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REVIEW ARTICLE

A Narrative Review of Early Oral Stepdown Therapy for the Treatment of Uncomplicated *Staphylococcus aureus* Bacteremia: Yay or Nay?

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Historically, intravenous (IV) antibiotics have been the cornerstone of treatment for uncomplicated *Staphylococcus aureus* bacteremia (SAB). However, IV antibiotics are expensive, increase the rates of hospital readmission, and can be associated with catheter-related complications. As a result, the potential role of oral antibiotics in the treatment of uncomplicated SAB has become a subject of interest. This narrative review article aims to summarize key arguments for and against the use of oral antibiotics to complete treatment of uncomplicated SAB and evaluates the available evidence for specific oral regimens. We conclude that evidence suggests that oral step-down therapy can be an alternative for select patients who meet the criteria for uncomplicated SAB and will comply with medical treatment and outpatient follow-up. Of the currently studied regimens discussed in this article, linezolid has the most support, followed by fluoroquinolone plus rifampin.

Keywords. *Staphylococcus aureus*; bacteremia; antimicrobials; oral administration; step-down therapy.

Staphylococcus aureus is a serious, common cause of both hospital- and community-acquired bacteremia [1]. Prompt recognition and treatment of *S. aureus* bacteremia (SAB) are vital to improving patient outcomes [2, 3]. Unfortunately, there is a lack of high-quality studies to guide treatment practices [4–6]. As a result, treatment guidelines are based primarily on observational studies, clinical experience, and expert opinion [6].

For decades, intravenous (IV) antibiotics have been used to treat most patients with SAB due to the high risk of occult metastatic infection [2–4, 7]. By contrast, treatment of SAB with oral antibiotics was generally considered only in patients in whom maintaining parenteral access was problematic [8, 9]. Recently, the question has resurfaced as to whether oral antibiotics can be used to treat select patients with uncomplicated SAB [10], and there is a growing number of reports supporting this practice [11–15]. Uncomplicated SAB, as defined by the Infectious Diseases Society of America treatment guidelines for methicillin-resistant *S. aureus* (MRSA) infection, is the presence of all the following:

- negative follow-up blood cultures 48–96 hours after the index positive blood culture;
- defervescence by 72 hours after the initiation of appropriate antibiotic therapy;
- exclusion of endocarditis;
- absence of major prosthetic/implanted devices, for example, cardiac defibrillators and/or pacemakers, orthopedic rods and plates, or baclofen pumps; and
- absence of metastatic sites of infections.

A patient not meeting all these criteria is considered to have complicated SAB and is not the focus of this article [16].

There are several benefits to switching from IV to oral antibiotic therapy when appropriate. The 30-day readmission rate for patients discharged on IV therapy ranges from around 17% to 27% [10, 17–20]. Adverse drug events (ADEs) account for up to a quarter of these readmissions [20]. Several studies have demonstrated a higher rate of ADEs with IV antibiotic use [21–23]. Catheter-associated complications (CACs) are also common, occurring in up to 20% of patients discharged with a central venous catheter [10, 17, 24]. Patients taking oral antibiotics avoid the risk of CACs.

In addition, switching from an IV to oral route of administration can reduce antibiotic costs by 23%–48% [25]. In 1 study of intensive care unit (ICU) patients, switching from IV to oral antibiotics decreased antibiotic-associated costs by more than

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half [26]. These studies calculated drug cost alone and did not include secondary costs. This is also true in the outpatient setting. In a study of pediatric patients, the direct medical cost of outpatient parenteral antibiotic therapy (OPAT) was 9 times higher than oral therapy and up to 11 times higher in a subgroup analysis of patients with osteomyelitis, complicated pneumonia, and intra-abdominal infections [27]. Moreover, the insurance-mandated process of obtaining prior approval for OPAT resulted in discharge delays and increased direct hospital cost by more than half [28].

Having an available oral step-down therapy option may be particularly helpful in certain patient populations where long-term IV access is more complex. For example, in patients who are hemodialysis dependent (or predialysis), clinicians may wish to avoid the risk of CACs altogether as having options for venous access in these patients is crucial. People who inject drugs (PWID) constitute another population where oral alternatives might be preferentially used if available, given that compliance with antibiotic therapy can be ensured.

This article considers the available evidence for and against the use of oral antibiotics as early step-down from parenteral therapy in uncomplicated SAB. The literature varies greatly in its definition of early oral therapy. For this discussion, early oral therapy can be considered to be after 7 to 10 days of IV therapy. Although there are many factors that contribute to the decision of whether to switch from IV to oral antibiotic therapy, including feasibility, safety, accessibility, cost, and patient-specific considerations, we focus on evidence addressing the efficacy of specific oral antibiotics used in an early step-down fashion to treat and cure patient with uncomplicated SAB.

METHODS

For collection and review of evidence supporting oral antibiotic treatment of SAB, the authors performed word-based and MeSH term searches in PubMed Central formed from combinations of variations of the following terms: "*Staphylococcus aureus*," "bacteremia," "oral," and specific antibiotic or antibiotic class. A list of searches and the number of articles returned is included in Supplementary Table 1. Search results were sorted by PubMed Best Match. Full abstracts were reviewed for appropriateness and relevance to the discussion. Articles that included any description of treatment for uncomplicated, complicated, or secondary *S. aureus* bacteremia with an oral antibiotic were reviewed further. For each search, abstract review continued until abstract contents were considered not relevant. The references of each selected article were also reviewed. Any articles not previously identified were subsequently reviewed for possible inclusion. The authors attempted to limit articles to those investigating treatment of bacteremia with IV to oral switch or oral antibiotic therapy alone. A few exceptions were made to include important landmark studies that greatly inform this discussion. Human subject randomized controlled trials (RCTs), cohort, and case–control studies were included. Case reports were occasionally included in the absence of other trials (Table 1).

EVIDENCE TO SUPPORT THE EFFICACY OF USING SPECIFIC ORAL ANTIBIOTIC STEPDOWN THERAPY TO TREAT UNCOMPLICATED SAB

The choice of which oral antibiotic regimen to consider for step-down treatment of uncomplicated SAB is important. Below, we evaluate the existing evidence for specific oral antibiotic regimens to effectively treat uncomplicated SAB.

Linezolid

Linezolid is 100% orally bioavailable; therefore, oral and IV administration achieve comparable plasma drug concentrations [46]. A significant body of literature supports the use of early switch from IV to oral linezolid for the treatment of select patients with uncomplicated SAB (Table 2).

Several studies reported that linezolid, given IV or orally, is as effective as standard therapy in the treatment of SAB. Two compassionate use studies evaluating the effectiveness of linezolid in treating *S. aureus* infections, including a total of 71 SAB cases between them, reported cure rates ranging from 63.2% to 85.7% (12/16 and 18/21 evaluable cases, respectively) [30, 31]. A randomized controlled trial (RCT) comparing linezolid IV to oral switch to teicoplanin for the treatment of gram-positive infections included 33 patients with SAB; of these, 13/15 (86.7%) linezolid vs 9/18 (50.0%) teicoplanin patients achieved clinical cure [32]. In pooled analysis of 5 randomized controlled trials, which included 144 patients with SAB, 28/74 (36%) linezolid and 25/70 (36%) vancomycin patients achieved clinical cure (odds ratio [OR], 1.47; 95% confidence interval [CI], 0.50 to 2.65) [33]. Similarly, an additional RCT and 2 cohort studies published later, comparing linezolid IV to oral switch with accepted IV therapy and including a total of 402 SAB cases combined, demonstrated that there was no difference in microbiological and clinical cure rates (Table 2) [29,34–36].

Unfortunately, none of the studies above were adequately powered to establish noninferiority of oral linezolid to standard of care for the treatment of SAB specifically. Additionally, in March 2007, the US Food and Drug Administration (FDA) issued a boxed warning against the use of linezolid for the treatment of catheter-related bloodstream infections after an open-label study comparing linezolid with vancomycin, oxacillin, or dicloxacillin found a higher mortality rate in patients receiving linezolid who had gram-negative bacteremia, mixed gram-positive and gram-negative bacteremia, or no infectious agent identified [47]. Notably, there was no difference in gram-positive bacteremia mortality rates. Collectively, the body of evidence supports the use of linezolid as an oral step-down to complete a course of therapy for select patients with uncomplicated SAB.

Table 1. Published Studies Describing Oral Antibiotic Therapy for *S. aureus* Bacteremia

Author	Year	Study Type	Sample[a]	Study Question
Linezolid				
Stevens et al. [29]	2002	Randomized, open-label trial	460 ITT patients, 242 with culture-confirmed *S. aureus* infections; 43 had confirmed MRSA bacteremia	Linezolid (IV→PO) vs IV vancomycin for MRSA; assessed clinical cure for those presenting for follow-up
Moise et al. [30]	2002	Open-label, nonrandomized, noncomparative study	191 *S. aureus* infections in 183 adult and pediatric patients; 40 SAB episodes, 24 with MRSA episodes, 21 of which were evaluable	Compassionate use of linezolid (PO or IV) for vancomycin failure or intolerance in MRSA infections
Birmingham et al. [31]	2003	Open-label, nonrandomized, noncomparative study	828 gram-positive infections in 796 adult or pediatric patients; 31 MRSA bacteremia	Compassionate use of linezolid (IV or PO) for gram-positive infections
Wilcox et al. [32]	2004	RCT	430 adult (>13 years old) patients with gram-positive infections, 33 with SAB	Linezolid (IV or IV→PO) vs teicoplanin (IV→IM) for gram-positive infections
Shorr et al. [33]	2005	Pooled analysis of RCTs[b]	5 RCTs, 3228 patients total, evaluating the use of linezolid (IV or IV→PO) vs vancomycin IV in 144 patients with primary or secondary SAB; 64 MRSA and 80 MSSA	Linezolid (IV or IV→PO) vs vancomycin IV for primary or secondary SAB
Wilcox et al. [34]	2009	Open-label, randomized noninferiority trial	726 adults (>13 years old) ITT patients with suspected catheter-related infection, 526 with gram-positive infections, 157 with *S. aureus*, 145 with SAB	Evaluated linezolid (IV or PO) vs IV vancomycin for catheter-related SAB; no difference in microbiological cure
Usery et al. [35]	2015	Retrospective cohort	122 SAB cases due to MRSA treated with linezolid, vancomycin, or daptomycin	Evaluated linezolid vs daptomycin vs vancomycin in MRSA bacteremia
Willekens et al. [36]	2018	Prospective matched cohort	135 adult patients with SAB; 45 oral linezolid vs 90 SPT cases	Evaluated outcomes of linezolid (IV→PO) vs SPT propensity score–matched cohort for treatment of SAB
Fluoroquinolones				
Bouza et al. [37]	1989	Open-label noncomparative trial	68 adult patients with bacteremia, 2 with SAB	Evaluated clinical cure for 2/2 (100%) patients with SAB who received ciprofloxacin
Dworkin et al. [8]	1989	Open-label noncomparative trial	14 adult PWID complicated by *S. aureus* right-sided endocarditis with ciprofloxacin IV→PO + rifampicin PO	Evaluated 10 patients who were not withdrawn
Heldman et al. [9]	1996	Open-label randomized trial	573 PWID, 93 sustained staphylococcal bacteremia concerning for right-sided endocarditis, 87 SAB; 5 of which were MRSA	Evaluated oral ciprofloxacin + rifampin vs IV oxacillin or vancomycin + gentamicin for clinically evaluable right-sided staphylococcal endocarditis patients vs patients who were microbiologically cured at 6–7 days post-treatment
Schrenzel et al. [38]	2004	RCT	127 ITT adult patients with staphylococcal infection, 119 evaluable for clinical cure, 104 *S. aureus* infections, 98 were evaluable	Evaluated oral fleroxacin + rifampicin vs IV flucloxacillin or vancomycin for SAB; no difference in clinical cure between 44/56 (78.6%) fleroxacin + rifampicin patients vs 32/42 (76.2%) IV therapy patients
Beganovic et al. [39]	2019	Retrospective cohort	428 cases of SAB due to MSSA; 103 (24.1%) received levofloxacin or moxifloxacin (IV or PO); 212 (49.5%) received IV oxacillin, cefazolin, or nafcillin	Evaluated MSSA bacteremia treatment in propensity-matched cohort of veterans treated with a single antibiotic
Trimethoprim/sulfamethoxazole				
Markowitz et al. [40][c]	1992	RCT	228 adult PWID with suspected *S. aureus* infections were randomized; 101 were evaluable; 67 had SAB, primary or secondary, and 11 had right-sided endocarditis	Evaluated TMP-SMX IV vs vancomycin IV for SAB
Goldberg et al. [41]	2010	Retrospective cohort	1005 cases of SAB in 954 adult patients, 451 patients with MRSA	Evaluated oral or IV TMP-SMX vs IV vancomycin for MRSA bacteremia in a matched 1:2 ratio
Paul et al. [42]	2015	RCT	252 patients with severe MRSA infections randomized, 91 patients with SAB	Evaluated oral TMP-SMX vs IV vancomycin for MRSA severe infections; excluded those with left-sided endocarditis or who had received study drugs previously
Harbarth et al. [43]	2015	Randomized, open-label noninferiority trial	150 adult patients with MRSA infection randomized, 18 with MRSA SAB	Evaluated IV to oral switch linezolid vs IV to oral switch TMP-SMX + rifampin for MRSA infections; successful cure in 6/9 (66.7%) linezolid vs 7/9 (77.8%) TMP-SMX + rifampin patients
Tissot-Dupont et al. [44]	2019	Before/after intervention study	341 patients with *S. aureus* endocarditis; 170 pre-intervention control patients and 171 postintervention patients	Compared 2 protocols for the treatment of *S. aureus* endocarditis

Table 1. Continued

Author	Year	Study Type	Sample[a]	Study Question
Clindamycin				
Martinez-Aguilar et al [45].	2003	Retrospective cohort	99 pediatric patients with invasive *S. aureus* infections, all of whom survived; 9 with SAB; 25 additional had secondary SAB and were not included in bacteremia analysis and not identified separately	Evaluated treatment of MRSA and MSSA invasive infection with clindamycin (IV or PO), IV nafcillin, IV vancomycin, other β-lactams, and TMP-SMX (only 1 case)
Other				
Carney et al. [14]	1982	Retrospective cohort	45 episodes of SAB in 34 adult patients with cancer	Described the outcomes of oral step-down therapy in 21/45 episodes of SAB
Thwaites et al. [15]	2010	Prospective cohort	630 patients with SAB in the UK and Vietnam with 1 Nepal patient included	Described treatment of SAB in the UK and Nepal; documented that >50% of patients received partial oral antibiotic therapy and 14 patients received only oral antibiotics; no information regarding outcomes
Jorgensen et al. [13]	2019	Retrospective cohort	492 adult patients with MRSA SAB discharged with oral antibiotics only vs parenteral antibiotics	Evaluated the difference in 90-day clinical failure between patients who received oral step-down therapy compared with those who received OPAT for SAB
Iversen et al. [12]	2019	RCT	400 adult patients with left-sided endocarditis, 87 with *S. aureus* as the causative pathogen	Evaluated patients with left-sided endocarditis due to *Enterococcus faecalis*, *S. aureus*, *Streptococcus* or coagulase-negative staphylococci comparing partial oral (after at least 10 days IV) vs total parenteral antibiotic therapy; primary outcomes were the difference in all-cause mortality, unplanned cardiac surgery, embolic events, or relapse of blood cultures

Abbreviations: IM, intramuscular; ITT, intention-to-treat; IV, intravenous; MRSA, methicillin-resistant *S. aureus*; MSSA, methicillin-sensitive *S. aureus*; OPAT, outpatient parenteral antibiotic therapy; PO, per os (oral); RCT, randomized controlled trial; SAB, *Staphylococcus aureus* bacteremia; SPT, standard parenteral therapy; TMP-SMX, trimethoprim-sulfamethoxazole.

[a]Does not include information regarding sex and age distribution as SAB patients were often a subgroup of a larger analysis and therefore the provided demographics are not reflective of the SAB cases.

[b]Includes the 2002 Stevens et al. study reported above and 4 others not reported above due to explicit use of only IV linezolid or not well defined.

[c]Included because it was a landmark trial and curtailed further research evaluating oral TMP-SMX in the treatment of *S. aureus* bacteremia and/or endocarditis.

Fluoroquinolones

Despite comparable bioavailability of IV and oral fluoroquinolone formulations, few large trials have attempted to establish fluoroquinolones as a viable treatment for SAB [48]. As a result, the body of evidence supporting the use of fluoroquinolones in general, and oral fluoroquinolones in particular, for the treatment of uncomplicated SAB is limited. *S. aureus*, and particularly MRSA, can exhibit high rates of resistance to fluoroquinolones [49, 50]. The high prevalence of fluoroquinolone resistance and the potential for rapid development of de novo resistance in previously susceptible *S. aureus* strains prompted the Centers for Disease Control and Prevention to recommend in 2006 against the use of fluoroquinolones for the treatment of MRSA infections [51]. This recommendation was reconsidered in 2017 when the oral fluoroquinolone delafloxacin was approved by the FDA for the treatment of acute bacterial skin and skin structure infections (ABSSSIs), including those caused by MRSA [52]. Delafloxacin has a higher barrier to resistance due to the hypothesis that both gyrase and topoisomerase IV host targets would need to develop mutations to employ resistance [53].

In 1989, 2 small pilot studies reported successful clinical cure of 2 SAB patients and 10 *S. aureus* right-sided endocarditis patients with ciprofloxacin and ciprofloxacin (IV to oral switch) plus rifampin, respectively [8, 37]. More recently, in 2019, a large retrospective study of single-exposure antibiotics for the treatment of MSSA bacteremia found no difference in propensity-matched scores of time to mortality for patients who received only levofloxacin or moxifloxacin and those who received IV nafcillin or cefazolin (hazard ratio [HR], 1.33; 95% CI, 0.30 to 5.96) [39]. Although in the 2 identical-design phase III trials totaling 2030 patients that evaluated delafloxacin treatment of ABSSSI, a total of 34 patients (17 randomized to delafloxacin and 17 to comparison therapies) were found to have bacteremia after enrollment, these trials did not specifically evaluate secondary SAB outcomes, and due to the lack of key details such as the species of the bloodstream pathogen, our ability to draw inferences on the utility of delafloxacin in uncomplicated SAB is limited [54–56].

Fluoroquinolone with rifampin

In 1996, a large study including 87 patients with *S. aureus* right-sided endocarditis found similar microbiologic cure rates between oral ciprofloxacin plus rifampin and IV oxacillin or vancomycin plus gentamicin (OR, 0.4; 95% CI, 0.01 to 5.5; $P = .6$) [9]. Similar results were found when evaluating treatment of SAB with oral fleroxacin plus rifampicin compared with IV flucloxacillin or vancomycin (Table 2) [38].

Table 2. Details of Study Arms, Outcomes, and Antibiotic Administration for Published Studies Describing Oral Antibiotic Therapy for *S. aureus* Bacteremia

Author & Year	Study Arm	Study Arm Outcome	Standard Therapy Arm	Standard Therapy Outcome	Outcome Analysis	Days IV Before PO Switch
Linezolid						
Stevens et al. [29] 2002	Linezolid 600 mg IV twice daily → change to linezolid 600 mg PO twice daily at investigator discretion, at least 7 days	9/15 (60.0%) of evaluable MRSA bacteremia achieved clinical cure	Vancomycin 1 g IV twice daily	7/10 (70.0%) of evaluable MRSA bacteremia achieved clinical cure	—	Specific information about linezolid route of administration or duration was not given for SAB patients
Moise et al. [30] 2002	Linezolid oral or IV 600 mg twice daily (adult); 10 mg/kg oral or IV (pediatric or <40 kg)	18/21 (85.7%) clinically evaluable bacteremic patients achieved clinical cure	—	—	—	58/191 (30.4%) received IV and oral linezolid; days of each not given; 76/191 (39.8%) received oral linezolid
Birmingham et al. [31] 2003	Linezolid oral or IV 600 mg twice daily (adult); 10 mg/kg oral or IV (pediatric or <40 kg)	16/31 evaluable; 12/16 (63.2%) achieved clinical cure; 10/14 (71.4%) microbiological cure	—	—	—	Specific information about linezolid route of administration or duration was not given for SAB patients
Wilcox et al. [32] 2004	Linezolid (IV→PO) 600 mg twice daily	13/15 (86.7%) SAB patients achieved clinical cure with linezolid	Teicoplanin (IV→IM)	9/18 (50%) SAB patients achieved clinical cure with teicoplanin	—	Specific information about linezolid route of administration or duration was not given for SAB patients
Shorr et al. [33] 2005	Linezolid IV or IV→PO 600 mg twice daily	28/74 (36%) of ITT SAB achieved clinical cure; 14/25 (56%) of evaluable MRSA bacteremia achieved clinical cure; 41/59 (69%) achieved microbiological cure	Vancomycin 1 g IV twice daily	25/70 (36%) of ITT SAB achieved clinical cure; 13/28 (46%) MRSA bacteremia achieved clinical cure; 41/56 (73%) achieved microbiological cure	Odds ratio for linezolid vs vancomycin clinical cure was 1.47 (95% CI, 0.50 to 2.65)	Specific information about linezolid route of administration or duration was not given for SAB patients
Wilcox et al. [34] 2009	Linezolid 600 mg (route not specified)	38/52 (75.0%) SAB and 22/25 (88.0%) MRSA bacteremia achieved clinical cure; 46/56 (82.1%) SAB; 21/26 (80.8%) MRSA bacteremia achieved microbiological cure	Vancomycin 1 g twice daily with option to change to oxacillin 2 g IV or dicloxacillin 500 mg oral every 6 hours for MSSA	29/42(69.0%) SAB and 16/21 (76.2%) MRSA bacteremia achieved clinical cure; 35/42 (83.3%) SAB; 18/21 (85.7%) MRSA bacteremia achieved microbiological cure	95% CI for SAB clinical cure was –12.3 to 24.2 for MRSA bacteremia, –10.4 to 34.0 for SAB, –16.3 to 13.9 for MRSA bacteremia, –26.2 to 16.4 for microbiological cure; *P* values for these analyses not provided	Specific information about linezolid route of administration or duration was not given for SAB patients
Usery et al. [35] 2015	Linezolid 600 mg twice daily (IV or PO not specified)	12/15 (80%) had complicated bacteremia; 9/15 (60%) achieved clinical cure; 14/14 linezolid (100%) achieved microbiological cure; 6/15 (40%) linezolid died	Vancomycin IV	48/54 (88.9%) of vancomycin and 51/53 (96.2%) daptomycin patients had complicated bacteremia; 31/53 (58.5%) daptomycin and 33/54 (61.1%) vancomycin achieved clinical cure; 44/47 (93.56%) daptomycin and 45/50 (90%) vancomycin achieved microbiological cure; 10/53 (18.9%) daptomycin and 5/54 (9.3%) vancomycin died	*P* = .9624 for clinical cure; *P* = .6777 for microbiological cure; *P* = .0186 for mortality	—

Table 2. Continued

Author & Year	Study Arm	Study Arm Outcome	Standard Therapy Arm	Standard Therapy Outcome	Outcome Analysis	Days IV Before PO Switch
Willekens et al. [36] 2018	Linezolid IV→PO 600 mg twice daily	1/45 (2.2%) 90-day relapse, 0/45 (0.0%) 14-day mortality, and 1/45 (2.2%) 30-day mortality	SPT included: cloxacillin, cefazolin, extended β-lactams, carbapenems, daptomycin, cefepime and teicoplanin for MSSA and daptomycin, vancomycin and linezolid IV for MRSA	Propensity score-matched cohort had 4/90 (4.4%) 90-day relapse; 6/90 (6.7%) 14-day mortality and 12/90 (13.3%) 30-day mortality	*P* values: .87 for 90-day relapse, .18 for 14-day mortality, .08 for 30-day mortality	IV to PO linezolid switch performed after 3–9 days of IV therapy
Fluoroquinolones						
Bouza et al. [37] 1989	Ciprofloxacin IV, IV→ PO or PO; for IV, doses ranged from 200 to 400 mg daily; for PO, doses ranged from 1000 to 1500 mg daily	2/2 (100%) achieved clinical cure	—	—	—	Specific information about ciprofloxacin route of administration or duration was not given for SAB patients
Dworkin et al. [8] 1989	Ciprofloxacin 300 mg IV + rifampicin 300 mg PO twice daily for 7 days changed to ciprofloxacin 750 mg PO + rifampicin 300 mg PO twice daily for 21 days	5 patients were lost to follow-up without record of readmission; 5 patients readmitted with other infections or re-infection	—	—	95% CI for clinical cure was 76%–100%	Mean duration of IV ciprofloxacin was 6–7 days, followed by mean duration of 21 days of oral ciprofloxacin
Heldman et al. [9] 1996	Ciprofloxacin 750 mg PO + rifampin 300 mg PO twice daily	18/19 (94.7%) achieved microbiological cure	Oxacillin 2 g IV every 4 hours or vancomycin 1 g IV twice daily + gentamicin IV for first 5 days	22/25 (80.0%) achieved microbiological cure	Odds ratio for microbiological treatment failure (oral vs SPT) was 0.4 (95% CI, 0.01 to 5.5; *P* = .6)	Oral ciprofloxacin + rifampin began on admission
Schrenzel et al. [38] 2004	Fleroxacin 400 mg PO daily + rifampicin 600 mg PO daily	15/19 (79%) catheter-related SAB; 10/11 (91%) primary SAB achieved clinical cure; 15/19 (79%) catheter-related SAB and 10/10 (100%) primary SAB achieved microbiological cure	Flucloxacillin 2 g IV every 6 hours or vancomycin 1 g IV twice daily	10/11 (91%) catheter-related SAB, 4/5 (80%) primary SAB achieved clinical cure; 9/10 (90%) catheter-related SAB and 5/5 (100%) primary SAB achieved microbiological cure	Relative risk was 0.8 (95% CI, 0.4 to 1.3; *P* = .81), 1.4 (95% CI, 0.3 to 5.9; *P* = .54), 0.8 (95% CI, 0.5 to 1.3; *P* = .63), and undefined (*P* = .33)	Fleroxacin + rifampicin oral therapy was started on admission or after up to 24 hours of IV fleroxacin + rifampin therapy
Beganovic et al. [39] 2019	Levofloxacin or moxifloxacin (administration route and dose unknown)	Of 32 patients for whom patient characteristics were balanced, there was no difference in time to mortality	Nafcillin, oxacillin, or cefazolin IV (dose unknown)	Of 32 patients for which patient characteristics were balanced, there was no difference in time to mortality	Hazard ratio of 1.33, with 95% CI of 0.30 to 5.96	Specific information about levofloxacin or moxifloxacin route of administration or duration was not given
Trimethoprim/sulfamethoxazole						
Markowitz et al. [40] 1992	TMP-SMX 320 mg/1600 mg IV twice daily	Overall cure rate for all infections was 37/43 (86.0%); no subanalyses of bacteremia	Vancomycin 1 g IV twice daily	Overall cure rate for all infections was 57/58 (98.3%), no subanalyses of bacteremia	All infection *P* = .014	Oral therapy was not evaluated in this study
Goldberg et al. [41] 2010	TMP-SMX oral or IV, dose not given	13/38 (34.2%) 30-day mortality; 3/38 (7.9%) relapse or persistent bacteremia	Vancomycin IV, dose not given	31/76 (40.8%) 30-day mortality; 13/67 (11.8%) relapse or persistent bacteremia	Odds ratio of 30-day mortality TMP-SMX vs vancomycin was 0.76 (95% CI, 0.34 to 1.7) and for relapse or persistent bacteremia 0.42 (95% CI, 0.11 to 1.56)	No specific information given about duration or route of TMP-SMX administration

Table 2. Continued

Author & Year	Study Arm	Study Arm Outcome	Standard Therapy Arm	Standard Therapy Outcome	Outcome Analysis	Days IV Before PO Switch
Paul et al. [42] 2015	TMP-SMX 320 mg/1600 mg IV with potential to change to PO at physician discretion	Failed to meet noninferiority standards for all infections; demonstrated a trend toward higher all-cause 30-day mortality in the ITT bacteremia patients 14/41 (34%)	Vancomycin 1 g IV twice daily	9/50 (18%) 30-day all-cause mortality	Multivariate adjusted 7-day treatment failure for all infections was 2.00 (95% CI, 1.09 to 3.65); odds ratio for bacteremia-specific 30-day all-cause mortality in the ITT analysis was 1.90 (95% CI, 0.92 to 3.93)	No specific information given about duration or route of TMP-SMX administration
Harbarth et al. [43] 2015	TMP-SMX (IV→PO) 160 mg/800 mg 3 times daily + rifampin IV or PO 600 mg daily	6/9 (66.7%) clinical cure in ITT bacteremia patients	Linezolid (IV→PO) 600 mg	7/9 (77.8%) clinical cure in ITT bacteremia patients	Risk difference of 11.1 (95% CI, –31.2 to 50.0) for bacteremia	For all infections, TMP-SMX IV therapy was given in 18 (24.0%) patients for a median of 6 days before oral switch; linezolid was given IV in 11 (14.7%) patients for a median of 1 day before oral switch
Tissot-Dupont et al. [44] 2019	TMP-SMX 960 mg/4800 mg IV every 4 hours + clindamycin 1800 mg IV 3 times daily for 7 days → TMP-SMX 160 mg/800 mg PO (6 tablets per day)	7/171 (4.1%) had relapse; 6/171 (3.5%) had recurrence	Oxacillin 12 g IV daily for MSSA or vancomycin 30 mg/kg/ d IV for MRSA	10/170 (5.9%) had relapse; 12/170 (7.06%) had recurrence	$P = .046$ for relapse and $P = .15$ for recurrence	Defined in intervention, patients received 7 days of IV TMP-SMX + clindamycin before oral switch to TMP-SMX PO; there were significant caveats with the design of this study[a]
Clindamycin						
Martinez-Aguilar et al. [45] 2003	Clindamycin 40 mg/kg/d IV or PO	20/46 (43.5%) MRSA and 18/52 (34.6%) MSSA invasive infections were treated with clindamycin only (39/46 patients with MRSA invasive infection and 24/52 patients with MSSA received clindamycin as their final antibiotic)	Nafcillin, vancomycin, other β-lactam	18/46 (39.1%) with MRSA and 15/52 (28.8%) with MSSA invasive infections were treated with vancomycin IV, of whom 6/18 (33.3%) with MRSA and 0/52 (0%) with MSSA completed therapy with vancomycin IV	—	Although oral clindamycin was given as a therapeutic choice, the authors note that most received predominantly IV clindamycin; specific numbers not given
Other						
Carney et al. [14] 1982	21/45 (46.7%) treated with dicloxacillin, cephalexin, or erythromycin	0/21 (0%) died from *S. aureus;* only 1/21 (4.8%) (received erythromycin) had SAB relapse	Multiple IV therapy regimens	6/17 (35%) died from *S. aureus*	—	2–16 days of IV therapy were given before oral switch
Thwaites et al. [15] 2010	UK SAB patients	25% of included UK patients received oral antibiotic exclusively for >50% of their treatment duration	Vietnam/Nepal SAB patients	4% of included patients received oral antibiotics exclusively for >50% of their treatment duration	—	98% of patients were given IV antibiotic for some or all of their treatment; 14/630 (2.2%) received oral antibiotics only, of whom all had MSSA and 11/14 (78.6%) received flucloxacillin

Table 2. Continued

Author & Year	Study Arm	Study Arm Outcome	Standard Therapy Arm	Standard Therapy Outcome	Outcome Analysis	Days IV Before PO Switch
Jorgensen et al. [13] 2019	Oral linezolid, TMP-SMX, clindamycin, or doxycycline +/- adjuvant rifampin	5/70 (7.1%) had 90-day clinical failure; overall, 35/70 (50.0%) received linezolid, 24/70 (34.3%) TMP-SMX, 11/70 (15.7%) clindamycin, 2/70 (2.9%) doxycycline, and 2/70 (2.9%) adjuvant rifampin	OPAT with IV daptomycin, vancomycin, or ceftaroline	63/422 (14.9%) had 90-day clinical failure; overall, 194/422 (46.0%) received vancomycin, 194/422 (46.0%) daptomycin, 50/422 (11.8%) ceftaroline, and 16/422 (3.8%) adjuvant rifampicin	The adjusted hazard ratio for 90-day clinical failure with OPAT as the reference was 0.379 (95% CI, 0.131 to 1.101; $P = .0747$)	The median duration of inpatient IV therapy was 8 days in the outpatient oral antibiotic group and 10 days in the OPAT group
Iversen et al. [12] 2019	Oral regimens for the 87 *S. aureus* patients were based on penicillin and methicillin sensitivity; there were 13 combinations, of which the 3 most common were 15/45 (33%) dicloxacillin + rifampicin, 13/45 (29%) amoxicillin + rifampicin, and 3/45 (7%) moxifloxacin + rifampicin	3/47 (6.4%) had a primary outcome	IV antibiotics chosen based on European Society of Cardiology guidelines	3/40 (7.5%) had a primary outcome	Odds ratio was 0.84 (95% CI, 0.15 to 4.78; $P = .94$) for evaluation of all bacterial sources	Per protocol, 10 or more days and at least 7 days of IV treatment after valve surgery were given before transition to oral antibiotics

Abbreviations: CI, confidence interval; ITT, intention-to-treat; IM, intramuscular; IV, intravenous; MRSA, methicillin-resistant *S. aureus*; MSSA, methicillin-sensitive *S. aureus*; OPAT, outpatient parenteral antibiotic therapy; PO, per os (oral); SAB, *Staphylococcus aureus* bacteremia; SPT, standard parenteral therapy; TMP-SMX, trimethoprim-sulfamethoxazole.

[a]The TMP-SMX + clindamycin group had significantly lower rates of fever, heart murmur, mycotic aneurysm, and vegetations at baseline; only 40% of the TMP-SMX/clindamycin group received the protocol drugs from the start of treatment, and 19% had their protocol treatment interrupted.

Although there is some evidence to suggest that certain fluoroquinolones given alone may have efficacy in the treatment of SAB, given the known risk of de novo development of rapid resistance, the combination of a fluoroquinolone and rifampin is much more promising. There is limited evidence available, but for select patients who may not be able to tolerate linezolid or conventional IV antibiotics, this is a potential therapy. Ongoing trials, like the RODEO trial, which is evaluating the use of oral switch levofloxacin and rifampin after 10 days of IV therapy for infective endocarditis, may offer further support for the efficacy of a fluoroquinolone + rifampin strategy [57].

Fluoroquinolones as a drug class carry an FDA boxed warning that includes increased risk of tendinitis and tendon rupture, peripheral neuropathy and central nervous system effects, and exacerbation of myasthenia gravis muscle weakness, in addition to official warnings alerting prescribers to an increased risk of aortic aneurysm and dissection in specific patient groups [58]. As with all oral antibiotic therapies, counseling of the risk–benefit ratio is needed before making the therapeutic decision to change from IV to oral therapy.

OTHER ORAL ANTIBIOTICS

Trimethoprim-Sulfamethoxazole

The use of oral trimethoprim-sulfamethoxazole (TMP-SMX) in the treatment of SAB is controversial. In at least 2 studies, TMP-SMX performed worse than IV vancomycin for treatment of invasive *S. aureus* infections [40, 42]. Markowitz et al. found significantly lower cure rates when treating all *S. aureus* infections with IV TMP-SMX (37/43, 86.0%) when compared with IV vancomycin (57/58, 98.3%; $P = .014$) [40]. Subsequently, Paul et al. found that oral TMP-SMX failed to meet noninferiority standards compared with IV vancomycin for the treatment of severe MRSA infections. Among the subset of study subjects with SAB (n = 91), the adjusted odds ratio for treatment failure with oral TMP-SMX was 2.00 (95% CI, 1.09 to 3.65) [42]. Both Markowitz et al. and Paul et al. (an open-label study) had major limitations, including only a small sample of SAB patients randomized to the TMP-SMX arm (27 and 41, respectively) and an incomplete definition of disease severity. The entire sample in Markowitz et al. was composed of PWID, and 27% did not complete follow-up. Furthermore, 10% of the patients randomized to TMP-SMX in the Paul et al. study received adjunctive rifampin. Other studies have compared oral, IV, and IV to oral switch TMP-SMX with IV vancomycin and demonstrated no difference in SAB relapse or 30-day mortality; however, these studies had significant limitations (Table 2) [41, 44].

The use of TMP-SMX with an adjunct *S. aureus*–active agent, like rifampin, has also been evaluated. In 2015, Harbarth et al. found no significant difference in clinical cure between IV to oral linezolid (6/9 patients, 66.7%) and IV to oral TMP-SMX plus rifampin (7/9 patients, 77.8%; risk difference, 11.1; 95% CI, –31.2 to 50.0) for treatment of MRSA bacteremia,

suggesting that this could be a potential option in the future [43]. Nevertheless, TMP-SMX should be generally avoided as oral step-down therapy for uncomplicated SAB until more encouraging data are available (Table 2).

Clindamycin, Doxycycline, and Minocycline

Clindamycin, doxycycline, and minocycline have not been studied extensively as alternative agents for SAB. Clindamycin has 90% oral bioavailability but requires activation via digestion in the gastrointestinal tract and is susceptible to underdosing due to rapid clearance in patients weighing >75 kg [59, 60]. A single study describing the treatment of pediatric patients with invasive *S. aureus* infections, including 34 with primary or secondary bacteremia, showed that clinical cure was achieved for 38/98 (38.8%) invasive *S. aureus* infections treated with clindamycin IV or PO; however, no information was given on how many patients received PO [45]. Both doxycycline and minocycline have good oral absorption with an average of 95% and 95%–100%, respectively; however, high protein-binding and rapid tissue distribution have traditionally deterred the use of these medications for the treatment of SAB [61, 62]. The evidence for doxycycline and minocycline in the treatment of SAB is limited to a handful of case reports [63, 64].

Tedizolid

Tedizolid, an oxazolidinone antibiotic similar to linezolid, has an oral bioavailability of ~91%, which is lower than linezolid, and a plasma protein binding of 70%–90%, which is higher than linezolid at ~31% [46, 65]. There are currently no trials or case reports of oral tedizolid used for SAB. In the ESTABLISH-1 trial evaluating treatment of ABSSI with tedizolid, 8 patients had bacteremia and 5 were SAB; no subanalyses were performed [66].

Beta-lactams

In regions of the world where penicillin-susceptible *S. aureus* is common, clinicians sometimes use amoxicillin and other beta-lactams as oral step-down for the treatment of SAB [67]. Given the paucity of the literature surrounding this treatment method, there is insufficient information to definitively comment on this practice. Further studies are needed to address this issue.

OTHER STUDIES

In 2019, Iversen et al. published results from the Partial Oral versus Intravenous Antibiotic Treatment of Endocarditis (POET) trial. This study did not specifically evaluate patients with uncomplicated SAB, but rather compared full IV antibiotic therapy or initial IV antibiotics followed by oral antibiotics to treat native valve left-sided endocarditis caused by several bacteria, including *S. aureus.* The POET trial showed that a treatment strategy including a period of oral antibiotics following at least 10 days of IV antibiotics was noninferior to complete parenteral therapy. The primary end point of POET was a composite outcome consisting of all-cause mortality, unplanned cardiac surgery, embolic events, and relapse of blood cultures [12]. Oral therapies used for the subset of *S. aureus* patients included several combinations of 2 active agents from different drug classes. The most common were dicloxacillin plus rifampin (15/45 patients, 33.3%), amoxicillin plus rifampin (13/45 patients, 28.9%), and moxifloxacin plus rifampin (3/45 patients, 6.7%). While there was no difference in the composite outcome between patients receiving only IV (3/40 patients, 7.6%) and those receiving partial oral antibiotic therapy (4/37 patients, 6.4%) for *S. aureus* left-sided endocarditis (95% CI, 0.15 to 4.78; $P = .84$), the study was underpowered to draw conclusions in the subgroup of patients with *S. aureus* endocarditis (Table 2). In addition, several factors limit our ability to apply the findings to patients with uncomplicated SAB. First, the trial included a relatively low number of SAB patients in the oral therapy arm (n = 47). Many of the drug combinations are unfamiliar to clinicians and contain antibiotic agents with a significant potential for toxicity. Finally, the study sample contained no cases of MRSA and only 5 patients with injection drug use, limiting our ability to generalize these findings. Nonetheless, the results of POET support the concept that oral antibiotics can be used as step-down from parenteral therapy in highly select patients with uncomplicated SAB.

Before the POET trial, in 2019, Jorgensen et al. published a retrospective cohort study evaluating early oral step-down therapy for uncomplicated or complicated MRSA bacteremia with linezolid, TMP-SMX, clindamycin, or doxycycline vs traditional OPAT and found no difference in 90-day clinical failure [13]. This study included persons with IV drug use, a particular population of interest when considering early oral step-down therapy for SAB. Unfortunately, no subanalyses were performed to evaluate the oral therapies separately, and clinical failure was limited to patients who were readmitted only to the researchers' institution. For MSSA bacteremia specifically, use of successful partial oral step-down therapy with dicloxacillin, cephalexin, and flucloxacillin (outside the United States) has also been reported (Table 2) [14, 15].

THE ARGUMENT AGAINST ORAL STEPDOWN THERAPY FOR SAB

Although there is some evidence to suggest that oral step-down therapy might be effective in select cases of uncomplicated SAB, many clinicians remain hesitant to adopt this new practice. IV antibiotics have been standard practice for SAB for decades. By contrast, the consequences of undertreating SAB with oral antibiotics can result in suboptimal outcomes. Several arguments against oral step-down therapy for SAB are outlined below.

Differentiating Complicated and Uncomplicated SAB

The most significant barrier to using oral antibiotics for the treatment of uncomplicated SAB is the difficulty in

differentiating complicated from uncomplicated infection. A number of studies have reported high rates of clinically unsuspected metastatic infections in patients with SAB [68–70]. Most recently, almost one-third of patients enrolled in a randomized clinical trial for uncomplicated SAB were ultimately found to have complicated SAB [71]. This can be attributed to 2 major issues. First, the criteria differentiating complicated from uncomplicated SAB do not always account for the full clinical picture. Second, the diagnosis of multiple complications of SAB is often delayed, resulting in the misclassification and, subsequently, undertreatment of complicated SAB.

Criteria Do Not Always Account for the Full Clinical Picture

Although the current definitions for uncomplicated SAB may seem well-defined, the clinical reality is often less clear-cut. Areas of controversy surrounding each criterion exist [72]. For example, the existing criteria only mention positive blood cultures taken 48 hours after the index culture, ignoring the possible significance of a repeat positive blood culture taken before 48 hours [16]. Indeed, a recent multicenter prospective investigation reported that each additional day of SAB increased mortality by 16% compared with having a single day of bacteremia [73]. Moreover, the criteria specify that metastatic infection be excluded before designating an infection as uncomplicated SAB, but do not define the diagnostic workup (the challenges of this diagnostic workup are discussed later) [72]. These areas of diagnostic uncertainty limit clinicians' ability to effectively base treatment decisions on these criteria. Although these criteria continue to evolve as evidence and technology progress, until there are clear and comprehensive criteria for identifying uncomplicated SAB, treatment cannot reliably be based on this dichotomy.

Delay in Diagnosis of Complicated SAB

Beyond ambiguities in the definition, differentiating complicated from uncomplicated SAB is further challenged by the diagnostic delay of metastatic infections [4]. Epidural abscesses are a potential complication of SAB that can be difficult to diagnose. The majority of patients with epidural abscesses do not initially present with the classic triad of back pain, fever, and neurological signs, and the diagnosis is often missed early in the clinical course of infection [74]. A study by Darouiche et al. found that in a sample of patients ultimately diagnosed with an epidural abscess, only 17 (40%) were admitted with a suspected diagnosis of epidural abscess [75].

A similar pattern can be seen in vertebral osteomyelitis (VO). In 1 study evaluating physician diagnostic impressions, VO was considered in the initial differential for only 24% of patients eventually diagnosed with VO [76]. Similar to epidural abscess, VO can also present with nonspecific complaints, making it difficult to diagnose [77]. Several studies have found that the median time to diagnosis from the onset of symptoms ranged between 46 and 54 days [76, 77]. These studies suggest that spinal imaging might be required to definitively rule out metastatic infection in patients who otherwise appear to have uncomplicated SAB.

As an individual criterion, determining the presence or absence of endocarditis is key to differentiating complicated from uncomplicated infection. Endocarditis often is missed clinically and only diagnosed upon autopsy. Studies published in 1986, 1999, and 2001 found that 17%–55% of autopsy-confirmed cases of endocarditis were not diagnosed before autopsy [78–80]. In the most recent study, of 31 patients with a missed clinical diagnosis of endocarditis, 83.9% had not been evaluated by echocardiography, suggesting that a diagnosis of endocarditis was not considered clinically [79]. Our ability to diagnose endocarditis has improved considerably since then. However, a study including patients up to 2013 found that premortem clinical information was a poor indicator of postmortem diagnosed heart valve disease in general and that the sensitivity for endocarditis was only 32.4% (95% CI, 17.4% to 50.5%) [81]. In a 2017 meta-analysis of 30 studies, Bai et al. examined the negative likelihood ratio (NLR) of clinical predictors and clinical prediction rules to estimate risk for infective endocarditis in patients with SAB. Out of the 15 clinical predictors evaluated, only 1 (clearance of bacteremia within <72 hours) had an NLR <0.1. Out of the 9 published clinical predication rules examined, only 5 had NLRs <0.1. They conclude that although some clinical prediction rules show promise, further validation by high-quality evidence is needed [82].

In addition to clinical information, the diagnosis of endocarditis relies heavily on imaging that has historically been dominated by echocardiography. The higher sensitivity of transesophageal echocardiography (TEE) compared with transthoracic echocardiography (TTE) has made it the gold standard for endocarditis diagnosis [7, 16, 68]. However, these current recommendations are based on low-grade evidence [7]. Despite recommendations, TTEs continue to be used more often than TEEs. This is due in part to the invasiveness and potential complications associated with TEE [83, 84] in addition to considerations such as availability, logistical burden, and cost. Some studies have found that a negative TTE carries enough negative predictive value to rule out endocarditis in a select subset of patients without risk factors for endocarditis [70, 85–88]. Despite this reassurance, Fowler et al. demonstrated that 15/77 (19%) patients with negative TTEs were found to have endocarditis on TEE [68], and another report found that the use of TEE to determine therapy duration for patients with catheter-associated SAB was a cost-effective alternative to 2- or 4-week empirical therapy [89]. In addition, a meta-analysis of 16 studies found that TTE had a sensitivity of only 61% (NLR, 0.42; 95% CI, 0.26 to 0.61) compared with TEE as the gold standard. The negative likelihood ratio could be improved by selecting the subset of patients without prosthetic valves (NLR, 0.36; 95% CI, 0.22

to 0.55) or by using more stringent criteria to define a conclusively negative TTE (NLR, 0.17; 95% CI, 0.1 to 0.28). The authors conclude that although in patients without prosthetic heart valves conclusively negative TTE greatly decreases the likelihood of endocarditis, all other patients will require TEE to effectively rule out endocarditis [89, 90]. Collectively, these studies underscore that while echocardiography should now be regarded as standard of care for the evaluation of patients with SAB, the specific type of echocardiography (eg, TTE vs TEE) remains unresolved and is likely dependent upon individual patient circumstances.

Failure to correctly identify conditions such as epidural abscesses, vertebral osteomyelitis, and infective endocarditis can result in a missed diagnosis of complicated SAB. As technology advances and our understanding of these conditions grows, our ability to diagnose them is improving. For example, recent advancements in imaging for endocarditis have provided alternatives to echocardiography [91]. Similarly, ^{18}F-FDG PET/CT has proven useful in the early diagnosis of metastatic complications of SAB [92]. However, for some complications such as native valve endocarditis, the sensitivity of ^{18}F-FDG PET/CT remains relatively low (68%; 95% CI, 49% to 83%) [93]. In addition, there is a limit to how far we should go to prove that a case of SAB is uncomplicated. Factors such as the cost of newer imaging techniques and patient safety may prohibit these diagnostic tools from being utilized consistently in all patients with SAB.

Uncomplicated SAB Is Uncommon

Beyond the difficulty of differentiating complicated from uncomplicated cases of SAB, patients meeting all the criteria for uncomplicated SAB are uncommon. The low incidence of uncomplicated cases is reflected in the recruitment and enrollment rates of these cases in various clinical trials. As the SABATO trial screened for enrollment of uncomplicated SAB patients, the ratio of patients screened to uncomplicated SAB cases enrolled was 28:1 [94]. This pattern is not uncommon: both the NIH Algorithm and ASSURE trials also encountered screen:enroll ratios of 30:1 and 33:1, respectively [71, 95]. These uncharacteristically high screening-to-enrollment ratios are indicative of the relative infrequency of uncomplicated SAB.

The cause for this increase in the frequency of complicated SAB is multifactorial. Over time, the epidemiology and clinical course of SAB have changed. In a 2019 study by Souli et al. examining SAB cases between 1995 and 2015, individuals who developed SAB tended to have more comorbidities over time, with over half of patients with SAB enrolled in 2015 having an indwelling prosthetic device (and thereby not having uncomplicated SAB by definition). In addition, the rates of metastatic infections increased by 0.9% annually. Over the 21-year period, a shift in the genotypic clones of *S. aureus* also occurred, as the frequency of the highly virulent USA300 strain steadily increased as a cause of SAB. The USA300 strain was also found to be independently associated with a higher rate of metastatic infection (OR, 1.42; 95% CI, 1.02 to 1.99) [96]. Taken together, these factors increase the odds that patients with SAB encountered in the early 21st century will fail to meet the criteria for uncomplicated infection.

Despite the frequency of complicated SAB, there is a lack of evidence to guide treatment of various types of complicated SAB. Patients with SAB complicated by infective endocarditis are different than those complicated by osteomyelitis. Studies that could have provided insight into management of specific types of complications often have too few SAB patients to draw meaningful conclusions [12, 97]. Without the ability to confidently identify uncomplicated SAB and differentiate it from the subtypes of complicated SAB, offering oral antibiotic therapy to patients may pose a risk of undertreating a potentially lethal complication.

Best Treatment Unknown

Although research has begun to offer some insights, current clinical practice and guidelines are based on low-grade evidence, and the best treatment for SAB remains unclear with regards to both antibiotic selection and duration of therapy [6, 7]. In a 2014 literature review of SAB management by Holland et al., only 1 study of the 81 articles reviewed was considered to provide high-level evidence per the Grades of Recommendation, Assessment, Development and Evaluation system criteria. Of the remaining articles, 3 were classified as moderate-level, 22 as low-level, and 55 as very low-level evidence [7]. Since then, few high-quality studies have been published [71, 98, 99]. To date, there is no consensus on the best treatment strategies for SAB, particularly in uncomplicated infections.

CONCLUSIONS

There is little high-level evidence to inform decisions around early oral therapy for uncomplicated SAB. Clinicians should critically appraise new evidence carefully before integrating new practices into their clinical care. The use of oral antibiotics should be considered on a case-by-case basis, and the potential benefits should be weighed against the risks. Discussion with patients should be guided by the principles of informed consent and shared decision-making.

Within these confines, the current existing evidence suggests that oral step-down therapy can be a reasonable alternative for the treatment of select patients with uncomplicated SAB, provided that the *S. aureus* isolate is documented as susceptible, the patient is properly educated on the importance of strict adherence to the medication regimen, and the patient can reliably follow up as an outpatient. Although these cases of uncomplicated SAB represent only a subset of those diagnosed, and identifying them may prove challenging, data suggest that oral antibiotics may sometimes be considered in this group. Published data particularly support the use of oral linezolid.

A fluoroquinolone plus rifampin may sometimes be reasonable. Additional oral antibiotic regimens, while promising, do not currently have adequate evidence to recommend their use in SAB. Most importantly, these results emphasize the need for a well-designed randomized clinical trial to answer once and for all the safety and effectiveness of oral antibiotics for partial treatment of uncomplicated SAB.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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