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Duration of Antibiotic Therapy for *Staphylococcus aureus* Bacteremia: The Long and the Short of It

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Keywords

Staphylococcus aureus; bacteremia

The optimal duration of antibiotic therapy for *Staphylococcus aureus* bacteremia (SAB) remains controversial despite over a half century of debate. In the 1940s, limited supplies of the "wonder drug" penicillin compelled physicians to prescribe the shortest effective duration of therapy for invasive *S. aureus* infections (1). More recently, concerns for antibacterial resistance, drug-related toxicity, and cost have prompted clinicians treating patients with SAB to again ask "how short is long enough?"

The controversy over therapy for SAB has ultimately consolidated into two approaches: "short course" antibiotic therapy of two weeks duration, and "long course" therapy extending for four weeks or more. Both approaches have benefits and risk. Short course therapy for SAB offers an opportunity to abbreviate patient exposure to antibiotics and intravascular access, but lacks sufficient evidence of efficacy to establish it as standard practice (Table) (2–4). On the other hand, long courses of IV antibiotics offer a "belt and suspenders" reliability to treating patients with SAB, but subject them to cost, inconvenience, and risk associated with extended courses of parenteral antibiotics (5). High quality data are needed to help clinicians know which patient needs what duration of therapy.

In this issue of *CMI,* Abbas et al evaluated the effect of duration of therapy (DOT) on mortality and relapse in patients with SAB. In a retrospective, single-center cohort study, the authors used clinical criteria to identify 225 patients with Uncomplicated SAB and 305 patients with Complicated SAB. They then considered the impact of DOT, dichotomized into durations of ≤14 days or >14 days, on 90-day mortality rates in these two groups of patients. The investigators carefully accounted for confounding in the analysis, excluding patients who died or who were lost to follow up prior to 14 days to account for immortal time bias, and including a propensity score analysis to account for lack of randomization. They found that in patients with Complicated SAB, DOT >14 days was associated with

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higher survival rate than DOT ≤ 14 days. By contrast, patients with Uncomplicated SAB exhibited no such improved survival when they received DOT > 14 days. Based upon these findings, the authors suggest that “shorter DOT may be sufficient for patients with uncomplicated SAB”.

While the results were somewhat intuitive, the study design had limitations. Even after addressing the confounding effect of early mortality, patients who received ≤14 days of therapy were approximately twice as likely to have a ‘primary/unknown’ focus of bacteraemia (28.0 % vs 13.9%; p 0.002) and to die within 90 days (29.3% vs 15.8%; p 0.005) than patients who received >14 days of therapy. Complicated SAB is notorious for ‘hiding in plain sight’, and the risk for under-recognition of complicated SAB has been recently demonstrated [6]. In a randomized controlled trial that employed a standardized diagnostic algorithm to define duration of antibiotic therapy for patients with staphylococcal bacteraemia, nearly one-third of study subjects initially classified as having uncomplicated SAB were ultimately found to have complicated SAB in the course of the diagnostic work-up [6].

Second, key components of SAB management may have been inconsistently accessed. Patients in the overall cohort that died by 90 days were significantly less likely to receive Infectious Diseases consultation or undergo echocardiography, both of which are associated with improved patient survival (7). Rates of use of other elements of care associated with better outcomes in patients with SAB, such as obtaining follow-up blood cultures (5, 8) and pursuing source control (9, 10), were not described.

Finally, patients in this study had fewer comorbid conditions than patients with SAB in other regions of the world. For example, rates of diabetes (13%) and hemodialysis (8%) in the current report were only around one-third of those reported in a large prospective cohort of patients with SAB spanning over two decades at our institution (diabetes 38%; hemodialysis 21%) (11). Such differences in patient comorbidities significantly influence the duration of antibiotic treatment and the prognosis of the infections being treated. Thus, the generalizability of the current study is limited in non-Swiss institutions.

Clinicians in 2019 must face the uncomfortable reality that if we think we are treating a case of uncomplicated SAB, there is a good chance that we are wrong. Thus, a standardized approach to treating SAB is critically important in the management of SAB and is associated with improved outcomes (12). Such a standardized approach should include mandatory Infectious Disease consultation, echocardiography, and follow up blood cultures for all patients with SAB. Even with such standardized approaches, cases of Complicated SAB may occasionally be misidentified as Uncomplicated (6). For this reason, we continue to recommend that all patients with SAB, including those with seemingly Uncomplicated SAB, should undergo a standardized evaluation and receive a minimum of 14 days of antibiotic therapy until high quality clinical data are in place to safely manage them otherwise.

Abbas et al are to be commending for rigorously evaluating outcomes of SAB at their institution, and for their balanced interpretation that the findings “merit further (prospective) confirmation in other settings, preferably through a RCT”. There are clearly patients with

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SAB who can be cured with abbreviated courses of therapy, including those utilizing highly orally bioavailable antibiotics. We eagerly await the results from two ongoing randomized clinical trials, SAB7 (13) and SABATO (14), that are evaluating these approaches. Until clinicians have the luxury of data, however, reports such as those by Abbas et al should be regarded as important observations that are necessary but not sufficient to justify the widespread adoption of abbreviated durations of therapy for patients with SAB.

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Table

Studies reporting on duration of therapy in patients with *Staphylococcus aureus* bacteremia

Study	Design	Sample size	Results	Conclusions
Holland 2018 (6)	Randomized controlled trial	116 patients with SAB	Unsuspected complicated SAB occurred in 32% when diagnostic algorithm used Clinical success achieved in 73% patients with Uncomplicated SAB	Study was inadequately powered for SAB endpoint. DOT 2 weeks should be used with caution and only if patients have undergone rigorous evaluation for metastatic infection.
Jernigan 1993 (15)	Meta-analysis of 11 studies	132 patients with uncomplicated catheter-related SAB who were treated with short course therapy	Complication rate in patients with catheter related SAB was 25% Mortality rate for catheter-related SAB was 15%	DOT >2 weeks should be used until a prospective study is available
Chong 2013 (16)	Prospective cohort	111 patients with uncomplicated SAB	DOT <14 days was significantly associated with relapse 7.9% versus 0% in DOT ≥14 days; (p=0.036). Crude mortality in patients with DOT <14 was not statistically different than DOT ≥14 (18.4% vs 21.9%, p=0.67)	Even with a low risk of complication, SAB without a known source should be treated for ≥14 days
Rahal 1986 (17)	Randomized controlled trial	84 patients with SAB; 32 patients completed treatment	31.3% of patients with SAB without endocarditis who treated with 2 weeks of antibiotics were cured.	Study was inadequately powered to draw conclusions regarding optimal duration of therapy. Unable to reliably detect complications in patients treated for only 2 weeks
Iannini 1976 (18)	Retrospective cohort	29 patients with SAB associated with removable source of infection	Patients with SAB received median DOT 15.2 days: no relapses	10 to 21 days of patients may be sufficient for catheter associated SAB as long as focus of bacteremia is removed
Ehni 1989 (19)	Prospective observational	13 patients with catheter associated SAB	7.7% Relapse rate in patients treated with <17 days of therapy	DOT <17 days for catheter associated SAB with close follow up may be safe
Raad 1992 (20)	Retrospective cohort	55 patients with catheter-associated SAB	16% vs 0% patients SAB treated for <10 days vs ≥ 10 days relapsed, respectively (p= 0.05).	DOT should not be < 10 days but may be ≤ 14 days. Fever and/or bacteremia that persists for ≥ 3 days after catheter removal and initiation of antibiotics should require prolonged treatment
Mylotte 1987 (21)	Prospective observational	28 patients with catheter associated SAB	82% of patients who recovered received ≤2 weeks of therapy	Catheter associated SAB may be treated for no more than 14 days if catheter is removed.
Malanoski 1995 (22)	Retrospective cohort	102 patients with SAB; 55 of those patients had catheter-associated SAB	Relapse rates in patients treated 10 – 15 days was 0% vs 4.7% in those treated > 15 days Late complications were associated with DOT <10 days	DOT of 10–15 days may be safe in cases of catheter associated SAB provided the Infected catheters is promptly removed DOT for SAB should not be shortened to <10 days
Zeylemaker 2001 (23)	Retrospective cohort	49 patients with catheter-associated SAB	Attributable death was 31% in DOT <14 days vs 20% in longer DOT.	DOT should not be shortened to <14 days
Jensen 2002 (24)	Prospective observational	278 patients with SAB	DOT <14 was significantly associated with mortality (OR, 0.84; 95% CI, 0.76–0.94) Overall mortality 34%	DOT for SAB should be > 14 days. Removal of infected focus of infection is integral to the outcome of SAB
Pigrau 2003 (25)	Retrospective cohort	87 patients with SAB; 64 with uncomplicated SAB	62/64 patients with uncomplicated SAB who were treated with 10–14 days were followed for 3 months: none relapsed.	DOT 10–14 days for uncomplicated catheter associated SAB may be sufficient

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Study	Design	Sample size	Results	Conclusions
Fatkenheuer 2004 (26)	Retrospective cohort	229 patients with SAB	DOT <14 days had no difference in survival compared to ≥ 14 days	DOT <14 days may be sufficient for SAB but should be interpreted with caution Guidelines for management of SAB are not routinely followed in practice and failure to do so may negatively affect mortality and outcomes
Thomas 2005 (27)	Prospective observational	276 with catheter associated SAB	No association between DOT and rate of relapse DOT ≤ 14 days was not associated with increased risk of relapse as compared to longer DOT	In patients who have favorable response to catheter removal and initial treatment, DOT <14 days may be sufficient
Kreisel 2006 (28)	Retrospective cohort	397 patients with SAB	No association between DOT ≤14 days and risk for recurrence (RR, 0.68; 95% CI, 0.44–1.04)	A DOT ≤ 14 days may be sufficient for uncomplicated SAB Patients with diabetes, HIV or with MRSA infections are at an increased risk for recurrence and should be followed closely
Ghanem 2007 (29)	Retrospective cohort	91 cancer patients with SAB	DOT <14 days is associated with increased complications in patients with malignancy	Caution should be used in treating patients with malignancy for ≤14 days

DOT, duration of therapy; SAB, *Staphylococcus aureus* bacteremia