NeoSep1

COUNTRY SPECIFIC APPENDIX - <COUNTRY>

NEOSEP1 SITES

List of relevant details per site

CENTRAL MICROBIOLOGY LABORATORY

Add central laboratory identified for country.

FIRST-LINE RANDOMISATION LISTS

Based on local protocols and typical patients, sites have identified specific subgroups of neonates based on combinations of whether they were born pre-term or term, inborn or outborn, age at sepsis onset, and presence of specific signs and symptoms, e.g. of meningitis. These basically reflect the clinical view of the risk that sepsis is due to a less or more resistant organism and therefore that its treatment requires narrower or broader treatment options. Each subgroup of babies would be assigned to one of the lists below by the site, based on their clinical experience. However, if for example, a particular type of pathogen became more prevalent, the site could assign the subgroup to a different list, generally reflecting broadening of activity, and individual antibiotics could also be removed from specific lists to reflect this.

Table 1: First-line randomisation lists

List	Randomised between	Description and typical subgroup
A	Penicillin* + gentamicin Fosfomycin + amikacin Flomoxef + amikacin Fosfomycin + flomoxef	Most narrow option plus three repurposed novel regimens, excluding third generation cephalosporin. Used for early onset / in born populations considered to be at relatively low risk.
B	Penicillin* + gentamicin Cefotaxime or ceftriaxone Fosfomycin + amikacin Flomoxef + amikacin Fosfomycin + flomoxef	#1 but also including third generation cephalosporin. Used for early onset / in born populations at relatively low risk in sites where cephalosporins are used.
C	Penicillin* + gentamicin Cefotaxime or ceftriaxone Fosfomycin + amikacin Flomoxef + amikacin Fosfomycin + flomoxef Ceftazidime + amikacin Piperacillin/tazobactam + amikacin	Range of options from narrower to broader with some ESBL coverage. Used for early onset / inborn at higher risk or late onset / outborn considered to be at lower risk where there are questions about the relative benefits of broader spectrum antibiotics
D	Cefotaxime or ceftriaxone Fosfomycin + amikacin Flomoxef + amikacin Fosfomycin + flomoxef Ceftazidime + amikacin Piperacillin/tazobactam + amikacin	#3 but excluding penicillin* + gentamicin as this would not be considered an option in some sub-populations
E	Fosfomycin + amikacin Flomoxef + amikacin Fosfomycin + flomoxef	Broader spectrum options including the three repurposed novel regimens. Used for late

List	Randomised between	Description and typical subgroup
	Ceftazidime + amikacin Piperacillin/tazobactam + amikacin Meropenem	onset/outborn populations considered to be at moderate to high risk.
F	Fosfomycin + amikacin Flomoxef + amikacin Fosfomycin + flomoxef Ceftazidime + amikacin Meropenem	#5 but excluding piperacillin/tazobactam + amikacin which would not be used in neonates with meningitis at some sites and during periods where specific pathogens e.g. *Pseudomonas aeruginosa* were dominating local microbiology.

*Penicillin refers to a site-directed choice of one of ampicillin, benzylpenicillin, cloxacillin or amoxicillin.

SECOND-LINE RANDOMISATION LISTS

Reflecting the fact that switching to second-line generally reflects relapse or failure to respond initially, for each first-line regimen, sites will select appropriate second-line regimens from the lists below for second-line randomisation at their site. Sites may have separate second-line randomisation lists for neonates with and without high suspicion of meningitis if local practice would be to not use specific regimens (e.g. piperacillin/tazobactam) in neonates with high suspicion of meningitis. Sites could remove specific regimens from second-line randomisation lists for example if susceptibility patterns on the unit changed. Clinical practice in some sites includes maintaining amikacin in second-line regimens even if it has been included in first-line, and therefore this would be a local decision. There is no requirement to randomise a neonate to second-line if the options on the relevant randomisation list are not judged appropriate by the treating physician for that neonate (including where susceptibility results are available, see **Section 7.4**); in this case the neonate would be switched to a second-line regimen chosen based on clinical judgement.

Table 2: Second-line randomisation lists

First-line	Second-line options for site-specific randomisation lists chosen from
Penicillin* + gentamicin	Cefotaxime or ceftriaxone Fosfomycin + amikacin Flomoxef + amikacin Fosfomycin + flomoxef Ceftazidime + amikacin Piperacillin/tazobactam + amikacin† Meropenem Locally selected therapy
Cefotaxime or ceftriaxone	Fosfomycin + amikacin Flomoxef + amikacin Fosfomycin + flomoxef Ceftazidime + amikacin Piperacillin/tazobactam + amikacin† Meropenem Locally selected therapy
Fosfomycin + amikacin	Flomoxef + amikacin Fosfomycin + flomoxef Ceftazidime + amikacin Piperacillin/tazobactam + amikacin† Meropenem

First-line	Second-line options for site-specific randomisation lists chosen from
	Locally selected therapy
Flomoxef + amikacin	Fosfomycin + amikacin Fosfomycin + flomoxef Ceftazidime + amikacin Piperacillin/tazobactam + amikacin† Meropenem Locally selected therapy
Fosfomycin + flomoxef	Fosfomycin + amikacin Flomoxef + amikacin Ceftazidime + amikacin Piperacillin/tazobactam + amikacin† Meropenem Locally selected therapy
Ceftazidime + amikacin	Fosfomycin + amikacin Flomoxef + amikacin Fosfomycin + flomoxef Piperacillin/tazobactam + amikacin† Meropenem Locally selected therapy
Piperacillin/tazobactam + amikacin	Fosfomycin + amikacin Flomoxef + amikacin Fosfomycin + flomoxef Ceftazidime + amikacin Meropenem Locally selected therapy
Meropenem	Fosfomycin + amikacin Flomoxef + amikacin Fosfomycin + flomoxef Locally selected therapy

*Penicillin refers to a site-directed choice of one of ampicillin, benzylpenicillin, cloxacillin or amoxicillin.

† Piperacillin/tazobactam (or other antibiotics) could be removed from second-line randomisation lists for neonates with high suspicion of meningitis based on local clinical practice.