), urine culture (74.0% vs 91.9%; p < 0.001), follow up blood cultures (44.2% vs 83.0%; p < 0.001), and at least 2 weeks of parenteral therapy (83.5% vs 92.9%; p = 0.014) were observed after introduction of the bundle. There were no significant differences in 30-day mortality (18.6% vs. 20.5%; p = 0.596), but there was a reduction in episodes of relapsed infection in the post-intervention cohort (7.4% vs. 20.5%; p = 0.596), but there was a reduction in episodes of relapsed infection in the post-intervention cohort (7.4% vs. 20.5%; p = 0.596).

Conclusion: An integrated care bundle for the management of S. aureus bacteraemia resulted in increased use of quality of care indicators and infectious diseases review and improved patient outcome.

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**Staphylococcus aureus** bacteraemia (SAB) is the most common hospital acquired and the second most common community acquired bloodstream infection in the world [1]. Australian data suggests that it accounts for 1.48 per 1000 hospital admissions at a cost of AUD $22,000 per episode [2]. The mortality rate was stated at 76–83% in the pre-antibiotic era [3]. It remains a cause of significant morbidity and death, with mortality rates ranging from 16-40% at 90 days [2–9]. This rate has remained remarkably stable over time [7].

New Zealand has among the highest rates of staphylococcal infection in the world. From 2000-2011, the averaged incident rate was 127 per 100,000 per year for all staphylococcal infections and 14 per 100,000 per year for staphylococcal sepsis [10]. Māori and Pasifika peoples are 2–5 times more likely to suffer from staphylococcal infections than European/Pākeha New Zealanders [10,11]. Likewise, a disproportionate burden of morbidity from SAB is borne by Māori and Pasifika [5,7]. This is also true for also indigenous Australians [7,12]. However, this does not appear to translate into excess mortality [5,7,12]. In previous New Zealand research, the relative risk of developing SAB was 1.8 for Maori and 4.0 for Pasifika but European/Pākeha ethnicity carried a relative risk for mortality at 30 days of 1.4 [5]. In another Australasian study, 30-day mortality was 22.2% for Europeans, 9.7% for Māori, and 5.7% for Aboriginal and Torres Straight Island People [7].

Little is known about the molecular epidemiology of meticillin susceptible *S. aureus* (MSSA) in New Zealand, although a 2014 point prevalence survey noted that the CC1, CC188, CC5, and CC121 clones predominate [11]. The prevalence of meticillin resistant *S. aureus* (MRSA) in New Zealand is 8.9–10% [11,13]. Six MRSA clones accounted for 90.6% of all MRSA in a 2017 point-prevalence survey (AK3, Queensland clone MRSA, WR/AK1, EMRSA-15, USA300 MRSA, and WSPP MRSA) [14]. Panton-Valentine Leukocidin is expressed by 25.2% of both MRSA and MSSA in New Zealand [11].

SAB is characterised by its propensity to relapse. Apparent reinfections or metastatic complications within 90 days of cessation of therapy are usually found to be due to the same strain [15,16]. Multiple factors have been found to improve the management of SAB and its outcomes. Most prominently among these are bedside Infectious Diseases (ID) consultation and the use of β-lactam therapy to treat meticillin-susceptible isolates [6,8,17–21]. Conversely, the absence of formal Infectious Diseases consultation and parenteral treatment durations shorter than ten days have been found to place patients at risk of adverse outcomes [22–24]. Similarly, there are multiple patient factors that are suggestive of complicated *S. aureus* bacteraemia such as the presence of embolic stigmata on cutaneous examination, persistence of fever while on appropriate management, and persistence of bacteraemia at 48–96 hours while on appropriate antimicrobial therapy [3,25].

Development of integrated "bundles of care" with multiple evidence-based interventions has been found to have protective effects in the management of SAB [1,4,17]. Following the publication of a bundle of care study from Spain, a similar SAB management protocol was developed for use at Christchurch Hospital [4].

Christchurch Hospital is the main acute hospital operated by Canterbury District Health Board, which provides acute care to a population of 567,870 and is the tertiary referral centre for the upper South Island of New Zealand [26]. Christchurch Hospital co-locates with Christchurch Women’s Hospital in a campus of 833 beds [27]. Specialties offered include haematology and stem cell transplantation, renal transplantation, cardiothoracic surgery, neurosurgery, obstetrics and gynaecology, and plastic surgery.

**Methods**

A case of SAB was defined as a patient for whom at least one blood culture isolate identified as *S. aureus*. The bundle of care was designed with reference to the bundle study published by López-Cortés et al. [4]. A document was developed for educational purposes, providing a brief introduction, references, and details on the structured intervention. This document was placed in the clinical notes of each patient assessed by the Infectious Diseases Registrar in addition to the standard Infectious Diseases review documentation. In addition to automatic, non-discretionary ID review of cases of SAB, the bundle mandated echocardiography (transthoracic [TTE] in the first instance, transoesophageal [TOE] as required), early use of beta-lactam therapy (flucloxacillin or cefazolin), dosing advice and provided information on MRSA risk factors. Separate instructions were made regarding the importance of commencing appropriate therapy for MRSA (acknowledging the mortality benefit associated with appropriate initial therapy) [28]. Rates of invasive MRSA infection have been low in our setting, as such empiric MRSA treatment was not considered necessary for most patients, without specific risk factors. The protocol advised the collection of blood cultures 48–72 hours following the initiation of therapy. In addition, urine culture and microscopy were suggested as further surrogate measures of complicated bacteraemia, as has been noted elsewhere [7]. The need for prompt source control of foci of infection was emphasised, including the removal of infected vascular access devices. A minimum treatment duration of 14 days was mandated, consistent with published guidelines [8,29,30]. The SAB bundle was developed by JKG (with input from SCLM and STC) in December 2013, and formally implemented in January 2014.

The department of Infectious Diseases introduced a policy of automatic, non-discretionary review of patients with invasive isolates of *S. aureus* in mid-2013, late in the pre-intervention period but did not have a formalised departmental SAB guideline prior to the development of the bundle. Direct notification of results was made to the Infectious Diseases registrar by the Microbiology registrar or Clinical Microbiologist; resulting in bedside review.
A before and after study methodology was applied to assess the performance of the *S. aureus* bacteraemia bundle. De-identified data including patient demographics, diagnosis, antimicrobial susceptibility pattern, comorbidities, treatment outcome, and length of treatment were prospectively collated in a Microsoft Excel™ (Microsoft Corporation; Redmond, Washington, USA) database maintained by the Infectious Diseases registries for all cases of *S. aureus* bacteraemia diagnosed between 1st January 2014 and 30th June 2015. The comparator dataset was retrospectively drawn from cases of *S. aureus* bacteraemia identified from 1st January 2009 to 31st December 2013. These were identified by interrogation of Canterbury Health Laboratories’ Delphic LIS™ platform ( Sysmex corporation, Kobe, Japan). A Charlson comorbidity index was calculated for each patient for the relevant admission [31].

Cases of SAB were recorded as community-acquired, health-care-associated, or hospital-acquired as per the criteria outlined by Friedman et al. [32]. Diagnoses of deep foci of infection were confirmed by radiological or microbiological investigation as appropriate. All cases of endocarditis were diagnosed using the modified Duke criteria [33].

Patients were included in the study if they were 18 years of age or above. Patients were excluded if they were lost to follow-up. The main outcome variables of the before and after study were the adherence to the quality of care indicators of Infectious Diseases review, follow up blood cultures, echocardiography, beta lactam therapy (where appropriate), urine culture and a 14-day minimum parenteral course. A β-lactam was defined as any β-lactam antimicrobial with appropriate anti-staphylococcal activity. Appropriate use of a β-lactam was defined as greater than 50% of the total parenteral treatment duration. Secondary outcome measures were all cause mortality at 7, 14, and 30 days; and relapsed infection (either bacteraemia or confirmed deep-site infection due to *S. aureus*) in the 90 days following the cessation of planned antimicrobial therapy. The first episode of bacteraemia for each patient was included for analysis.

Identification of isolates of *S. aureus* either employed phenotypic techniques, automated identification with BD Phoenix™ (Becton, Dickinson, and Company; Franklin Lakes, New Jersey, USA), or Matrix Assisted Laser De-ionisation Time of Flight (MALDI-TOF. Bruker Corporation; Billerica, Massachusetts, USA). Antimicrobial susceptibility testing was performed using either disk-based methodology or automated microdilution (BD Phoenix™). Screening for meticillin resistance was done using cefoxitin disks and employed standard protocols. Clinical Laboratory and Standards Institute (CLSI) standards for antimicrobial susceptibility testing were employed by the laboratory until 2012, with European Committee on Antimicrobial Susceptibility Testing (EUCAST) standards being employed subsequently.

The study group engaged in consultation with the Canterbury District Health Board’s Te Komiti o Whakarite, and ethical approval for the study was subsequently given by the University of Otago/Canterbury District Health Board Ethics Committee (reference 15222).

### Statistical analysis

Categorical variables were reported as proportions with the total number in each study group as the denominator. Continuous variables were reported as means and standard deviations for normally distributed variables and medians and ranges for non-normally distributed data. Univariate analysis was performed using Fisher’s exact test or Pearson X² test where appropriate for categorical variables, and the Independent samples t-test for continuous variables. All p-values calculated were 2-tailed, and p-values <0.05 were considered significant. Statistical analysis was performed using SPSS™ v25.0 (IBM, Chicago, Illinois, USA).

### Results

During the study period there were 598 adult cases: 447 in the pre-intervention period (2009–13) and 151 in the bundle period (2014–15). Six cases were lost to follow up in the pre-intervention cohort and one in the bundle cohort. The demographics of the two groups were equivalent for age (mean 64.7 years vs 63.8; *p*=0.588), ethnicity, and gender (Table I). The bundle cohort had a higher proportion of community acquired SAB (41.6% vs 54.3%; *p*=0.007) but proportions of hospital acquired SAB were similar (21.9% vs 18.5%; *p*=0.378). There was no significant difference between the mean Charlson comorbidity indices of the two groups (3.92 vs 4.15; *p*=0.549) (Table II).

| Ethnicity** | Pre-intervention | Post-intervention | P value |
|-------------|-----------------|-----------------|---------|
| Pacific Island | 18 (4.0) | 3 (2.0) | 0.312 |
| Asian | 5 (1.1) | 0 (0.0) | 0.337 |
| Middle East/Latin American/African | 2 (0.4) | 0 (0.0) | 1.000 |
| Other | 16 (3.6) | 11 (7.3) | 0.058 |

Key: *mean (standard deviation). ** total (percentage).

| S. aureus typ** | Pre-intervention | Post-intervention | P value |
|-----------------|-----------------|-----------------|---------|
| Penicillin susceptible | 73 (16.3) | 8 (5.3) | 0.001 |
| Methicillin resistant | 2 (0.4) | 6 (4.0) | 0.004 |

| Acquisition** | Pre-intervention | Post-intervention | P value |
|----------------|-----------------|-----------------|---------|
| Community acquired | 186 (41.6) | 82 (54.3) | 0.007 |
| Healthcare associated | 163 (36.5) | 41 (27.2) | 0.047 |
| Hospital acquired | 98 (21.9) | 28 (18.5) | 0.378 |

** Table I**

Demographics

| Total | Pre-intervention | Post-intervention | P value |
|-------|-----------------|-----------------|---------|
| Age* | 64.7 (±17.8) | 63.8 (±18.8) | 0.588 |
| Female** | 168 (37.6) | 57 (37.8) | 0.971 |

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| Ethnicity** | Pre-intervention | Post-intervention | P value |
|-------------|-----------------|-----------------|---------|
| European/Pakeha | 363 (81.2) | 124 (82.1) | 0.803 |
| Maori | 38 (8.5) | 13 (8.6) | 0.967 |
| Other | 16 (3.6) | 11 (7.3) | 0.058 |

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Continuous variables were reported as means and standard deviations for normally distributed variables and medians and ranges for non-normally distributed data. Univariate analysis was performed using Fisher’s exact test or Pearson X² test where appropriate for categorical variables, and the Independent samples t-test for continuous variables. All p-values calculated were 2-tailed, and p-values <0.05 were considered significant. Statistical analysis was performed using SPSS™ v25.0 (IBM, Chicago, Illinois, USA).

### Statistical analysis

Categorical variables were reported as proportions with the total number in each study group as the denominator.
there was a significant increase in the number of patients who received a minimum parenteral treatment duration of 14 days (83.5% vs 92.9%; \( p = 0.014 \)) as well as significant increase in the proportion of patients who had source control of drainable foci or removal of affected lines in the first 72 hours (85.2% vs 94.7%; \( p = 0.040 \)). There was no difference between the two groups in the proportion of patients who received \( \beta \)-lactam therapy for MSSA infection (Table IV).

**Discussion**

In this single-centre, tertiary hospital study, an integrated care bundle for the management of \( S. \ aureus \) bacteraemia was followed by a marked increase in the performance of most quality of care indicators. It did not make a significant impact on the proportion of patients who received beta-lactam based therapy, but this reflects the high utilisation of adequately prescribed antimicrobials in the pre-intervention cohort. While the rate of relapse in the pre-intervention group was low by reported standards [16,18,34], the bundle was associated with a reduction in the percentage who relapsed. This is consistent with the positive effects of Infectious Diseases review and the selected quality of care interventions which have also been demonstrated elsewhere [4,8]. Mortality rates were consistent with other studies performed in Australasia [2,5,7,12].

The rate of relapse of SAB in our setting is among the lowest rates of relapse reported, even in the pre-intervention period [4,7,16]. Even so, the use of a structured intervention may have conferred further benefit. Beyond ensuring an adequate therapeutic duration, which is the single factor most likely to result in relapse, a SAB bundle likely acts as an attention to detail tool, ensuring that the disparate parts of SAB management are brought together in a timely and consistent fashion. Where bundles of care have been introduced for the management of SAB, they have generally been found to increase the uptake of investigations such as echocardiography and repeat blood cultures [4,6]. While bundles of care consistently increase the rate of usage of beta-lactam therapy for the management of methicillin susceptible SAB, other outcome measures are less consistent. In certain settings, such as that reported by Lopez-Cortes et al. [4] the introduction of a SAB bundle may reduce mortality, whereas in other settings, benefits have been limited to the performance of key clinical investigations mentioned above, or a relapse prevention benefit [4,6]. This may reflect the baseline conditions of the healthcare systems or hospital in which a SAB bundle is introduced rather than inherent flaws in the management approach. The lack of mortality benefit shown in this study may reflect

| Table II | Comorbidities | Pre-intervention | Post-intervention | \( P \) value |
|----------|---------------|------------------|-------------------|-------------|
| **Charlson Comorbidity Index*** | 3.92 (±3.28) | 4.15 (±3.18) | 0.45 |
| **Comorbidities**** | | | |
| Diabetes Mellitus (DM) | 21 (4.7) | 8 (5.3) | 0.767 |
| without complications | | | |
| DM with complications | 61 (13.6) | 26 (17.2) | 0.282 |
| COPD | 20 (4.5) | 3 (2.0) | 0.223 |
| Solid organ malignancy | 33 (7.4) | 16 (10.6) | 0.213 |
| (without metastases) | | | |
| Solid organ malignancy (with metastases) | 26 (5.8) | 9 (5.6) | 0.948 |
| Lymphoma | 10 (2.2) | 2 (1.3) | 0.738 |
| Chronic liver disease (moderate to severe) | 10 (2.2) | 0 (0.0) | 0.073 |
| Connective tissue disease | 8 (1.8) | 3 (2.0) | 1.000 |
| Cerebrovascular disease | 33 (7.4) | 7 (4.6) | 0.243 |
| Peripheral vascular disease | 37 (8.3) | 8 (5.3) | 0.230 |
| Congestive cardiac failure | 56 (12.5) | 19 (12.6) | 0.986 |
| Myocardial infarction | 32 (7.2) | 11 (7.3) | 0.999 |
| Chronic kidney disease (> stage 2) | 60 (13.4) | 28 (18.5) | 0.125 |
| Leukaemia | 11 (2.5) | 2 (1.3) | 0.533 |

*Key: * mean (standard deviation). **total (percentage).
Table IV

Outcome measures

| Intervention | Pre- | Post- |
|-------------|-----|------|
| Early Mortality/Palliation* | 38 (8.5%) | 13 (8.6%) | 0.967 |
| 7 Day Mortality | 51 (11.4) | 16 (10.6) | 0.784 |
| 14 Day Mortality | 60 (13.4) | 22 (14.6) | 0.723 |
| 30 Day Mortality | 83 (18.6) | 31 (20.5) | 0.596 |
| Relapsed infection | 33 (7.4) | 2 (1.3) | 0.004 |

Diagnostic Key

Performance Indicators*

| N=396 | N=135 |
|-------|-------|
| ID consultation | 343 (86.6) | 128 (94.8) | 0.009 |
| Any Echocardiogram | 302 (76.3) | 130 (96.3) | <0.001 |
| TOE | 45 (11.4) | 24 (17.8) | 0.056 |
| Urine culture | 293 (74.0) | 124 (91.9) | <0.001 |
| Repeat Blood Culture | 175 (44.2) | 112 (83.0) | <0.001 |

Treatment Key

Performance Indicators (KPI) ²

| N=387 | N=129 |
|-------|-------|
| ≥14 days parenteral therapy | 323 (83.5) | 119 (92.9) | 0.014 |
| B-lactam for MSSA† | 371 (96.7) | 119 (96.7) | 1.000 |
| All KPI | 92 (23.8) | 95 (73.6) | <0.001 |

Source control of drainable foci <72hrs*

| N=216 | N=75 |
|-------|------|
| 184 (85.2) | 71 (94.7) | 0.040 |

Mean days parenteral Rx ³

| 27.3 (±17.9) | 23.8 (±13.6) | 0.048 |

Key.

* Total (percentage).
** Assessed among survivors at day 7.
MRSA excluded from denominator.
† Assessed among survivors at day 14.
³ Mean (standard deviation).

the high rates of Infectious Diseases review, utilisation of beta-
lactam therapy, early source control and effective therapeutic
durations even in the baseline cohort, comparing favourably to
the post-intervention data reported by López Cortés et al. [4].

Our study reports one of the highest rates of TTE performed
in studies of SAB, but also one of the lower rates of TOE. The
rates of endocarditis reported in our study were 9.2% and 8.6%
respectively in the pre- and post-intervention groups
(p=0.835). These rates are consistent with those found in other
studies of SAB, including those with much higher published
rates of TOE [35–39]. Despite the low rate of utilisation of TOE,
the rates of endocarditis diagnosis in this study are consistent
with those reported in other case series [9,35–38]. Some
authors suggest forgoing TOE if repeat blood cultures are
negative and no additional deep foci of infection are identified
[38]. There can be little dispute that TOE is the superior
echocardiographic modality for confirming diagnoses of endo-
carditis [37]. However, TTE is an effective risk stratification
tool in SAB when used in conjunction with follow-up blood
cultures, appropriate radiological investigation, and Infectious
Diseases specialty guidance. Other authors have reported that
TTE may miss 10–16% of diagnoses of endocarditis [7,36]. Using
these figures, a blanket TOE policy may have potentiated the
diagnoses of 1–2 further cases of endocarditis in our study. The
impact of this on likely therapeutic duration of patients may
have been negligible given that mean durations of therapy in
both cohorts were similar to those recommended by the
European Cardiological Society and Australian therapeutic
guidelines group for S. aureus endocarditis [40,41]. Fur-
thermore, studies in Europe have suggested that short course
therapy of 14 days of an isoxazolyl penicillin, such as oxacillin,
with or without gentamicin may be sufficient for the treatment
of right sided endocarditis in selected patients [42,43]. Despite
our low rate of TOE usage, we think that TOE should be per-
formed if a diagnosis of endocarditis is considered highly likely
or SAB occurs in the setting of prosthetic heart valves or
intracardiac devices, or for surgical assessment and planning in
confirmed cases of infective endocarditis.

Our study noted an increase in the incidence of MRSA bac-
teraemia during the study period. While there is currently no
national surveillance of SAB in New Zealand to reference this
against, point prevalence rates of MRSA were noted to increase
from 10.2 per 100,000 to 20.4 per 100,000 from 2009-2015 in
nationwide surveys [14]. These rates were markedly higher in
Māori and Pasifika (38.5 per 100,000 and 76.2 per 100,000
respectively) populations. In a related 2014 point-prevalence
survey, 8.9% of S. aureus isolates in New Zealand were metic-
illin resistant [11], although results for the Southern region,
which includes Canterbury District Health Board, noted a lower
prevalence of 5.1% [11].

Among the strengths of this study are the high level of
coordination between the Microbiology laboratory and Infect-
iuous Diseases department, potentiating the strategy of
expectant review. The single-centre nature of the study may
be considered a weakness, but in the relatively remote setting
of the Canterbury region, a single, large, acute hospital setting
with centralised laboratory processing enabled easier standard-
isation of the management of complex conditions such as
SAB. Other strengths include the use of evidence-based care
indicators and structured nature which would make this
intervention replicable in similar settings. This study will have
the inherent limitations of before and after study designs and
non-assessed variables may have had impact on the results.

In conclusion, our results add further support to the growing
body of evidence that a structured care bundle improves the
management of SAB by increasing the utilisation of key inves-
tigations as well as increasing the proportion of patients who
receive adequate courses of therapy. In addition, it may pro-
de additional benefit in terms of relapse prevention.

Credit author statement

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Jared K Green: conceptualisation, formal analysis, investi-
gation, data curation, writing draft, writing: reviewing and
ing the strategy of, projection administration.
Julia Howard: investigation, writing draft writing: reviewing
and editing.
Avinesh Shankar: investigation, data curation.
Richard Clinghan: investigation.
Tessa Luff: investigation.
Mark Birch: supervision.
Alan Pithie: supervision.
Anja Wernon: supervision.
Sarah Metcalf: supervision, writing: reviewing and editing.
Stephen Chambers: investigation, writing: reviewing and editing, supervision.

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Conflicts of interest statement
No Conflicts.

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