UWTASP

tele-antimicrobial stewardship program

May 4, 2021

How Strong is the Force with Oral Antibiotics?

Oral Antibiotic Use in *Staphylococcus aureus* Bacteremia

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Which Darth Sidious Are We For Oral Antibiotics in SAB?

Objectives

- Briefly review *Staphylococcus aureus* bacteremia
- Discuss different oral antibiotics and evidence for use in *Staphylococcus aureus* bacteremia

Staphylococcus aureus Bacteremia (SAB)

- Pre-antibiotics, SAB mortality rates were 75-83%
- Mortality rates have decreased since and have a 30-day all-cause mortality of around 20%

S. aureus BSI

Complicated
Positive f/u blood cultures
Persistent fever
TTE/TEE consistent for endocarditis
Signs of metastatic infection

Uncomplicated (Low risk)
Intravascular device removed
Negative blood cultures within 24-72 h
Defervescence w/i 72h of positive culture
No metastatic diseases or endocarditis
No prosthetic material

Van Hal SJ et al. Clin Microbiol Rev. 2012 Apr; 25(2): 362–386.
Holland TL et al. *JAMA.* 2018;320(12):1249-1258.

Potential benefits of oral stepdown

- Potential benefits
  - Reduced complications related to IV therapy
  - Shorter hospital stay
  - Reduced cost
- Who may benefit?
  - Dialysis patients (minimize central access complications)
  - Injection drug users (long term IV access is a poor option)
  - Lifestyle not conducive for long term IV access
  - Issues with insurance coverage for long term IV antibiotics

Willekens et al. Clin Infect Dis . 2019 Jul 18;69(3):381-387.
Schrenzel et al. Clin Infect Dis . 2004 Nov 1;39(9):1285-92.
Jorgensen et al. J Antimicrob Chemother . 2019 Feb 1;74(2):489-498.

What are our oral antibiotic choices?

Antibiotics (Bioavailability)	Notes
Beta lactams (50-85%)	• Well tolerated • Some have lower bioavailability • Often 3-4 times a day dosing
Fluoroquinolones (70-99%)	• Lower barrier to resistance development • Multiple FDA warnings for ADEs
Linezolid (99%)	• Myelosuppression associated with use >14 days • Interactions with serotonergic agents
Tetracyclines (95%)	• High protein binding • Limited clinical experience with bacteremia
Sulfamethoxazole Trimethoprim (90%)	• Myelosuppression with high dose/long term use • Hyperkalemia, renal impairment
Clindamycin (90%)	• Association with *C. difficile* infections • Often 3-4 times a day dosing • Data limited to pediatrics
Rifampin (>90%)	• Significant CYP interactions • Not typically used alone

Hale et al. J Hosp Med. 2018 May 1;13(5):328-335; Loos U et al. Klin Wochenschr . 1985 Dec 2;63(23):1205-11.

Linezolid (IV or PO) vs Vancomycin

1997-2000
Compassionate Use Program

2002, 2003
Compassionate use studies for LZD in SA infections with cure rates from 63.2% to 85.7% for SAB[1,2]

2005
Pooled analysis (5 RCTs) - LZD vs VAN
SAB subgroups showed similar clinical cure rates[3]

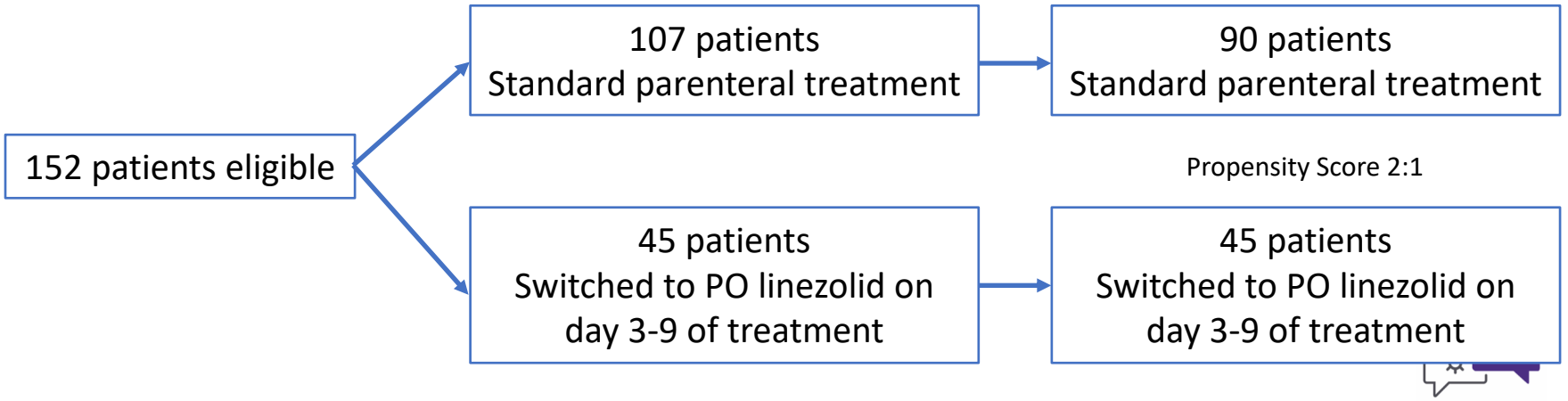
2009
RCT - CRBSI and cSSSI for SA
LZD vs VAN
No difference in microbiological cure[4]

[1]Moise PA et al. Antimicrob Chemother 2002; 50:1017–26.
[2]Birmingham MC et al. Clin Infect Dis 2003; 36:159–68.
[3]Shorr AF et al. Chemother 2005; 56:923–9.
[4]Wilcox MH et al. Clin Infect Dis 2009; 48:203–12.

LZD = linezolid; VAN = vancomycin; CRBSI = catheter related bloodstream infection; CSSSI = complicated skin and skin structure infection

Early Oral Switch For Linezolid

	Early Oral Switch to Linezolid for Low-risk Patients With Staphylococcus aureus Bloodstream Infections: A Propensity-matched Cohort Study
Willekens R et al. 2018 N = 135	Prospective cohort study at a Spanish university hospital (1000-bed) Inclusion: SAB, clinically stable, source control, negative f/u blood culture Exclusion: Death ≤7 d, complicated SAB, osteoarticular infections Groups well matched aside from PO linezolid group having less chronic renal disease and less days of IV therapy



Similar Clinical Outcomes

- Most common infections were CRBSI (~50%), SSTI (~16%), and PNA (~9.5%)
- Median duration of IV treatment in PO linezolid group was 7 days (IQR 6-8)
- PO linezolid group had shorter median length of stay (8 vs 19 days) and similar clinical outcomes (90 d relapse, 14 d mortality, 30 d mortality)

Summary: Linezolid

- Most of historical data compared linezolid as IV or IV to PO switch but generally showed no outcome differences with standard treatment groups
- Most evidence for uncomplicated SAB, switching to PO at around 7 days
- Switching to PO linezolid reduces length of stay but does not lead to inferior clinical outcomes

Fluoroquinolone Monotherapy

- Despite high bioavailability and activity against S. aureus, there is concern for development of resistance during treatment
- Moxifloxacin and delafloxacin may have a higher barrier to resistance than levofloxacin and ciprofloxacin
- A 2019 retrospective study found no difference in mortality with levofloxacin or moxifloxacin IV monotherapy as compared to cefazolin/nafcillin/oxacillin for MSSA BSI[1]

[1]Beganovic M et al. Open Forum Infect Dis. 2019 Jul; 6(7): ofz270.

Fluoroquinolones + Rifampin

- Addition of rifampin is often used given FQ risk for de novo resistance development as most of evidence is in complicated SAB with longer durations
- 1996 RCT - oral ciprofloxacin + rifampin vs IV oxacillin or vancomycin, plus gentamicin in IVDU for SA right sided endocarditis showed similar microbiologic cure[1]
- 2004 RCT - oral fleroxacin + rifampicin vs IV flucloxacillin or vancomycin for the subgroup of SAB showed no difference in clinical cure[2]

[1]Heldman AW et al. Am J Med 1996; 101:68–76.
[2]Shrenzel J et al. Clin Infect Dis 2004; 39:1285–92.

Summay: Fluoroquinolones

- Concern for development of resistance on monotherapy for SAB
- Low evidence that certain FQs given alone may be efficacious for SAB
- FQ + rifampin is a more commonly described but often in complicated SAB
- Risk and benefit should be considered given multiple FDA boxed warnings for FQs and drug interactions with rifampin

Sulfamethoxazole/Trimethoprim (SMX/TMP)

- There is some uncertainty in the efficacy SMX/TMP therapy for SAB
- SMX/TMP performed worse than IV vancomycin for invasive SA infections in 2 studies, especially in subgroups with SAB[1,2]
- Conversely, a small retrospective cohort comparing IV SMX/TMP to IV vancomycin for MRSA bacteremia demonstrated similar mortality rates[3]
- A retrospective observational study reported similar outcomes for PO vs IV therapy in uncomplicated and complicated SAB[4]
  - 66.4% of the PO group received SMX/TMP

[1]Markowitz et al. Ann Intern Med. 1992 Sep 1;117(5):390-8.
[2]Paul et al. BMJ. 2015 May 14;350:h2219.
[3]Goldberg et al. J Antimicrob Chemother . 2010 Aug;65(8):1779-83
[4]Perez-Rodriguez et al. Int J Infect Dis . 2021 Jan;102:554-560.

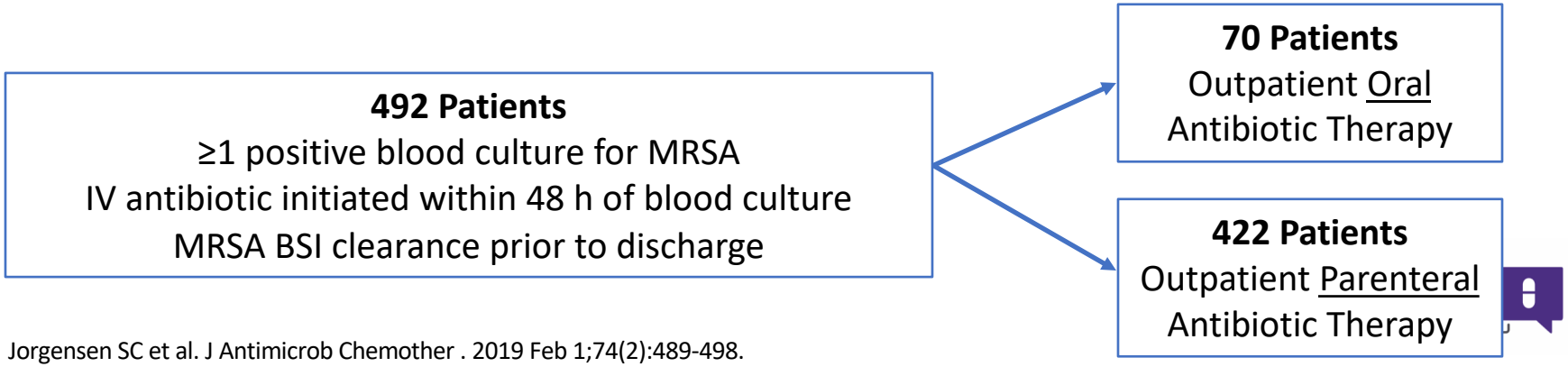
Beta Lactams

- Multiple day dosing and lower bioavailability make these antibiotics less appealing
- Small 2020 retrospective cohort - 90-day mortality was similar in patients who received oral beta lactams versus IV flucloxacillin for low-risk SAB
  - PO flucloxacillin most common (71%), then cephalexin (6%)
  - Median duration to oral switch was 5 days (IQR 4-6)
  - 90-day mortality in oral vs IV group were 2% vs 1% (p = 0.42), respectively

Bupha-Intr O et al. Antimicrob Agents Chemother. 2020 Jun 23;64(7):e02345-19

Transition to Outpatient Oral Antibiotic Therapy (OOAT)

	Sequential intravenous-to-oral outpatient antibiotic therapy for MRSA bacteraemia: one step closer
Jorgensen et al. 2019 N = 492	Retrospective cohort study Inclusion: ≥18 y/o, ≥1 positive blood culture for MRSA, IV antibiotic initiated within 48 h of blood culture, MRSA BSI clearance prior to discharge Exclusion: polymicrobial BSI or death Primary Outcome: 90 day clinical failure (MRSA BSI recurrence, deep-seated MSRA infection, or all cause mortality)

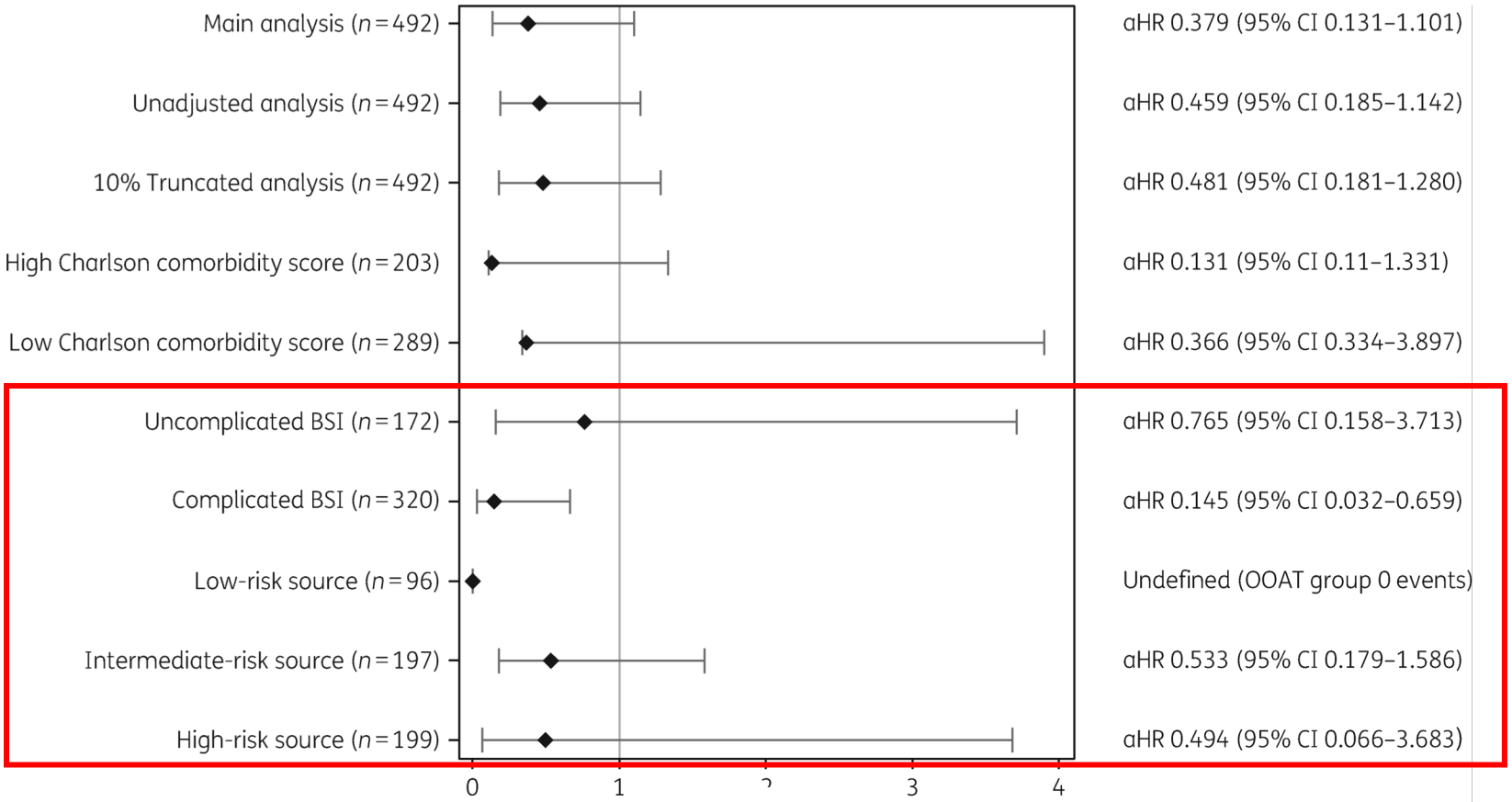


Jorgensen SC et al. J Antimicrob Chemother . 2019 Feb 1;74(2):489-498.

Patient Characteristics

- ICU admission at index culture 46%
- Source control pursued in 44.7% of patients
- Most oral patients received linezolid (50%), SMX/TMP (34.4%), and clindamycin (15.7%)
- Endovascular (21.5%), skin/soft tissue (25%), IV catheter (24%), bone/joint (20.9%), and PNA (17.1%) sources most common
- Median 8 days of inpatient IV antibiotics in oral therapy group

Similar Outcomes For 90 Day Clinical Failure



aHR < 1 favours oral therapy
aHR > 1 favours parenteral therapy

Summary: OOAT

- Oral antibiotics may be an option for outpatient therapy following a cleared MRSA BSI
- 90-day clinical failure was similar in both complicated and uncomplicated MRSA BSI
- Linezolid and SMX/TMP most commonly used
- Median of 8 days (IQR 5-12) before switch to oral antibiotics

Take Home Message

- There is a growing body of evidence for using oral antibiotics in SAB
- Oral antibiotic use in SAB can be considered in those that are clinically stable, source controlled, no metastatic site per ID consult, close follow up, and otherwise uncomplicated/low risk
- Switch to orals reduces days of IV therapy and length of hospital stay
- Most recent studies make the IV to PO switch at around after 7 days of IV therapy
- Ultimately it is a shared decision with the provider and the patient

Holland TL. 2020. Antimicrob Agents Chemother 64:e00317-20.

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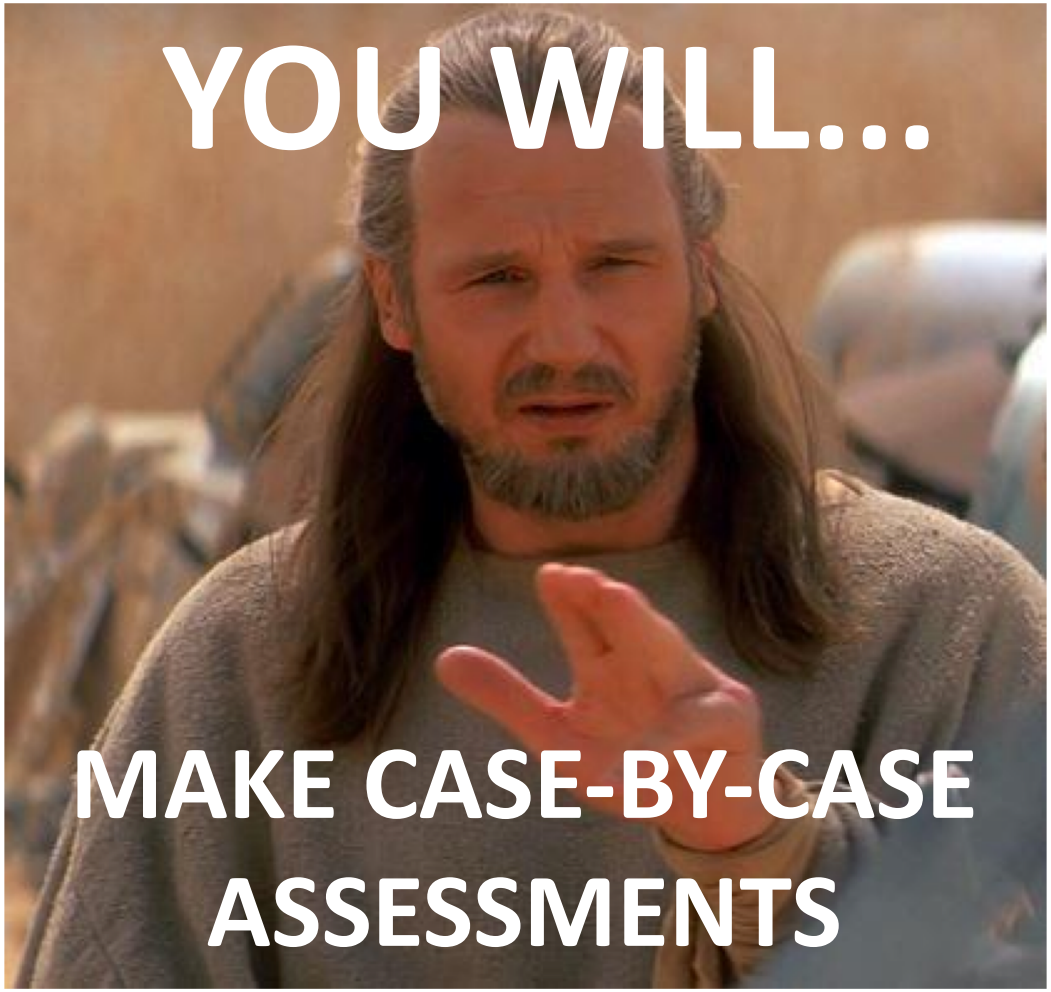

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- https://clinicaltrials.gov/ct2/show/NCT01792804
- SABATO
- https://clinicaltrials.gov/ct2/show/NCT03514446
- sAB7

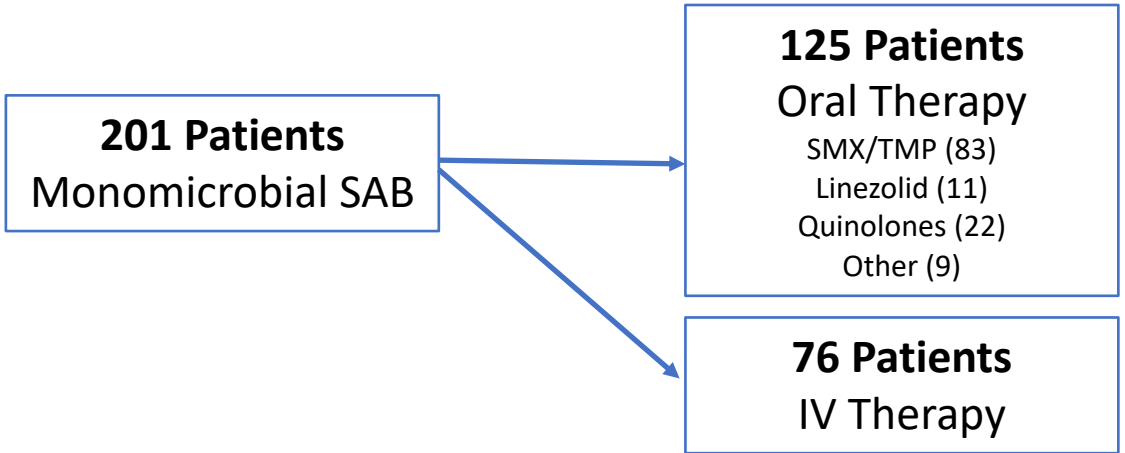
Similar Clinical Outcomes

Outcome	Oral Linezolid N (%)	Standard Treatment N (%)	P-value
90 d relapse	1 (2.2)	4 (4.4)	0.87
14 d mortality	0 (0)	6 (6.7)	0.18
30 d mortality	12 (13.3)	12 (13.3)	0.08
LOS, median days (IQR)	8 (7-10)	19 (15-30)	<0.01

- Most common infections were CRBSI (~50%), SSTI (~16%), and PNA (~9.5%)
- Median duration of IV treatment in PO linezolid group was 7 days (IQR 6-8)
- 90-day relapse, 14-day mortality, and 30-day mortality were similar
- PO linezolid group had shorter length of stay

Oral Sequential Therapy in Uncomplicated and Complicated SAB

	The benefits and safety of oral sequential antibiotic therapy in non-complicated and complicated *S. aureus* bacteremia
Perez-Rodriguez et al. 2020	Retrospective observational study (n = 201) Inclusion: Monomicrobial SAB and adequate DOT (≥14 d if uncomplicated, ≥28 d if complicated) Exclusion: Endocarditis, endovascular infections, death before clinical stability, >90 d antibiotic therapy Primary outcome: 90 day recurrence of SA infection Secondary outcome: mortality for overall causes at 90 d after bacteremia, length of stay, IV treatment duration



Similar Outcomes in IV vs PO

	IV (n = 76) n (%)	**Oral (n = 125)** n (%)	**P-value**
Clinical Cure	73 (97)	123 (98)	0.632
Recurrence	4 (6)	3 (3)	0.251
Death	12 (16)	9 (7)	0.095

- IV group had more ICU admissions, cancer, osteoarticular disease, and unknown disease
- PO group had less LOS 18 vs 36 days ($p < 0.001$) and less days of IV 13 vs 22 days ($p < 0.001$)
- Most common oral antibiotics were SMX/TMP, quinolones, and linezolid
  - Younger patients received more FQ
  - Median oral FQ use was longer 18 vs 11 and 13 days ($p = 0.026$)
- Multivariate analysis shows
  - Chronic renal failure, osteoarticular source, and SSTIs were associated with recurrence
  - MRSA infections were associated with mortality 90 d after bacteremia

SABATO – Early Switch to PO

- **Staphylococcus Aureus Bacteremia Antibiotic Treatment Options (SABATO)**
  - Multicenter, open-label, RCT, n = 215
  - Objective

Study Type :	Interventional (Clinical Trial)
Actual Enrollment :	215 participants
Allocation:	Randomized
Intervention Model:	Parallel Assignment
Masking:	None (Open Label)
Primary Purpose:	Treatment
Official Title:	Early Oral Switch Therapy in Low-risk Staphylococcus Aureus Bloodstream Infection
Actual Study Start Date :	December 2013
Actual Primary Completion Date :	March 26, 2020
Actual Study Completion Date :	March 26, 2020

  - Length of stay
  - Survival at 14, 30, 90 days
  - Complications of IV therapy

https://clinicaltrials.gov/ct2/show/NCT01792804