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Management of *Staphylococcus aureus* bacteraemia (SAB) in the oncology patient: Further evidence supports prompt removal of central venous catheters and shorter duration of intravenous antimicrobial therapy

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SUMMARY

Background: *Staphylococcus aureus* bacteraemia (SAB) is associated with relatively high risk of complications and high levels of mortality. Internationally, SAB management guidelines lack consensus and especially so regarding oncology patients. This is likely a reflection of insufficient randomised control trials (RCT) and the diversity of SAB patient populations. However, there are 2011 guidelines recommending a minimum of 14 days of appropriate IV antibiotic therapy for SAB.

Objective: We wished to determine whether our practice of shortened duration of intravenous antimicrobial therapy in favour of oral administration proved as effective as recommended guidelines in a mixed oncology patient cohort.

Methods: Retrospective review of patient records that included any SAB episode among oncology patients from January 2002 to December 2015. Medical chart reviews were undertaken to determine patient demographics, clinical management & antimicrobial therapy, duration of stay, presence of a central venous catheter (CVC) and outcome.

Results: Our CVC removal rate was just 73% in SAB where CVC was the identified source of infection, with an attributable mortality rate (<4%) far lower than would be expected. Antimicrobial therapy durations were considerably lower (10 days) than current recommendations of 14 days IV therapy. The recurrence rate of 15% was also significantly lower than has been reported previously.

Conclusions: Our observations contribute new insights concerning the management of SAB in oncology patients. Our findings suggest that therapeutic approaches should perhaps

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remain individualised and reflective of patient characteristics taking into consideration the complex nature of oncology patients.

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Introduction

Staphylococcus aureus bacteraemia (SAB) is associated with relatively high risk of complications and high levels of mortality. A 2014 meta-analysis of prospective observational studies internationally found a 90-day mortality of almost 30%, confirming previous reports [1]. In that context, our study was conducted in Ireland, during a period in which incidence of SAB declined from 0.346 per 1000 Bed Days Used (BDU) in 2004, to 0.271 in 2018 [2]. Encouragingly, while methicillin-resistant *Staphylococcus aureus* (MRSA) bacteraemia accounted for 23.8% of episodes in 2011 and decreased to 19.5% in 2014, that number had further declined to only 12.8% in 2018.

Internationally, SAB management guidelines lack consensus [3]. This is likely a reflection of insufficient randomised control trials (RCT) and the diversity of SAB patient populations [4]. However, there are 2011 guidelines recommending a minimum of 14 days of appropriate antibiotic therapy for SAB, with more prolonged courses where there is evidence of persistent deep-seated infection [5,6]. An Icelandic population-based study defined appropriate antibiotic therapy duration as ≥ 10 days IV therapy with an appropriate agent for uncomplicated infection and ≥ 24 days for complicated infection, and demonstrated lower relapse rates and mortality [7]. Notably, those guidelines have evolved considerably from those suggested in a 1982 paper of 4–6 weeks antibiotic therapy for SAB [8]. Choice of appropriate antimicrobial therapy is also challenging, due somewhat to the aforementioned paucity of definitive RCTs and the emerging threat of vancomycin resistant *S. aureus* (VRSA). Currently, β -lactams offer relatively rapid, long-term clearance and are seen as more effective than glycopeptides [9,10]. Cefazolin (a cephalosporin) is deemed non-inferior to penicillins and may be a useful alternative to reduce dosage frequency [11]. Aminoglycosides, specifically gentamycin, are frequently co-administered with β -lactams for a presumed synergistic effect despite insufficient evidence in the clinical setting [5]. Two RCTs have reported that oral administration of some antibiotics can have efficacy equivalent to IV administration [12,13]. Therefore, our study attempts in part to provide new insight regarding this latter approach. Irrespective of duration and chosen antimicrobial agent, source control is widely acknowledged to be an important aspect of treating SAB, with failure to remove a source of ongoing infection often precipitating failure of blood sterilisation. This is particularly relevant to intravascular devices such as central venous catheters (CVC), which for instance represent approximately one third of healthcare-associated infections in the United States [14]. Strong associations have been demonstrated between failure to remove these, relapse of infection and risk of mortality [14,15], conversely, prompt removal has been associated with uncomplicated bacteraemia (i.e., no secondary deep-seated focus of infection and no recurrence within 3 months) [16]. Other factors associated with poor outcomes include persistent bacteraemia, septic

shock, co-morbidities including cancer and community acquisition of infection [17].

There are few data regarding SAB in specific oncology populations. SAB occurring in oncology patients is overwhelmingly CVC-associated as many of these patients have long-term tunnelled CVCs *in situ* to facilitate administration of chemotherapy [18]. Mortality associated with SAB in oncology patients has been reported as being as high as 33%, higher than mortality associated with other pathogens in this population [19]. A Spanish study of neutropenic cancer patients with SAB found that 14% (4 of 28) of patients had septic metastases identified [18], while a 2007 United States study described a high incidence of CVC-related SAB complications with 19% of implicated patients having intravascular complications [20].

Framed this way, German guidelines concerning catheter-related bloodstream infection in haematology/oncology patients recommend CVC removal in all patients with SAB, citing high relapse rates if retention is attempted [21]. An earlier retrospective review (2001) of CVC-associated SAB found higher mortality with shorter duration of treatment [22] while the US study mentioned above reported that removal of the catheter within 3 days was associated with a lower relapse rate [20]. More recently, an important large observational study across several centres in France revealed a SAB complication rate of 36% [23]. Subgroup analysis found an endocarditis rate of 11.9% in non-nosocomial SAB. The occurrence of CVC-related septic thrombosis with associated deep-seated infections has been described in association with SAB in cancer patients and a higher relapse rate demonstrated with shorter treatment duration (14 days versus >14 days) in this group, highlighting the importance of identifying deep-seated foci in these patients and adjusting treatment duration accordingly [24].

Our study attempted to elucidate the complexity of SAB amongst oncology patients, and specifically with regard to the difficulty of CVC management in SAB. More specifically, we performed a retrospective review of oncology patient records with respect to CVC SAB acquisition (from Jan 2002 until December 2015) to determine whether acceptable patient outcomes were achieved through local practice of prompt catheter removal and relatively short duration of IV antibiotic administration before switch to oral delivery.

Methods

Study design

Retrospective review of patient records that included any SAB episode among University Hospital Limerick (Ireland) oncology patients from January 2002 to December 2015. Medical chart reviews were undertaken to determine patient demographics, clinical significance of microbiological result, clinical management & antimicrobial therapy, duration of stay, presence of a CVC and outcome. The laboratory information

system (LIS) was interrogated for data concerning blood culture procurement, time to positivity and antibiotic sensitivity profiles. Only anonymised data are presented.

Setting

The Mid Western Cancer Centre is based at UHL, a 480-bed hospital in the mid-west of Ireland that is the regional tertiary referral centre for a combined population of 400,000 and which has been the site of notable hospital acquired infection outbreaks [25–27] and subsequent innovations in patient management [28]. The Mid Western Cancer Centre is one of 8 designated cancer centres in the Republic of Ireland and provides specialised breast and colorectal cancer surgery services as well as a medical oncology and radiotherapy services.

Definitions

An episode of SAB was defined as the presence of systemic symptoms including a temperature $>38^{\circ}\text{C}$ or $<36.5^{\circ}\text{C}$, apnoea, tachycardia, bradycardia, hypotension, confusion or agitation along with at least one positive blood culture. Resolution was determined by a subsequent sterile blood culture with a reversal of symptoms.

Recurrence was defined as the reestablishment of systemic symptoms with at least one positive blood culture following a period of resolution (>48 h). In this setting, complications were defined as SAB recurrence or the presence of deep-seated foci that were attributed to SAB infection. A CVC associated SAB was defined as the presence of the same bacteria in a given blood culture being successfully cultured from a catheter line tip (>15 colony forming units (Maki rolling method)) or the surrounding skin insertion site, differential time to positivity with same pathogen >2 h between CVC and peripheral simultaneously drawn blood cultures sets, or symptomatic improvement within 48 hours of removal of the CVC in the setting of associated sterile peripheral blood cultures. Neutropenia was defined as a neutrophil count $<1.0 \times 10^9/\text{L}$ with neutrophilia being defined as a neutrophil count $>7.5 \times 10^9/\text{L}$.

Laboratory methods

Biomérieux BacT/Alert 3DTM was used for blood culture incubation. *Staphylococcus aureus* species were identified using Pastorex Staph-Plus latex agglutination (Bio-Rad, Marnes-la-Coquette, France) and DNase agar (LIP Fannin, Galway, Ireland). Since July 2012 mass spectrometry was available for confirmation (MALDI-ToF MS, Bruker Daltonik, Bremen, Germany). Antimicrobial susceptibility testing was performed using Sensititre broth microdilution (TREK Diagnostic Systems Inc., Cleveland, USA) and oxacillin E-test (BioMérieux, AB Biodisk, Solna, Sweden).

Data analysis

Data were stored and analysed using Microsoft Excel 2016.

Results

Over the 14-year period from January 2002 to December 2015, 53 episodes of SAB occurred in 45 patients. All episodes of SAB in our dataset were deemed to be of clinical significance. Females accounted for 62% ($n=28$) of episodes. The median age of initial episode was 52 (range 21–73). The spectrum of recorded malignancies closely reflected Irish national prevalence data. [29] Among the cohort, solid tumours accounted for 87% ($n=39$) of malignancies. Breast carcinoma was most frequent (40%, $n=18$), followed by colorectal (27%, $n=12$), testis (7%, $n=3$), and oesophagus (4%, $n=2$). The primary malignancies in the remaining patients (8%, $n=4$) were gastric, lung, ovarian, and prostatic. Malignancy data were unavailable for one case and the rest of patients had miscellaneous malignancies (11% $n=5$). This cohort of patients comprised a mixture of those receiving treatment for either primary disease or for relapse/progression of disease at the time of the initial SAB diagnosis.

Risk factor stratification

In retrospect, five of the patients who had a CVC-related bloodstream infection could have been identified as at risk of SAB prior to CVC insertion. Our review of case notes revealed a previous Hickman removed because of a CVC-associated coagulase negative *Staphylococcus* bacteraemia (CoNS) (1 patient); Peripheral Venous Catheter (PVC) phlebitis (1 patient); post-operative wound infection (1 patient); local infection at the site of a previous CVC (peripherally inserted central catheter) (1 patient) and Hickman (the same patient); or skin rash at the time of line insertion (1 patient). Fourteen further patients experienced problems with CVC prior to the onset of SAB; in 1 case, the line insertion took 2 attempts due to a faulty guidewire (1 patient), while fever and rigors developed immediately after the CVC was inserted (1 patient), albeit that bacteraemia was not documented until 7 days later. The remaining twelve patients had documented CVC exit-site infection (one several months prior to the bacteraemia), the patient had a documented CVC exit-site infections a number of months prior to the new CVC insertions. Of this cohort, 50% ($n=6$) had received oral antibiotics. The remaining patient had a documented wide-spread skin rash.

SAB source identification and subsequent management

A CVC was *in situ* at the time of SAB diagnosis in 96% ($n=51$) of episodes in 43 patients and was deemed the source in 90%

Table 1

Management of complicated vs. uncomplicated CVC-associated SAB in oncology patients

	Number of episodes ^a	CVC removed within 48 h (%)	Mean days from SAB to CVC removal (Range)	Mean days IV antibiotic with activity (Range)	Mean days targeted IV antibiotic (Range)
Complicated	19	5 (26.3)	3.7 (0–13)	5.1 (0–14)	2.4 (0–12)
Uncomplicated	26	5 (19.2)	4.1 (0–13)	4.5 (0–10)	1.6 (0–10)

^a Data were incomplete for 3 episodes.

Table 2
Characteristics, Management and Outcomes of CVC-associated SAB (Removal vs. Salvage)

	Number of episodes	Systemic symptoms (%)	Median days from insertion to SAB (Range)	Median days from chemotherapy access to SAB (Range)	Persistently positive blood culture at ≥ 48 h (%)	Neutropenia (%)	Abscess/cellulitis /thrombosis (%)	Evidence of metastatic infection (%)	Median days IV antibiotic with activity (Range)	Median days targeted IV antibiotic (Range)	Recurrence (%)	Death
CVC Removed	32 ^a	28 (87.5)	37 (7–206)	10.5 (1–87)	6 (18.8)	7 (21.8)	8 (25)	6 (18.8)	4.5 (0–14)	0 (0–12)	4 (12.5)	1 (3.1)
CVC Salvaged	12	11 (91.6)	39 (5–91)	11 (6–51)	2 (16.6)	4 (33.3)	1 (8.3)	1 (8.3)	3 (0–13)	0 (0–5)	3 (25)	0

^a Data were incomplete for 3 episodes.

(n=48) of SAB episodes (40 patients). 4% (n=2) had a chest source and 6% (n=3) were undetermined. Of those episodes implicating a CVC as source, 69% (n=33) were confirmed via positive swab culture from CVC site, 15% (n=7) were confirmed by isolation of *S. aureus* from CVC tip, 6% (n=3) were confirmed by differential time to positivity, and 8% (n=4) were confirmed on grounds of clinical evidence of line site infection. Finally, 2% (n=1) were assumed to be line source as only cultures procured from the line were positive while peripheral cultures were sterile.

Of the 48 episodes with a CVC source, 35 episodes involved tunnelled CVCs with an external port and 9 episodes involved tunnelled CVCs with a subcutaneous port. A single peripherally-inserted central catheter (PICC) was also implicated. Interventional radiology assisted line placement in 36 cases, while 17% (n=8) were placed in theatre and only one (1) on the ward. The latter nine placements were most likely performed by registrar physicians.

In 94% (n=45) of episodes the patient was documented as systemically unwell at the time of recorded bacteraemia. In 43% (n=23) of patients, neutrophilia was recorded at the time of documented bacteraemia, 27% (n=14) of patients were neutropenic at the time of the bacteraemia and in 30% (n=16) the neutrophil count was within range. Following SAB diagnosis and therapy, documented sterile blood cultures were obtained in 71% (n=37) and not obtained in 29% (n=15), data were unavailable for 1 episode. In the 37 episodes where sterile blood cultures were obtained, the mean number of days from the initial positive blood culture to documented sterility was 4.3.

Regarding CVC source episodes, the median number of days from CVC insertion to SAB diagnosis was 49 (median 33, range 7–206). In 87% (n=46) of episodes, the CVC had been used to administer chemotherapy prior to SAB onset. The mean number of days from the most recent device access for chemotherapy to SAB onset was 15 (median 11, range 1–87). Of the 48 CVC source episodes, the offending line was removed in 73% (n=35) although data were incomplete for 3 of these episodes (available data are reflected in Tables where possible). Of the 45 episodes, 19 were deemed complicated (as per earlier definition). However, evidence of complications did not correlate with meaningfully quicker removal of CVCs or longer durations of IV antibiotic therapy (Table 1).

Where the CVC was removed (32 episodes with complete data), the median number of days from SAB diagnosis to line removal was 3 (range 0–15). These episodes were associated with higher numbers of systemic symptoms and abscesses/thromboses, but there was no statistical difference in subsequent recurrence of SAB between these cases and the 27% (n=12) episodes where the CVC was left *in situ* and attempts made to salvage the insertion (Table 2), 13% versus 25% respectively. However, statistical difference may not have been achieved due to the relatively low numbers of patients involved. Analysis of episodes where CVCs were removed within 48 hrs of SAB diagnosis rather than later than 48 hrs identified earlier removal of CVC where median duration of IV therapy approximated 7 days or, in other words, where prior therapy over 7 days had failed to achieve clinical benefit (Table 3). Notably, with both approaches (irrespective of evidence of multifocal infection or line abscesses) the median time to achieving sterile blood cultures following removal of the CVC was 2 days. This indicates that irrespective of when the

Table 3

Characteristics and Management of CVC-associated SAB: CVC removed within 48 hours vs. not removed within 48 hours or not removed at all

	Number of episodes	Systemic symptoms (%)	Neutropenia (%)	Line site abscess (%)	Deep venous thrombosis (%)	Evidence of multifocal infection (%)	Median days IV antibiotic with activity (Range)	Median days targeted IV antibiotic (Range)
CVC removed within 48 h	10	10 (100)	3 (33.3)	2 (20)	1 (10)	0	7 (2–14)	0 (0–12)
CVC not removed within 48 h	32	28 (87.5)	7 (21.8)	2 (6.2)	1 (3.1)	2 (6.2)	4 (0–13)	0 (0–6)

CVC is removed antimicrobial efficacy can be consistent (albeit that further larger cohort studies are need to verify this), although the single death associated with SAB *per se* was observed in the patient cohort that had delayed CVC removal (Table 4) (Table 5).

Antimicrobial resistance and duration of antibiotic therapy

Resistance amongst isolates was infrequent; 92% (n=49) sensitive to flucloxacillin. MRSA accounted for 8% (n=4) of isolates. None of the isolates were VRSA. Empiric antimicrobial therapies including either monotherapy piperacillin-tazobactam or piperacillin-tazobactam with gentamicin were administered. The mean number of therapy days with either IV or PO antibiotics likely to have had activity against the SAB was 10.2 (1 episode where antibiotics were discontinued to prioritise palliative care was excluded). The mean number of days of IV antibiotics likely to have had activity against the SAB was 4.9 (exclusions as before). The mean number of days of optimal targeted antibiotic therapy (agent/route/dose) was 1.5 (exclusions as before). A combination of piperacillin-tazobactam 4.5 g TDS IV with flucloxacillin 1 g QDS IV was deemed adequate therapy by the clinical oncology team (wishing to negate risk of polymicrobial infection) rather than monotherapy high dose IV flucloxacillin. Irrespective of whether CVCs were removed within 48 hrs or not, antimicrobial treatment durations were markedly lower than the 14 days of intravenous therapy recommended by current guidelines.

SAB recurrence

The overall recurrence rate in our 45 patient cohort was 15.6% (n=7 episodes in 7 patients). The mean time to recurrence was 93 days. In one excluded case, SAB recurrence occurred almost 8 months later and, as the second isolate

antibiogram did not show homology with the initial isolate, it is unlikely to represent recrudescence of the initial infection. For the remainder of recurrences, the antibiograms were indistinguishable from the initial isolate. A CVC was the source in all the patients who developed recurrence. The mean treatment duration for initial SAB with IV or PO antibiotics likely to have had some activity against the pathogen in 6 of the 7 patients who developed recurrence was 11.2 days. The mean duration of intravenous antibiotic treatment with an agent likely to have some activity against the pathogen was 4.3 days. Four patients had not received any optimal targeted SAB therapy at initial presentation (i.e., had not received high dose IV flucloxacillin), while two had each been treated for 3 days. In three out of six cases, the CVC had not been removed at initial SAB diagnosis. In the three cases where line removal was documented, the median time from documented bacteraemia to line removal was 3 days. In all cases, documented sterile blood cultures were obtained following the initial SAB and the median time to sterile blood cultures was 2 days. No complications or metastatic foci of infection had been identified at initial presentation in any of the patients in whom recurrence occurred.

Discussion

Our observations contribute new insights concerning the management of SAB in oncology patients, albeit derived from retrospective data and not a prospective study. The ethos of prescribing antimicrobials in the ULHG oncology unit is extremely judicious, only prescribing in response to the clinical signs and symptoms exhibited by the patient and being ever mindful of the sequelae associated with inappropriate prescribing in patient already exposed to other toxic agents such as chemotherapy. Likewise, there is strong emphasis on the removal of possible sources of infection, such as intravascular devices, in a timely manner.

Table 4

Outcomes of CVC-associated SAB: CVC removed within 48 hours vs. not removed within 48 hours or not removed at all

	Number of episodes	Persistently positive blood culture at \geq 48 h (%)	Median days to last positive blood culture (Range)	Median days to sterile blood culture (Range)	Recurrence (%)	Death due to SAB
CVC removed within 48 h	10	1 (20)	0 (0–2)	2 (1–8)	2 (40)	0
CVC not removed within 48 h	32	7 (21.8)	0 (0–12)	2 (0–14)	5 (15.6)	1 (3.1)

Table 5
Antibiotic therapy in oncology patients with CVC SAB

	Number of episodes	Median days PO/IV antibiotic likely to have some activity (Range)	Median days IV antibiotic likely to have activity (Range)	Median days from line removal to stopping PO/IV antibiotic likely to have some activity (Range)	Median days from line removal to stopping IV antibiotic likely to have activity (Range)
CVC removed within 48 h	9 ^a	11 (8–41)	7 (2–14)	9 (7–40)	4 (0–12)
CVC removed but not within 48 h	20	10 (6–14)	4.5 (0–10)	5.5 (0–11)	1 (0–10)
CVC salvaged	12	7 (2–27)	3 (0–13)	-	-

^a One episode was excluded as palliative care was prioritised and antimicrobial therapy was not progressed.

Notably, our CVC removal rate was just 73% in SAB where CVC was the identified source of infection, with an attributable mortality rate far lower than would be expected. Furthermore, antimicrobial therapy durations were considerably lower (10 days) than current recommendations of 14 days IV therapy [21]. The recurrence rate of 15% was also significantly lower than has been reported in the literature previously [4].

It is important to consider that most prior studies have described haematological malignancies accounting for a greater portion of SAB cases [19,30]. In contrast, in our study solid tumours were present in 98% of cases, with breast and colorectal carcinoma accounting for the greatest proportion. However, as stated, the prevalence of encountered cancers closely represented Irish national prevalence data, with the exception of lung carcinoma [29]. Indeed, this may be reflective of relatively low CVC insertion rates in lung carcinoma patients and a comparatively poor prognosis. Although not analysed in our study, advanced and progressive malignancies have greater association with SAB [8].

Prior administration of chemotherapy seems an unlikely risk factor given that most cases occurred at least 15 days following the most recent chemotherapy delivered via CVC. Research emphasis has frequently been placed on potential risk stratification and identifying predictors of SAB mortality. Studies have looked at multiple parameters including neutrophil counts, tumour type, patient demographics and method of CVC insertion [4,21,31,32]. Despite this emphasis, few parameters have proven useful, with no standardised risk model available currently. This is perhaps an indication of the complex nature of oncology patient cohorts. Our current study found the neutrophil count to be a poor marker for bacteraemia in this patient group. However, we did identify potential risk factors in nearly half (42%) of cases; tentatively offering an approach for high-risk categorization. It was striking that the risk factors identified related mostly to prior *S. aureus* colonisation suggesting a potential benefit of prophylactic decolonisation in similar patient groups prior to or allied with CVC insertion. It is equally arguable that, as shown by Stewart *et al.* (2016), good CVC insertion technique and satisfactory line management may provide the greatest potential for SAB risk reduction [33].

Throughout the period of this study, as detailed earlier, a drug combination of piperacillin-tazobactam with or without gentamicin was deemed appropriate empirical therapy. Thereafter, intravenous flucloxacillin was recommended by the microbiology clinical service when SAB was identified for

optimal treatment. Several studies have concluded that β -lactams, e.g. flucloxacillin, to be superior to glycopeptides, namely vancomycin for treatment of MSSA bloodstream infections [5]. Flucloxacillin was further justified by the low observed incidence of MRSA (8%) and awareness of local epidemiology in the oncology ward. Variation in patient characteristic requires prudent choice of therapy as a similar study from 2018 reported a MRSA prevalence of 21%, thus highlighting the requirement for a pragmatic approach to drug choice [32]. Irrespective, despite a mean of only 2 days optimal therapy, piperacillin-tazobactam with flucloxacillin proved both appropriate and effective on the basis of determined mortality and complication rates.

In that context, and as duration of antimicrobial therapy in SAB patients remains a topic of interest [5,21,32], we determined our effective therapy duration to be 10 days but with IV therapy duration of only 5 days. This contrasts with current recommendation of 14 days IV therapy [5,6]. Importantly, there was no evidence to support concerns of increased recurrence, mortality and septic metastasis published previously [21]. Clearly though, further research in the form of suitably powered prospective randomised controlled trials of current recommendations versus our approach is needed to assess whether the shorter duration of therapy is applicable more broadly across malignancies and, specifically, in complicated SAB.

In general, a paucity of studies has generated uncertainty as to whether oral therapy is non-inferior to IV therapy in this setting. Our findings indicate that relatively early adoption of oral administration following 5 days of IV therapy may be effective. This observation complements a statement in Dutch guidelines that "...safety and efficacy of an early switch from intravenous to oral antibiotics (mostly quinolones) can probably be extrapolated to other antimicrobial agents with high bioavailability ..." ([https://www.swab.nl/swab/cms3.nsf/uploads/65FB380648516FF2C125780F002C39E2/\\$FILE/swab_sepsis_guideline_december_2010.pdf](https://www.swab.nl/swab/cms3.nsf/uploads/65FB380648516FF2C125780F002C39E2/$FILE/swab_sepsis_guideline_december_2010.pdf)) and the results of two published RCTs in which oral therapy alone was found to be equally as successful in achieving cure as IV therapy [12,13]. Therefore, it seems reasonable to suggest that a greater use of oral therapy in SAB may decrease hospital length of stay and reduce associated healthcare costs. However, a prospective appropriately-designed study would be needed to validate this approach. Although outside the scope of this study, it may be useful to assess early adoption of oral therapy in the outpatient

setting, leading perhaps to a reduced requirement for nurse visits for outpatient parental antimicrobial therapy (OPAT) IV administration and/or a lesser need for patient self-administration of IV in favour of oral antimicrobial use.

As shown, albeit that our cohort size was limited, the attributable mortality rate in our study (<4%) was markedly lower than that reported in similar patient groups. Bello-Chavolla *et al.* reported a mortality rate of 17% while Edgeworth reported a rate of 33% [4,32]. Furthermore, our observed rate of recurrence, at 15%, was lower than expected compared with Edgeworth's rate of 23% under similar circumstances [4]. Given that our figures were achieved utilising shortened therapy durations, it poses the question whether current recommendations for SAB management are appropriate. This question is equally valid as our practice did not involve universal line removal in CVC source SAB despite current guidelines and recent report recommending prompt removal when possible, [5,14,21,30,31] albeit that this was due to individual patient-related factors and potential benefits of salvaging CVCs as reported elsewhere [34,35]. Overall, albeit derived from an analysis of retrospective data, this study suggests that there may be merit in pursuing a prospective study comparing our approach with currently-recommended CVC removal and 14 days of IV therapy to determine whether patients would benefit from a more individualised therapeutic approach. Such an approach may, ideally, reflect patient characteristics and take into consideration the complex nature of oncology patients allowing, perhaps, for the potential of personalised medicine and care based on cancer type, concomitant therapy and microorganisms involved.

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Author contributions

CPD, NHOC and RG contributed to analysis and interpretation of data, recognition of novel information, and drafting of the manuscript. PR, RC, MK, SSD and JP contributed to analysis and interpretation of data and drafting the manuscript. MK, RC and NHOC reviewed the patient records. All authors have reviewed and approve the manuscript.

Declaration of Competing Interest

The authors declare no competing personal or financial interests and have nothing to disclose.

References

- [1] Kaasch AJ, Barlow G, Edgeworth JD, Fowler Jr VG, Hellmich M, Hopkins S, et al. *Staphylococcus aureus* bloodstream infection: A pooled analysis of five prospective, observational studies. *Journal of Infection* 2014;68(3):242–51.
- [2] Health Protection Surveillance Centre. <http://www.hpsc.ie/AZ/MicrobiologyAntimicrobialResistance/EuropeanAntimicrobialResistanceSurveillanceSystemEARSS/ReferenceandEducationalResourceMaterial/SaureusMRSA/LatestSaureusMRSAdata/>; 2018.

- [3] Liu C, Strnad L, Beekmann SE, Polgreen PM, Chambers HF. Clinical practice variation among adult infectious diseases physicians in the management of *Staphylococcus aureus* bacteremia. *Clinical Infectious Diseases* 2019;69(3):530–3.
- [4] Edgeworth J. Intravascular catheter infections. *Journal of Hospital Infection* 2009;73(4):323–30.
- [5] Thwaites GE, Edgeworth JD, Gkrania-Klotsas E, Kirby A, Tilley R, Torok ME, et al. Clinical management of *Staphylococcus aureus* bacteraemia. *Lancet Infectious Diseases* 2011;11(3):208–22.
- [6] Holland TL, Arnold C, Fowler VG. Clinical management of *Staphylococcus aureus* bacteremia: A review. *JAMA - Journal of the American Medical Association* 2014;312(13):1330–41.
- [7] Asgeirsson H, Kristjansson M, Kristinsson KG, Gudlaugsson O. *Staphylococcus aureus* bacteraemia - Nationwide assessment of treatment adequacy and outcome. *Journal of Infection* 2011;62(5):339–46.
- [8] Carney DN, Fossieck Jr BE, Parker RH, Minna JD. Bacteremia due to *Staphylococcus aureus* in patients with cancer: Report on 45 cases in adults and review of the literature. *Reviews of Infectious Diseases* 1982;4(1):1–12.
- [9] Siegman-Igra Y, Reich P, Omi-Wasserlauf R, Schwartz D, Giladi M. The role of vancomycin in the persistence or recurrence of *Staphylococcus aureus* bacteraemia. *Scandinavian Journal of Infectious Diseases* 2005;37(8):572–8.
- [10] Khatib R, Johnson LB, Fakhri MG, Riederer K, Khosrovaneh A, Shams Tabriz M, et al. Persistence in *Staphylococcus aureus* bacteremia: Incidence, characteristics of patients and outcome. *Scandinavian Journal of Infectious Diseases* 2006;38(1):7–14.
- [11] Stryjewski ME, Szczech LA, Benjamim Jr DK, Inrig JK, Kanafani ZA, Engemann JJ, et al. Use of vancomycin or first-generation cephalosporins for the treatment of hemodialysis-dependent patients with methicillin-susceptible *Staphylococcus aureus* bacteremia. *Clinical Infectious Diseases* 2007;44(2):190–6.
- [12] Heldman AW, Hartert TV, Ray SC, Daoud EG, Kowalski TE, Pompili VJ, et al. Oral antibiotic treatment of right-sided staphylococcal endocarditis in injection drug users: Prospective randomized comparison with parenteral therapy. *American Journal of Medicine* 1996;101(1):68–76.
- [13] Schrenzel J, Harbarth S, Schockmel G, Genné D, Bregenzer T, Flueckiger U, et al. A randomized clinical trial to compare fleroxacin-rifampicin with flucloxacillin or vancomycin for the treatment of staphylococcal infection. *Clinical Infectious Diseases* 2004;39(9):1285–92.
- [14] Burnham JP, Rojek RP, Kollef MH. Catheter removal and outcomes of multidrug-resistant central-line-associated bloodstream infection. *Medicine* 2018;97(42):e12782.
- [15] Johnson LB, Almoujahed MO, Ilg K, Maalood L, Khatib R. *Staphylococcus aureus* bacteremia: Compliance with standard treatment, long-term outcome and predictors of relapse. *Scandinavian Journal of Infectious Diseases* 2003;35(11):782–9.
- [16] Price J, Baker G, Heath I, Walker-Bone K, Cubbon M, Curtis S, et al. Clinical and microbiological determinants of outcome in *Staphylococcus aureus* bacteraemia. *International Journal of Microbiology* 2010;2010:654858. <https://doi.org/10.1155/2010/654858>.
- [17] Fowler Jr VG, Olsen MK, Corey GR, Woods CW, Cabell CH, Reller LB, et al. Clinical identifiers of complicated *Staphylococcus aureus* bacteremia. *Archives of Internal Medicine* 2003;163(17):2066–72.
- [18] González-Barca E, Carratala J, Mykietiuik A, Fernández-Sevilla A, Gudiol F. Predisposing factors and outcome of *Staphylococcus aureus* bacteremia in neutropenic patients with cancer. *European Journal of Clinical Microbiology and Infectious Diseases* 2001;20(2):117–9.
- [19] Kang CI, Song JH, Chung DR, Peck KR, Yeom JS, Son JS, et al. Bloodstream infections in adult patients with cancer: Clinical

- features and pathogenic significance of *Staphylococcus aureus* bacteremia. *Supportive Care in Cancer* 2012;20(10):2371–8.
- [20] Ghanem GA, Boktour M, Warneke C, Pham-Williams T, Kassis C, Bahna P, et al. Catheter-related *Staphylococcus aureus* bacteremia in cancer patients: High rate of complications with therapeutic implications. *Medicine* 2007;86(1):54–60.
- [21] Wolf HH, Leithauser M, Maschmeyer G, Salwender H, Klein U, Chaberny I, et al. Central venous catheter-related infections in hematology and oncology: : guidelines of the Infectious Diseases Working Party (AGIHO) of the German Society of Hematology and Oncology(DGHO). *Annals of Hematology* 2008;87(11):863–76.
- [22] Zeylemaker MMP, Jaspers CA, van Kraaij MG, Visser MR, Hoepeiman IM. Long-term infectious complications and their relation to treatment duration in catheter-related *Staphylococcus aureus* bacteremia. *European Journal of Clinical Microbiology & Infectious Disease* 2001;20(6):380–4.
- [23] Le Moing V, Alla F, Doco-Lecompte T, Delahaye F, Piroth L, Chirouze C, et al. *Staphylococcus aureus* bloodstream infection and endocarditis - A prospective cohort study. *PLoS ONE* 2015;10(5):e0127385. <https://doi.org/10.1371/journal.pone.0127385>.
- [24] Raad I, Narro J, Khan A, Tarrand J, Vartivarian S, Bodey GP. Serious complications of vascular catheter-related *Staphylococcus aureus* bacteremia in cancer patients. *European Journal of Clinical Microbiology & Infectious Diseases* 1992;11(8):675–82.
- [25] O'Connor C, Powell J, Finnegan C, O'Gorman A, Barrett S, Hopkins KL, et al. Incidence, management and outcomes of the first cfr-mediated linezolid-resistant *Staphylococcus epidermidis* outbreak in a tertiary referral centre in the Republic of Ireland. *Journal of Hospital Infection* 2015;90(4):316–21.
- [26] O'Connor C, Cormican M, Boo TW, McGrath E, Slevin B, O'Gorman A, et al. An Irish outbreak of New Delhi metallo-beta-lactamase (NDM)-1 carbapenemase-producing Enterobacteriaceae: increasing but unrecognized prevalence. *Journal of Hospital Infection* 2016a;94(4):351–7.
- [27] O'Connor C, Philip RK, Kelleher J, Powell J, O'Gorman A, Slevin B, et al. The first occurrence of a CTX-M ESBL-producing *Escherichia coli* outbreak mediated by mother to neonate transmission in an Irish neonatal intensive care unit. *BMC Infectious Disease* 2017;17(1):16. <https://doi.org/10.1186/s12879-016-2142-6>.
- [28] O'Connor C, Philip RK, Powell J, Slevin B, Quinn C, Power L, et al. Combined education and skin antisepsis intervention for persistently high blood-culture contamination rates in neonatal intensive care. *Journal of Hospital Infection* 2016b;93(1):105–7.
- [29] Irish Department of Health Health. Cancer in Ireland 1994-2016 with estimates for 2016-2018: Annual Report of the National Cancer Registry. Available at: https://www.ncr.ie/sites/ncr/files/pubs/annualreport2018_26112018.pdf; 2018.
- [30] El Zakhem A, Chaftari AM, Bahu R, El Helou G, Shelburne S, Jiang Y, et al. Central line-associated bloodstream infections caused by *Staphylococcus aureus* in cancer patients: Clinical outcome and management. *Annals of Medicine* 2014;46(3):163–8.
- [31] Bassetti M, Peghin M, Trecarichi EM, Carnelutti A, Righi E, Del Giacomo P, et al. Characteristics of *Staphylococcus aureus* bacteraemia and predictors of early and late mortality. *PLoS ONE* 2017;12(2):e0170236. <https://doi.org/10.1371/journal.pone.0170236>.
- [32] Bello-Chavolla OY, Bahena-Lopez JP, Garcadiago-Fosass P, Volkow P, Garcia-Horton A, Velazquez-Acosta C, et al. Bloodstream infection caused by *S. aureus* in patients with cancer: a 10-year longitudinal single-center study. *Supportive Care in Cancer* 2018;26(12):4057–65.
- [33] Stewart BJ, Gardiner T, Perry GJ, Tong SY. Reduction in *Staphylococcus aureus* bacteraemia rates in patients receiving haemodialysis following alteration of skin antisepsis procedures. *Journal of Hospital Infection* 2016;92(2):191–3.
- [34] Chaftari P, Chaftari AM, Adachi J, Hachem R, Raad S, Natividad E, et al. Improvement in the diagnosis of catheter-related bloodstream infections in a tertiary cancercenter. *American Journal of Infection Control* 2017;45(3):e34–9.
- [35] Chaftari AM, Hachem R, Raad S, Jiang Y, Natividad E, Chaftari P, et al. Unnecessary removal of central venous catheters in cancer patients with bloodstream infections. *Infection Control & Hospital Epidemiology* 2018;39(2):222–5.