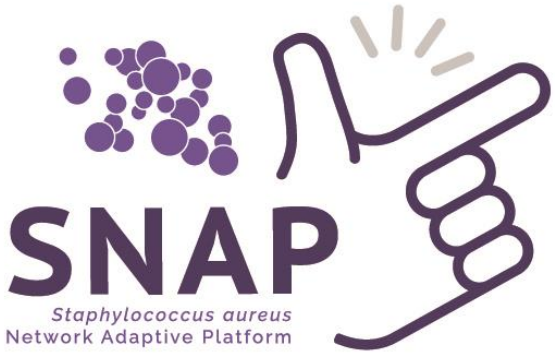

Pregnancy-Specific Appendix

Staphylococcus aureus Network Adaptive Platform trial (SNAP)

Pregnancy-Specific Appendix Version 3.0 dated 10 October 2024

Summary

This is an appendix within SNAP that aims to:

- Describe adaptations to the Core Protocol in order to test pregnancy outcomes and short- and long-term neonatal outcome data in pregnant patients hospitalised with SAB.
- To outline the safety of the investigational products in SNAP for pregnant women

SNAP: Synopsis of pregnancy specific protocol adaptations	
	SNAP PROTOCOL
TITLE	*Staphylococcus aureus* Network Adaptive Platform trial (SNAP)
BACKGROUND	*Staphylococcus aureus* bacteraemia (SAB) is a common and severe infection with a 90-day mortality of 15-30% despite current best available therapies. We are using an adaptive platform trial to allow us to simultaneously investigate the optimal treatments for the management of SAB. The trial will include 3 silos (PSSA, MSSA, and MRSA). We plan to test interventions within 3 initial domains, with the potential to add further domains to the platform.
ENDPOINTS	Primary platform endpoint: All-cause mortality at 90 days from platform entry. Secondary platform endpoints: refer to Core Protocol Section 6.8. Secondary pregnancy-specific endpoints: Same as core secondary outcomes, plus: 1. Spontaneous pregnancy loss (clinically recognised pregnancy involuntarily ending before 20 weeks) 2. Intrauterine foetal demise (foetal death that occurs after 20 weeks gestation but before birth. If the gestational age is unknown at the time of death, a foetus that weighs ≥350 g is considered an IUFD) 3. Stillbirth (baby born with no signs of life at or after 28 weeks' gestation) 4. Preterm birth (birth occurring before 37 weeks) 5. Congenital anomalies/birth defects that are present at birth or stillbirth that are of prenatal original that were detected within 6 weeks post delivery, arising from any pregnancy of a participant 6. Peripherally inserted central catheter (PICC)/other central venous catheter complications requiring line removal, during the total index hospitalisation 7. Any peripherally inserted central catheter (PICC)/other central venous catheter associated venous thromboembolism (superficial or deep venous thrombosis) during the total index hospitalisation 8. Neonatal ICU admissions 9. Neonatal mortality (infant death before 28 days of life) 10. Birth weight 11. Gestational age at birth
PLATFORM SPECIFIC INCLUSIONS	These are the same as for the overall Core Protocol Section 6.5. Eligibility criteria for inclusion in the pregnancy-specific domain would include any of the following:

	- Positive pregnancy test (urinary or serum HCG, intrauterine pregnancy by ultrasound) - Patient-report of pregnancy
PLATFORM SPECIFIC EXCLUSIONS	These are the same as for the overall Core Protocol Section 6.5.
STUDY DOMAINS	1. Antibiotic Backbone Domain 2. Adjunctive Treatment Domain 3. Early Oral Switch Domain 4. PET/CT Domain
NUMBER OF PARTICIPANTS	The initial trial funding and infrastructure will aim to enrol up to 6,000 participants into the platform. Not powered for sub-group analysis for pregnancy but if sufficient numbers, may be suitable for this. Harmonised outcome reporting will allow for meta-analysis with international studies.

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1. ABBREVIATIONS AND GLOSSARY

CrCl	Creatinine Clearance
CRF	Case Report Form
CRRT	Continuous Renal Replacement Therapy
DSA	Domain-Specific Appendix
DSWG	Domain-Specific Working Group
DSMC	Data and Safety and Monitoring Committee
ECOFF	Epidemiological cut-off values
GTSC	Global Trial Steering Committee
HD	Haemodialysis
HITH	Hospital In The Home
ICU	Intensive Care Unit
IUFD	Intrauterine Foetal Death
MIC	Minimum Inhibitory Concentration
OPAT	Outpatient Parenteral Antimicrobial Therapy
MRSA	Methicillin-resistant *Staphylococcus aureus*
MSSA	Methicillin-susceptible *Staphylococcus aureus*
PD	Peritoneal Dialysis
PI	Principal Investigator
PICC	Peripherally Inserted Central Catheter
PO	Oral administration
PSSA	Penicillin-susceptible *Staphylococcus aureus*
RSA	Region-Specific Appendix
SAB	*Staphylococcus aureus* Bacteraemia
SAE	Serious Adverse Event
SNAP	*Staphylococcus aureus* Network Adaptive Platform trial
TCPS2	The Tri-Council Policy Statement
TMP-SMX	Trimethoprim plus sulfamethoxazole

2. PROTOCOL APPENDIX STRUCTURE

The structure of this protocol is different to that used for conventional trials because this trial is highly adaptive and the description of these adaptations is better understood and specified using a 'modular' protocol design. While all adaptations are pre-specified, the structure of the protocol is designed to allow the trial to evolve over time, for example by the introduction of new domains or interventions or both, and commencement of the trial in new geographical regions.

The protocol has multiple modules, in brief, comprising a Core Protocol (overview and design features of the study), a Statistical Analysis Appendix (details of the current statistical analysis plan and models, including simulations to support trial design), multiple Domain-Specific Appendices (DSA) (detailing all interventions currently being studied in each domain), and multiple Region-Specific Appendices (RSA) (detailing regional management and governance).

The Core Protocol contains all information that is generic to the trial, irrespective of the regional location in which the trial is conducted and the domains or interventions that are being tested. The Core Protocol may be amended but it is anticipated that such amendments will be infrequent.

The Core Protocol does not contain information about the intervention(s) within each domain, because one of the trial adaptations is that domains and interventions will change over time. Information about interventions, within each domain, is covered in a DSA. These Appendices are anticipated to change over time, with removal and addition of options within an existing domain, at one level, and removal and addition of entire domains, at another level. Each modification to a DSA will be subject to a separate ethics application for approval.

The Core Protocol does not contain detailed information about the statistical analysis or simulations, because the analysis model will change over time in accordance with the domain and intervention trial adaptations but this information is contained in the Statistical Analysis Appendix. These Appendices are anticipated to change over time, as trial adaptations occur. Each modification will be subject to approval from the Global Trial Steering Committee (GTSC) in conjunction with advice from the Statistical Subcommittee and the Data and Safety Monitoring Committee (DSMC).

The Core Protocol also does not contain information that is specific to a particular region in which the trial is conducted, as the locations that participate in the trial are also anticipated to increase over time. Information that is specific to each region that conducts the trial is contained within a RSA. This includes information related to local management, governance, and ethical and regulatory aspects. It

is planned that, within each region, only that region's RSA, and any subsequent modifications, will be submitted for ethical review in that region.

The current version of the Core Protocol, DSAs, RSAs, and the Statistical Analysis Appendix is listed in the Protocol Summary and on the study website (https://www.snaptrial.com.au/).

3. PREGNANCY-SPECIFIC APPENDIX VERSION

The version of the Pregnancy-Specific Appendix is in this document's header and on the cover page.

3.1. *Version history*

Version 1.0: Approved by the Pregnancy Working Group on the 29th of March 2021

Version 2.0: Approved by the Pregnancy Working Group on the 24th of March 2023

Version 3.0: Approved by the Pregnancy Working Group on the 10th October 2024

4. PREGNANCY-SPECIFIC GOVERNANCE

4.1. *Working Group Members*

Chair: Prof Asha Bowen

Members:
Dr Isabelle Malhamé
Dr Erica Hardy
Prof Steven Tong
Dr Anita Campbell
Dr Rachel Webb
A/Prof Emma Best
Dr Srinivas Murthy
A/Prof Amanda Gwee
Dr Philip Britton
Dr Lesley Voss
Dr Kevin Schwartz
Dr Brendan McMullan

Dr Oded Scheuerman

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Dr Jesse Papenburg

Dr James Hatcher

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4.2. *Contact Details*

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5. PREGNANCY WORKING GROUP AUTHORISATION

The Pregnancy Working Group have read the appendix and authorise it as the official Pregnancy-Specific Appendix for the study entitled SNAP. Signed on behalf of the committee,

Chair Prof Asha Bowen  Date 10 October 2024

6. BACKGROUND AND RATIONALE

6.1. *Introduction*

Since 1994, the Institute of Medicine has recommended that pregnant women be presumed eligible for participation in clinical studies and the Tri-Council Policy Statement on the Ethical Conduct for Research Involving Humans (TCPS2 2018) states, under Article 4.3, "Women shall not be inappropriately excluded from research solely on the basis of their reproductive capacity, or because they are pregnant or breastfeeding" (1). The exclusion of pregnant women from clinical trials not only reduces the external validity of the results, but also renders a disservice to pregnant women with *Staph aureus* bacteraemia who would be denied optimal therapeutic agents in the future, on account of minimal data in pregnancy (2). As a result, pregnant women may be undertreated because of lack of therapeutic options evaluated in pregnancy, or inadequately treated because of exposure to therapies that are not evidence based and/or therapies that lack safety data (2). In addition, if stepdown oral therapy is found to be effective in the SNAP trial, results may be particularly beneficial to pregnant and postpartum women who may have an increased risk of thrombotic complications from long-term IV lines (3, 4). Moreover, pregnant women being of an overall median age <50 years are expected to have a lower risk of cardiovascular complications from *Staph aureus* bacteraemia.

7. TRIAL DESIGN

7.1. *Pregnancy-specific eligibility criteria*

In addition to the eligibility criteria outlined in the Core Protocol, pregnancy-specific safety considerations and outcome data relevant to this appendix are for patients enrolled in SNAP who are pregnant.

Eligibility criteria for inclusion in the pregnancy-specific domain would include any of the following:

- Positive pregnancy test (urinary or serum HCG, intrauterine pregnancy by ultrasound)
- Patient-report of pregnancy

7.2. ***Endpoints***

7.2.1. Primary outcome

The primary endpoint for this appendix is the SNAP primary outcome (all-cause mortality at 90 days after platform entry) as specified in Core Protocol Section 6.8

7.2.2. Secondary outcomes

All secondary outcomes as specified in the Core Protocol Section 6.8.

Pregnancy-specific secondary outcome measures will be:

1. Spontaneous pregnancy loss (clinically recognised pregnancy involuntarily ending before 20 weeks)
2. Intrauterine foetal demise (foetal death that occurs after 20 weeks gestation but before birth. If the gestational age is unknown at the time of death, a foetus that weighs ≥350 g is considered an IUFD)
3. Stillbirth (baby born with no signs of life at or after 28 weeks' gestation)
4. Preterm birth (birth occurring before 37 weeks)
5. Congenital anomalies/birth defects that are present at birth or stillbirth that are of prenatal original that were detected within 6 weeks post-delivery, arising from any pregnancy of a participant (5)
6. Peripherally inserted central catheter (PICC)/other central venous catheter complications requiring line removal, during the total index hospitalisation
    a. This outcome will be collected at hospital/OPAT discharge as a Y/N question. It will include any of the following: catheter-related blood stream infection; exit site infection; catheter-related superficial or deep venous thrombosis/thrombophlebitis; catheter blockage. It will NOT include PICC line rupture, leakage, displacement, or splitting unless it results in or occurs in addition to one of the above events.
7. Any peripherally inserted central catheter (PICC)/other central venous catheter associated venous thromboembolism (superficial or deep venous thrombosis) during the total index hospitalisation
8. Neonatal ICU admissions
9. Neonatal mortality (infant death before 28 days of life)
10. Birth weight
11. Gestational age at birth

Note that "total index hospitalisation" includes Initial hospital admission to an acute inpatient facility, including HITH/OPAT and stepdown inpatient rehabilitation/post-acute care (if continuous with the initial inpatient admission)

7.2.3. Rationale for these pregnancy specific outcomes

Collection of pregnancy specific outcomes will allow for the evaluation of obstetric and neonatal outcomes in the context of *S. aureus* bacteraemia.

8. TRIAL CONDUCT

8.1. *Pregnancy-specific data collection*

8.1.1. Pregnancy-specific study timeline

Table 1. Pregnancy-specific schedule of visits, data collection and follow-up.

Visit	**Platform Day 1**	**Acute Hospital discharge**[1]	**12 weeks gestation** (collect data from 12wks+0days to 12wks+6days)	**28 weeks gestation** (collect data from 28wks+0days to 28wks+6days)	**38 weeks gestation** (collect data from 38wks+0days to 38wks+6days)	**42 weeks gestation** (collect data from 42wks+0days to 42wks+6days)	**6 weeks after birth** (collect data from 6wks+0days to 6wks+6days)
Check eligibility (pregnancy)	X						
Informed consent	X						
Collect pregnancy-specific data as per the CRFs[2]	X	X	X	X	X	X	X

[1] End of the acute index admission (Continuous hospital admission to one or more acute inpatient facilities for the index episode. This does not include HITH/OPAT/COPAT and stepdown inpatient rehabilitation/post-acute care)

[2] All data to be collected by telephone call to the patient. If pregnancy loss occurs, discontinue secondary outcome follow-up for pregnancy related outcomes at the time of pregnancy loss. If the participant is in hospital at any of these time points, data can be collected, where possible, from the medical records.

8.1.2. Pregnancy-specific study visit day details

All core study visit details are specified in the Core Protocol (Section 8.8). Additional pregnancy-specific study procedures are outlined below. At pregnancy-specific study visit days we will be collecting pregnancy-specific outcomes. If discharged from hospital, data will be collected by telephoning the participant.

8.1.2.1. Screening

Screening procedures are outlined in the Core Protocol section 8.8. Additional eligibility criteria relevant to this appendix is outlined in section 7.1.

8.1.2.2. Platform Day 1

In addition to the activities outlined in the Core Protocol section 8.8, additional consent procedures for pregnant patients will occur as outlined in section 9.1.

8.1.2.3. Acute index hospital discharge

Collect data as per the pregnancy specific CRFs. This includes spontaneous pregnancy loss, intrauterine foetal demise, stillbirth, preterm birth, PICC/other central venous catheter complications.

8.1.2.4. 12 weeks gestation (12wks+0days to 12wks+6days)

Collect data as per the pregnancy specific CRFs. This includes spontaneous pregnancy loss, intrauterine foetal demise, stillbirth, preterm birth.

If pregnancy outcome occurs during this period, record pregnancy outcome.

8.1.2.5. 28 weeks gestation (28wks+0days to 28wks+6days)

Collect data as per the pregnancy specific CRFs. This includes spontaneous pregnancy loss, intrauterine foetal demise, stillbirth, preterm birth.

If pregnancy outcome occurs during this period, record neonatal ICU admissions, neonatal mortality, birth weight, and gestational age at birth.

8.1.2.6. 38 weeks gestation (38wks+0days to 38wks+6days)

Collect data as per the pregnancy specific CRFs. This includes spontaneous pregnancy loss, intrauterine foetal demise, stillbirth, preterm birth.

If pregnancy outcome occurs during this period, record neonatal ICU admissions, neonatal mortality, birth weight, and gestational age at birth.

8.1.2.7. 42 weeks gestation (42wks+0days to 42wks+6days)

Collect data as per the pregnancy specific CRFs. This includes spontaneous pregnancy loss, intrauterine foetal demise, stillbirth, preterm birth.

If pregnancy outcome occurs during this period, record neonatal ICU admissions, neonatal mortality, birth weight, and gestational age at birth.

8.1.2.8. When the infant is 6 weeks old (6wks+0days to 6wks+6days)

Collect data as per the pregnancy specific CRFs. This includes spontaneous pregnancy loss, intrauterine foetal demise, stillbirth, preterm birth and or the presence of a congenital anomaly/birth defect arising from any pregnancy of a participant (or partner).

If pregnancy outcome occurs during this period, record neonatal ICU admissions, neonatal mortality, birth weight, and gestational age at birth.

9. ETHICAL CONSIDERATIONS

9.1. *Pregnancy-specific consent issues*

In addition to the procedures for obtaining informed consent outlined in the Core Protocol, an additional pregnancy-specific information sheet will be provided to pregnant women to address details about the drugs included in the adaptive platform that pregnant women may be eligible to be randomised to and additional follow up procedures.

9.2. *Domain specific considerations*

For each domain, the existing safety data for each drug in pregnant women has been considered by the Pregnancy Working Group and Global Trial Steering Committee. Only therapeutics with established maternal, fetal and neonatal safety data will be eligible to be offered to pregnant women.

9.2.1. Domain specific therapeutics offered to pregnant women

9.2.1.1. Antibiotic Backbone Domain

PSSA/MSSA Backbone Domain Interventions

Study treatment (dose and duration) will be as per the PSSA/MSSA domain-specific appendix, with no alterations for pregnant patients.

In summary, dosing for PSSA/MSSA backbone antibiotics are as follows:

Table 2. Dosing for PSSA/MSSA backbone antibiotics.

Indication	Benzylpenicillin	Cloxacillin	Flucloxacillin	Cefazolin
Standard dose	1.8 g (3 MU) IV 4-hourly, or (2.4 g [4 MU] IV 6-hourly)	2 g IV 4-hourly	2 g IV 6-hourly	2 g IV 8-hourly
High dose Critically unwell (ie patients in ICU) or IE or CNS infection	2.4 g (4 MU) IV 4-hourly (FDA max dose 18 g/day)	2 g IV 4-hourly (FDA max dose 12 g/day)	2 g IV 4-hourly (FDA max 12 g/day)	2 g IV 6-hourly (FDA max dose 12 g/day)

ICU: intensive care unit. IE: infective endocarditis. CNS: central nervous system. IV: intravenous. MU: million units.

For renal dosage adjustments, please refer to the domain-specific appendices.

MRSA Backbone Domain Interventions

Study treatment (dose and duration) will be as per the MRSA domain-specific appendix, with no alterations for pregnant patients.

In summary, dosing for MRSA backbone antibiotics are as follows:

Table 3. Dosing for MRSA backbone antibiotics.

Vancomycin	Daptomycin	Cefazolin
Sites may follow local guidelines for the use of vancomycin. In general, it would be expected that dosing follows similar principles as those in the Australian Therapeutic Guidelines: Antibiotic and the consensus guidelines from the American Society of Health-System Pharmacists, the Infectious Diseases Society of America, the Paediatric Infectious Diseases Society, and the Society of Infectious Diseases Pharmacists. This includes a loading dose of 25 mg/kg (up to 3000mg) if considered appropriate by the treating clinician, initial maintenance dosing at 15-20 mg/kg q12h, with subsequent adjustment to maintain area under the concentration-time curve (AUC) of 400 to 600 mg.hr/L OR trough levels at 10-20 mg/L, and the initial level taken 48-72 hours after the initiation of the first dose. Please see the MRSA DSA for full details.	Where daptomycin is used we recommend that the higher 8-10mg/kg per day dosing be followed.	2 g IV 8-hourly

For renal dosage adjustments, please refer to the domain-specific appendices.

9.2.1.2. Adjunctive Treatment Domain

Study treatment (dose and duration) will be as per the adjunctive treatment domain-specific appendix, with no alterations for pregnant patients.

In summary, dosing for adjunctive antibiotics are as follows:

- Clindamycin 600mg IV q8h for 5 days
    - Substitute with IV lincomycin 600mg q8h if clindamycin is not available
    - No dosage adjustment is needed in renal impairment
    - OR option for PO clindamycin 450mg PO q8h, for part of all of the treatment course, at discretion of site PI.

9.2.1.3. Early Oral Switch Domain

Table 4. Hierarchy of recommended oral antibiotics for early oral switch by silo (i.e. susceptibility of *S. aureus*)

Silo	Recommended oral antibiotic according to allocated backbone domain	
PSSA	**Penicillin**	**(Flu)cloxacillin**
	1. Amoxicillin 2. Flucloxacillin/dicloxacillin 3. Cefalexin/cefadroxil	1. Flucloxacillin/dicloxacillin 2. Amoxicillin 3. Cefalexin/cefadroxil
MSSA	**(Flu)cloxacillin**	**Cefazolin**
	1. Flucloxacillin/dicloxacillin 2. Cefalexin/cefadroxil	1. Cefalexin/cefadroxil 2. Flucloxacillin/dicloxacillin
MRSA*	**Vancomycin/daptomycin**	**Vancomycin/daptomycin + cefazolin**
	1. Clindamycin 2. TMP-SMX	1. Clindamycin 2. TMP-SMX

*TMP-SMX only suitable during the 2nd trimester. Avoid in 1st and 3rd trimester.

Table 5. Antibiotic options for early oral switch in SAB – dosing, administration, pharmacological properties.

Principles:

- For beta-lactams, maximum doses have been recommended to overcome theoretical issues with drug exposure (bioavailability). Lower doses in specific circumstances have been recommended in the footnotes.
- Dosing regimens to minimise patient inconvenience have been prioritised, as explained in footnotes.
- Doses are suggestions only and alternate doses used as standard local practice can be maintained.
- Contraindications, including significant drug interactions, are not listed and are the responsibility of the prescribing team to review and manage. Some considerations are provided to aid the choice of drug.
- We have not recommended dose changes for obesity or pregnancy in the setting of early oral switch (i.e. step-down therapy after a period of intravenous therapy/source control/clinical stability). Despite a potential effect of obesity and pregnancy on pharmacokinetics (increased volume of distribution), we will not proceed to dose adjustment for step-down therapy.
- With increased creatinine clearance in pregnancy, there is a theoretical concern that the concentration of the antibiotics may not be over the required MIC for a sufficient period of time. However, general practice in obstetric dosing of antibiotics is to dose at the highest end of the dosing range, as is currently planned in the SNAP study.

Drug	**Standard Dose**	**Dose in renal impairment[1,2]**	**Bio-availability**	**Fasting**	**Protein binding**	**Pregnancy category[3]**	**Half life**	**Break point or ECOFF**
Amoxicillin	1g 6-hourly [4,5]	CrCl 10 to 30mL/min and CRRT: 1g 8-hourly. CrCl less than 10mL/min, HD and PD: 1g 12-hourly.	74-92%	No	17-20%	Safe to use all trimesters	1.2-1.5 hours	ND

[1] Dose derived from Australian Therapeutic Guidelines: Antibiotic v16, 2019, Sandford Guide and Licensed Product Information from FDA.

[2] HD: haemodialysis, PD: peritoneal dialysis.

[3] Please see Pregnancy appendix for further detail

[4] Dose derived from POET trial (Partial Oral versus Intravenous Antibiotic Treatment of Endocarditis) (6).

[5] Probenecid (dose: 500mg if CrCl 60 mL/min or more, 250mg if CrCl between 60 to 30 mL/min, do not use if CrCL less than 30 mL/min) may be co-administered with each dose of beta-lactam to improve drug exposure. Administer with amoxicillin 1g q6h or 1g q8h at the discretion of the treating clinician. We recommend giving probenecid with food to prevent nausea.

Cefadroxil	1g 12-hourly	CrCl 10-50mL/min or CRRT: 1g stat then 500mg 12-hourly. CrCl less than 10mL/min: 1g stat then 500mg 36-hourly. HD: 1g stat and 1g post HD PD: 500mg 24-hourly.	90%	No	20%	Safe to use all trimesters	1.5 hours	ND
Cefalexin	1g 6-hourly[6,7]	CrCl less than 10mL/min, HD or PD: 1g 12 hourly. CRRT: standard dose.	90%	No	10-19%	Safe to use all trimesters	1 hour	8 (ECOFF)
Ciprofloxacin PLUS rifampicin (use only in combination)	**Ciprofloxacin**750mg 12-hourly	CrCl less than 30mL/min, HD, PD: 750mg 24-hourly. CRRT: 250 to 500mg 12-hourly.	70%	No[8]	20-40%	Avoid in pregnancy	4 hours	BP: 0.001 ECOFF: 1.0
	Rifampicin: Weight <60kg: 600 mg per day; weight >60kg:	No change to standard dose.	70-90%	Yes[12]	80%	Reasonable to use in trimester 1 and 2; monitoring required trimester 3 (liver function tests at baseline, Week 1, 2 and 4). May be	3 hours	BP: 0.06 ECOFF: 0.016

[6] Clinical efficacy in uncomplicated SAB has been demonstrated at a dose of 1g orally q8h (7)

[7] Probenecid (dose: 500mg if CrCl 60 mL/min or more, 250mg if CrCl between 60 to 30 mL/min, do not use if CrCL less than 30 mL/min) may be co-administered with each dose of beta-lactam to improve drug exposure. Administer with cefalexin 1g q6h or 1g q8h at the discretion of the treating clinician. We recommend giving probenecid with food to prevent nausea.

[8] Ledergerber et al. Effect of standard breakfast on drug absorption and multiple-dose pharmacokinetics of ciprofloxacin (8)

[12] Ideally, administer 30 minutes before or two hours after a meal.

	900mg per day.[9,10,11]					associated with increased risk of haemorrhagic disorders in newborn.		
Clindamycin	450mg 8-hourly[13]	No change to standard dose	55% or 90%	No	94%	Reasonable to use all trimesters	2.4 hours	0.25
Cloxacillin	1g 6-hourly[14]	No change to standard dose.	32-50%	No[15]	94%	Reasonable to use all trimesters	0.5 hours	0.5
Dicloxacillin	1g 6-hourly[16,17]	CrCl less than 10mL/min, HD or PD: 1g q8h. CRRT: standard dose.	35-76%	No[18]	95%	Reasonable to use all trimesters	0.7 hours	0.5

[9] Doses above 600 mg per day should be divided into two doses.

[10] Use with caution in liver disease - can cause hepatotoxicity.

[11] Dose derived from the ARREST trial (9)

[13] For oral administration 450mg is the maximum dose licensed by the TGA. Clindamycin dosed 8-hourly showed significantly longer bactericidal activity against *S. aureus* when compared to 12-hourly regimens, (87.5 to 100% versus 49.6 to 77.1%, P < 0.001) (10)

[14] Probenecid (dose: 500mg if CrCl 60 mL/min or more, 250mg if CrCl between 60 to 30 mL/min, do not use if CrCL less than 30 mL/min) may be co-administered with each dose of beta-lactam to improve drug exposure. Administer with cloxacillin 1g q6h at the discretion of the treating clinician. We recommend giving probenecid with food to prevent nausea.

[15] Product information advises administration in the fasting state to maximise bioavailability, but this may make adherence difficult. Data that show decreased clinical efficacy when administered with food are lacking. We have recommended a high dose to optimise drug concentrations if administration in the fasted state is not possible.

[16] Dose derived from POET trial (6)

[17] Probenecid (dose: 500mg if CrCl 60 mL/min or more, 250mg if CrCl between 60 to 30 mL/min, do not use if CrCL less than 30 mL/min) may be co-administered with each dose of beta-lactam to improve drug exposure. Administer with dicloxacillin 1g q6h or 1g q8h at the discretion of the treating clinician. We recommend giving probenecid with food to prevent nausea.

[18] Product information advises administration in the fasting state to maximise bioavailability, but this may make adherence difficult. Data that show decreased clinical efficacy when administered with food are lacking. We have recommended a high dose to optimise drug concentrations if administration in the fasted state is not possible.

Doxycycline	100mg 12-hourly	No change to standard dose.	90%	No[19]	93%	Avoid in pregnancy	18 hours	ECOFF 0.5
Flucloxacillin	1g 6-hourly[20,21]	CrCl less than 10mL/min, HD or PD: 1g q8h. CRRT: standard dose.	44-55%	No[22]	95%	Reasonable to use all trimesters	0.75 hours	0.5
Fusidic acid PLUS rifampicin (use in combination only)	**Fusidic acid:** 500mg 8- to 12-hourly	No change to standard dose.	91%	No	95-99%	Data scarce in human pregnancy; avoid	8-10 hours	BP: 1 ECOFF: 0.5
	Rifampicin: Weight <60kg: 600 mg per day; weight >60kg: 900mg per day.[23, 24]	No change to standard dose.	70-90%	Yes[25]	80%	Reasonable to use in trimesters 1 and 2; monitoring required in trimester 3 (liver function tests at baseline, Week 1, 2 and 4). May be associated with increased risk of haemorrhagic disorders in newborn).	3 hours	BP: 0.06 ECOFF: 0.016

[19] Taking doxycycline on an empty stomach can cause nausea.

[20] Clinical efficacy in uncomplicated SAB has been demonstrated at a dose of 1g orally q8h (7)

[21] Probenecid (dose: 500mg if CrCl 60 mL/min or more, 250mg if CrCl between 60 to 30 mL/min, do not use if CrCL less than 30 mL/min) may be co-administered with each dose of beta-lactam to improve drug exposure. Administer with flucloxacillin 1g q6h or 1g q8h at the discretion of the treating clinician (11). We recommend giving probenecid with food to prevent nausea.

[22] Although the product information recommends administration in the fasting state to maximise bioavailability, administration with food is unlikely to reduce efficacy in most situations (12). We have recommended a high dose of flucloxacillin to optimise drug concentrations.

[23] Doses above 600 mg per day should be divided into two doses.

[24] Use with caution in liver disease - can cause hepatotoxicity.

[25] Ideally, administer 30 minutes before or two hours after a meal.

Levofloxacin PLUS rifampicin (use in combination only)	**Levofloxacin:** 750mg daily	CrCl 20-49mL/min: 750mg q48h. CrCl< 20mL/min,HD,PD: 750mg initial dose; then 500mg q48h CRRT: 250mg 24-hourly[26]	99%	No	24-38	Avoid in pregnancy	7 hours	ECOFF 0.25
	Rifampicin: Weight <60kg: 600 mg per day; weight >60kg: 900mg per day.[27, 28]	No change to standard dose.	70-90%	Yes[29]	80%	Safe to use trimester 1 and 2; monitoring required trimester 3 (liver function tests at baseline, Week 1, 2 and 4). May be associated with increased risk of haemorrhagic disorders in newborn).	3 hours	BP: 0.06 ECOFF: 0.016
Linezolid	600mg 12-hourly[30, 31]	CrCl less than 10mL/min, HD or PD: 600mg 24-hourly[32]. CRRT: standard dose.	100%	No	30%	No data in human pregnancy; avoid.	5 hours	BP: 4 ECOFF: ND

[26] Malone RS et al. Pharmacokinetics of levofloxacin and ciprofloxacin during continuous renal replacement therapy in critically ill patients (13)

[27] Doses above 600 mg per day should be divided into two doses.

[28] Use with caution in liver disease - can cause hepatotoxicity.

[29] Ideally, administer 30 minutes before or two hours after a meal.

[30] Risk of haematological toxicity increases with use beyond 14 days (14)

[31] Pyridoxine 50mg-100mg/day to prevent or delay anaemia can be considered if using linezolid for > 7 days; evidence for benefit conflicting (15)

[32] The optimal dose of linezolid in renal impairment is unknown, alternative doses include 300 mg 12-hourly or 600 mg 12-hourly. Patients are at an increased risk of thrombocytopenia if continued on 600mg 12-hourly in the setting of renal impairment. Therapeutic drug monitoring aiming for a trough concentration between 2 and 7mg/L is recommended for patients on linezolid with renal impairment (16).

Moxifloxacin PLUS rifampicin (use in combination only)[33]	**Moxifloxacin:** 400mg daily	No change to standard dose.	89%	No	30-50	Avoid in pregnancy	10- 14 hours	ECOFF 0.5
	Rifampicin: Weight <60kg: 600 mg per day; weight >60kg: 900mg per day.[34, 35]	No change to standard dose.	70-90%	Yes[36]	80%	Safe to use trimester 1 and 2; monitoring required trimester 3 (liver function tests at baseline, Week 1, 2 and 4). May be associated with increased risk of haemorrhagic disorders in newborn).	3 hours	BP: 0.06 ECOFF: 0.016
Tedizolid	200mg once daily	No change to standard dose.	91%	No	70-90%	Little data in pregnancy; should only be used if the benefit justifies the potential risk to the fetus.	12 hours	BP: ≤ 0.5
Trimethoprim plus sulfamethoxazole (TMP+SMX)	320/1600 mg 12-hourly or 160/800 mg 8-hourly	CrCl 26-50mL/min: normal for 14 days, then 160/800mg 12-hourly.	70-90%	No	44/70%	Avoid in first and third trimesters	11 hours	2 (TMP)

[33] Rifampicin may reduce serum concentrations of moxifloxacin, though the clinical significance of this interaction remains uncertain. Consider using another quinolone in combination with rifampicin.

[34] Doses above 600 mg per day should be divided into two doses.

[35] Use with caution in liver disease - can cause hepatotoxicity.

[36] Ideally, administer 30 minutes before or two hours after a meal.

		CrCl 15 to 25mL/min: normal for 3 days, then 320/1600mg 24-hourly. For CrCl less than 15mL/min: avoid use.[37]						

[37] Sulfamethoxazole can cause pancreatic insulin release, resulting in clinically significant hypoglycaemia, particularly in patients with renal impairment, receiving high doses, or concomitantly taking a sulfonylurea (17)

9.2.1.4. PET/CT Domain

Due to the radiation requirements for PET-CT and the risks of high-dose ionising radiation, pregnant people are excluded from this domain for safety reasons for the developing foetus. Other imaging modalities are preferred to PET-CT where imaging is clinically indicated (18-20).

10.GOVERNANCE ISSUES

10.1. *Funding of pregnancy-specific appendix*

Funding sources for SNAP are specified in the Core Protocol.

10.2. *Appendix-specific declarations of interest*

All investigators involved in SNAP maintain a registry of interests on the SNAP website. These are updated periodically and publicly accessible on the study website.

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