Early oral switch in *S. aureus* bacteraemia: evidence summary

Uncomplicated SAB

Complicated SAB

Specific antibiotics

Dagher M et al. A narrative review of early oral stepdown therapy for the treatment of *uncomplicated* SAB: yay or nay? OFID 2020

- Comprehensive summary literature to 2020:
  - Includes some with *complicated* SAB
  - Review organised according to oral antibiotic
    - Most evidence for linezolid, then fluoroquinolone + rifampicin
  - ‘We conclude that evidence suggests that oral step-down therapy can be an alternative for select patients who meet the criteria for uncomplicated SAB …’

Uncomplicated SAB

• Retrospective, single-centre: 100 low-risk SAB patients - most MSSA • 84 EOS after median 5 days IV; 86% of these had oral beta-lactams • 1 EOS patient had relapse in 90 days; no deaths attributable to SAB • **Conclusions: 1) EOS ok low-risk SAB; 2) beta-lactams ok for SAB EOS**	Efficacy of early oral switch with beta-lactams for low-risk Staphylococcus aureus bacteraemia. Bupha-Intr et al. Antimicrob Agents Chemother 2020
• Prospective, single-centre: low-risk SAB patients – 11% MRSA • 45 EOS linezolid day 3-9 of treatment, cf. 90 patients continued IV • No significant difference 90-day relapse or 30-day all-cause mortality; shorter length of hospital stay for EOS (8d versus 19d) • **Conclusion: EOS with linezolid = similar clinical outcomes to continued IV treatment, and shorter hospital length of stay**	Early oral switch to linezolid for low-risk patients with Staphylococcus aureus bloodstream infections: a propensity-matched cohort study. Willekens et al. CID 2018
• SABATO: randomised clinical trial: EOS at Day 5-7 of treatment of low-risk SAB, versus standard IV treatment	Results awaited
• SAB7: randomised clinical trial: 7 versus 14 days treatment for uncomplicated SAB	Results awaited

Complicated SAB

• Retrospective single-centre: 106 patients with complicated SAB (96% MSSA) - IE/endovascular excluded by CT-PET • 61% EOS after median 16 days IV; 88.5% received PO clindamycin • No difference 3-month mortality EOS versus IV group; no relapses; 12-day shorter length of hospital stay EOS group • **'… provides evidence to the efficacy and safety of IV-oral switch in a specific group of patients with complicated SAB without endovascular infection and complex deep seated infections.'**	Intravenous to oral switch in complicated Staphylococcus aureus bacteraemia without endovascular infection: a retrospective single-centre cohort study. Kouijzer et al. CID 2021.
• Prospective randomised trial of ciprofloxacin + rifampicin for right-sided staphylococcal IE in PWID (included some CONS) = similar microbiological and clinical cure rates cf. standard IV therapy	Oral antibiotic treatment of right-sided staphylococcal endocarditis in infection drug users: prospective randomized comparison with parenteral therapy. Heldman et al. Am J Med 1996
• Multicentre, randomized trial: oral fleroxacin + rifampicin versus IV treatment for SAB and deep-seated, non-bacteraemic staphylococcal infections (mostly MSSA; some CONS included) • Similar cure rate, microbiological/clinical failures in both groups • 12 days hospital stay (vs. 23 days in standard IV treatment group)	A randomized clinical trial to compare fleroxacin-rifampicin with flucloxacillin or vancomycin for the treatment of staphylococcal infection. Schrenzel et al. CID 2004.

Complicated SAB

• Retrospective, single-centre: 201 SAB patients (17% MRSA) • 62% EOS after median 13 days of IV (66% had TMP-SMX for EOS) • Both uncomplicated and complicated SAB; IE and endovascular infection excluded • No difference in cure, recurrence, death EOS versus IV; shorter hospital stays for EOS group	The benefits and safety of oral sequential antibiotic therapy in non-complicated and complicated *Staphylococcus aureus* bacteraemia. Perez Rodriguez et al. Int J Infect Dis 2020.
• Retrospective, single-centre: 70 MRSA-B patients had EOS (50% linezolid; 34% TMP-SMX) on discharge after median 8 days IV • Both complicated and uncomplicated SAB • 90-day failure rate non-significantly LESS in EOS group with significantly reduced hospital readmission risk • **Conclusion: selected MRSA-B patients may have at least equivalent clinical outcomes with oral antibiotics versus OPAT**	Sequential intravenous-to-oral outpatient antibiotic therapy for MRSA bacteraemia: one step closer. Jorgensen et al. J Antimicrob Chemother 2018
• **'POET'** (RCT of EOS versus continued IV treatment for IE): 87 patients with *S. aureus* IE; no MRSA; 54% EOS after median 17 days IV (combination amoxicillin/dicloxacillin with another agent) • No difference in primary outcome EOS versus continued IV	Partial oral versus intravenous treatment of endocarditis. Iversen et al. NEJM 2019.

Evidence for specific antibiotics

- Linezolid
- Fluoroquinolones
- Trimethoprim-sulfamethoxazole
- Beta-lactams
- Clindamycin

Linezolid in SAB

- Good body of evidence for efficacy of linezolid for EOS in uncomplicated MSSA and MRSA bacteraemia

- IV or oral (or IV-to-oral switch) linezolid at least as effective as standard therapy
  - Sig. proportion participants in these studies = EOS with linezolid
  - 1 study specifically about linezolid for EOS (Willekens)

- However:
  - Only two studies focussed specifically on SAB (Willekens, Usery)
    - Others also included non-bacteraemic *S. aureus* infections
  - None powered to specifically conclude that oral linezolid is non-inferior to standard treatment

Moise J Antimicrob Chemother 2002; Birmingham CID 2003; Shorr J Antimicrob Chemother 2005; Stevens CID 2002; Wilcox CID 2009; Usery Am J Med Sci 2015; Wilcox J Antimicrob Chemother 2004; Willekens CID 2019.

Fluoroquinolones in SAB

- *S. aureus* (esp. MRSA) can have high rates resistance (esp. ciprofloxacin) or can rapidly develop *de novo* resistance

- Most evidence is for fluoroquinolone + rifampicin:
  - Cipro + rifampicin for R-sided *S. aureus* IE in PWID: similar microbiological and clinical cure rates cf. standard IV therapy[1]
  - Oral fleroxacin + rifampicin for SAB and deep-seated *S. aureus* infections: equivalent to IV flucloxacillin or vancomycin[2]
  - RODEO-1: oral levofloxacin + rifampicin as EOS for L-sided *S.aureus* IE: results awaited[3]

- Large retrospective cohort of MSSA bacteraemia: no difference 30-day mortality moxi-/levofloxacin versus nafcillin/cefazolin (IV)[4]

(1) Heldman Am J Med 1996; (2) Schrenzel CID 2004; (3) Lemaignen BMJ Open 2020; (4) Beganovic OFID 2019; .

Trimethoprim-sulfamethoxazole (TMP-SMX)

- Two studies: TMP-SMX **inferior/NOT non-inferior** to IV vancomycin for invasive *S. aureus* infections (including SAB – MSSA and MRSA)[1,2] **but**:
  - TMP-SMX was initial treatment, not oral step-down; patients not necessarily clinically stable; blood cultures not necessarily negative; variable severity criteria i.e. this was not an EOS scenario

- Other studies demonstrate no difference in SAB relapse or 30-day mortality compared with standard treatment (but low quality)[3,4]

- Retrospective: 125 patients with complicated + uncomplicated SAB (excluding IE) had EOS after 8-17 days IV antibiotic - 66% oral TMP-SMX with no difference in 90-day recurrence between EOS and IV treatment[5]

- TMP-SMX + rifampicin: MRSA infection (only 9 patients with MRSA bacteraemia though): no significant difference clinical cure between those treated with linezolid versus TMP-SMX + rifamipcin[6]

(1) Paul BMJ 2015; (2) Markowitz Ann Intern Med 1992; (3) Goldberg J Antimicrob Chemother 2010; (4) Tissot-Dupont Int J Antimicrob Agents 2019; (5) Perez-Rodriguez IJID 2021; (6) Harbath J Antimicrob Chemother 2015

Beta-lactams – pharmacology

- Time-dependent antimicrobial activity
  - Expressed as **%fT>MIC** – the % of dosing interval where the free drug concentration is above the MIC

- We don't have validated %fT>MIC targets for EOS in SAB, but
  - Uncomplicated SAB: could be as low as 24% fT>MIC (animal models)[1,2,3]
    - Oral flucloxacillin 1g TDS or QID can achieve this[4]
  - Complicated SAB: a higher fT>MIC of >50% has been proposed[1,3]
    - Oral flucloxacillin 1g QID + probenecid 500mg QID can achieve this[1]
      - Same exposure found in some studies for patients taking flucloxacillin 2g q6 hourly IV

- Other beta-lactams actually have good oral absorption:
  - Amoxicillin 74-92% and cefalexin 90%[5]

- There is a post-antibiotic effect for *S.aureus:* might improve efficacy[5]

(1) Everts J Infect 2020; (2) Craig CID 1998; (3) Turnidge CID 1998; (4) Gardiner PLoSOne 2018; (5) MacGregor CID 1997.

Beta-lactams: clinical data

- Relatively sparse
- Bupha-Intr et al.: 84 patients with low-risk mostly MSSA-B treated with EOS
  - 86% oral beta-lactam, mainly flucloxacillin
  - Only one relapse, no SAB-related death[1]
- **'POET':** EOS versus continued IV treatment for IE
  - Included 87 patients with *S. aureus* IE (no MRSA)
  - 54% switched to oral antibiotics (35 of these had combination beta-lactam + another agent)
  - No difference in primary outcome for *S. aureus* IE groups though underpowered to draw conclusions

(1) Bupha-Intr Antimicrob Agents Chemother 2020; (2) Iversen NEJM 2019.

Clindamycin

- Attractive for EOS because good bioavailability & bone/abscess penetration
- 'Bacteriostatic', so traditionally has caused concern **but**
  - Little evidence worse clinical efficacy cf. 'bactericidal' drugs
- Few data on use in SAB treatment
- Kouijzer et al: 106 patients with complicated SAB
  - IE and endovascular infection excluded (echo, CT-PET)
  - 61 EOS after a median of 16 days IV
    - 88.5% of these received oral clindamycin
  - No relapses in either PO or IV group at 3 months

Kouijzer CID 2021

Other studies

- Review of oral antibiotics in endocarditis: data support further investigation[1]
  - Not exclusively *S. aureus* IE in this review
- '**OVIVA'** - oral antibiotics in bone and joint infection[2]: EOS non-inferior
  - Included *S. aureus* infections **but** SAB specifically excluded

(1) Spellberg JAMA Intern Med 2020; (2) Li NEJM 2019