NHS
Greater Glasgow and Clyde

CLINICAL GUIDELINE

Isolates reported as 'I' (susceptible increased exposure) - dosing schedules for neonates and children

A guideline is intended to assist healthcare professionals in the choice of disease-specific treatments.

Clinical judgement should be exercised on the applicability of any guideline, influenced by individual patient characteristics. Clinicians should be mindful of the potential for harmful polypharmacy and increased susceptibility to adverse drug reactions in patients with multiple morbidities or frailty.

If, after discussion with the patient or carer, there are good reasons for not following a guideline, it is good practice to record these and communicate them to others involved in the care of the patient.

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Important Note:

The Intranet version of this document is the only version that is maintained.
Any printed copies should therefore be viewed as 'Uncontrolled' and as such, may not necessarily contain the latest updates and amendments.

Antibiotic dosing guidelines: Treatment of isolates reported as 'I' – dosing schedules for neonates and children.

Purpose and Scope:

The purpose of this guideline is to provide antibiotic dosing guidance for use in neonates and children where isolates are reported as 'I' on microbiology reports, or where advised by the Microbiology or Infectious Diseases Teams. A susceptibility category of 'I' indicates that a specific dosing schedule is required in order for the antibiotic to effectively treat the infecting organism.

The scope of this guidance encompasses the management of neonates and children treated in NHS Greater Glasgow and Clyde. The doses advised in this guidance are relevant only in certain 'bug-drug' combinations and should be used ONLY where a susceptibility category of 'I' has been assigned, or where specifically recommended by a specialist in infection management.

The doses in the guidance may not be applicable to the management of meningitis. Clinical breakpoints for meningitis may differ from breakpoints for non-meningitic conditions – it must not be assumed that these breakpoints and susceptibility reports are interchangeable. Contact Microbiology for further advice.

The doses advised in this guidance are appropriate for patients with normal renal and hepatic function. Where there is known or suspected renal or hepatic impairment a risk vs benefit decision should be made, taking in to account the increased exposure required to treat the organism effectively.

Background:

Reporting of antibiotic susceptibility is from microbiology labs is changing, in line with updated EUCAST (European Committee on Antimicrobial Susceptibility Testing) recommendations. Previously, isolates reported as having 'intermediate' sensitivity were problematic as the definition failed to guide clinical practice, and there was a tendency to class this as 'non-susceptible'.

The new susceptibility definitions of 'S', 'I' and 'R' are defined below, and emphasise the close relationship between the susceptibility of the organism and exposure of the organism to an antibiotic at the site of infection. These definitions provide two levels of 'susceptible' and only one level of 'resistant'.

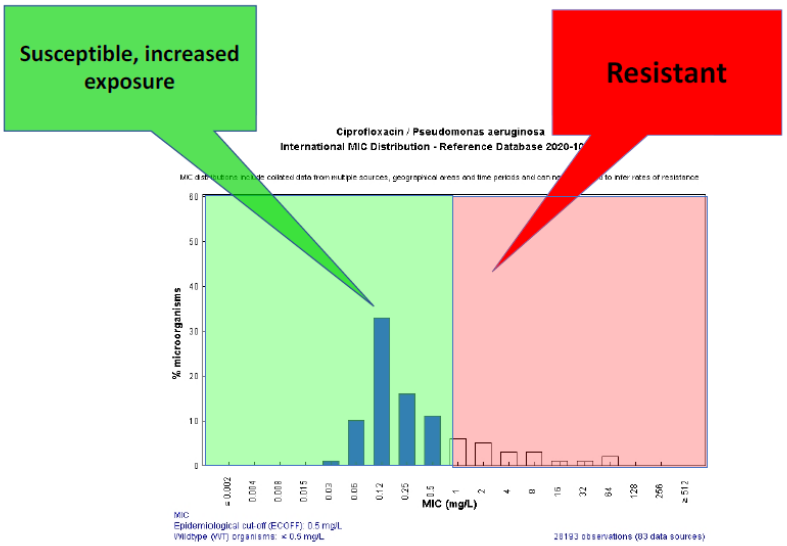
Acronym	Susceptibility status	Definition
S	Susceptible – standard exposure	High likelihood of therapeutic success using standard dosing regimens.
I	Susceptible – increased exposure	High likelihood of therapeutic success with exposure to the agent is increased by adjusting the dosing regimen or the concentration at the site of infection
R	Resistant	High likelihood of therapeutic failure. Use is discouraged irrespective of dose or mode of administration.

So what do we mean by *exposure?*

"Exposure" is a function of how the mode of administration, dose and dosing interval, in conjunction with the general pharmacokinetics and pharmacokinetics of the drug at the site of infection, will influence the antimicrobial affect. The clinical breakpoints of a number of bug-drug combinations have been reviewed and revised to match these new definitions.

Under new definitions, organisms that are intrinsically less sensitive to an agent cannot be categorized as 'S – standard exposure'. Where such isolates are devoid of any resistance mechanisms they will be categorized as 'I – increased exposure', identifying the need for more agent at the site of infection to achieve a successful clinical outcome with this species.

Example: *Pseudomonas aeruginosa* and *Ciprofloxacin*

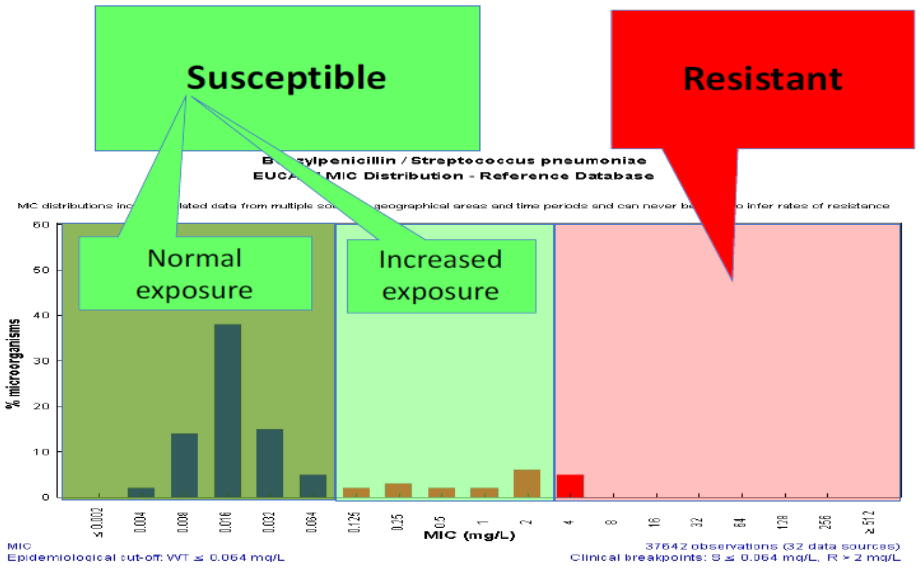


The clinical breakpoint for 'S' has been set at a value of ≤0.001mg/L, meaning that to be classed as fully sensitive at standard dosing, the 'minimum inhibitory concentration' (MIC) would need to be 0.001mg/L or below. An MIC >0.5mg/L confers resistance or 'R'. For MICs falling between 0.001mg/L and 0.5mg/L, a categorization of 'I' can be applied. As the MIC for this bug-drug combination will never be ≤0.001mg/L, 'I' will become the routine susceptible category.

Isolates of Pseudomonas aeruginosa will therefore only be defined as 'I' or 'R'.

For most bug-drug combinations <u>all 3 categories</u> may be used. Organisms with no inherent resistance will be categorized as 'S', whilst those with discrete mechanisms or resistance may still be treated successfully, depending on the MIC and site of infection, provided that they are exposed to enough drug.

Example: *Streptococcus pneumoniae* and *Benzylpenicillin*



Isolates where the MIC is <0.06mg/L (those with no intrinsic resistance) are 'S', whereas those with an MIC >2mg/L are 'R'. For isolates with some intrinsic resistance, where the MIC is between 0.06mg/L and 2mg/L, benzylpenicillin still offers a valuable treatment option, provided meningitis is not a concern and the dosing regimen selected provides increased exposure to the drug.

Aminoglycosides

EUCAST have also issued additional guidance on the *"Implementation and use of Revised Aminoglycoside Breakpoints".* As part of the review of antibiotics susceptibility testing, EUCAST have recommended that aminoglycoside breakpoints should only be reported with a susceptibility interpretation where the infection has originated from the urinary tract. In systemic infection, aminoglycosides must be used in combination with other active therapy, and the epidemiological cut off (ECOFF) used to distinguish between those with and without a resistance mechanism.

The Scottish Antimicrobial Prescribing Group (SAPG) and the Scottish Microbiology and Virology Network (SMVN) have reviewed the surveillance data for Scotland and concluded the aminoglycosides remain important agents in our empirical infection guidelines. There have been no reported concerns regarding clinical efficacy nor have there been significant changes in resistance patterns identified. In addition, aminoglycosides are integral to our wider antimicrobial stewardship programme, limiting the use of broader spectrum antibiotics. To this effect, Microbiology laboratories in Scotland will continue to report aminoglycoside susceptibility with 'sensitive' or 'resistant' interpretations, regardless of infection source. Agreement has been made that a comment will accompany gram negative bacteraemia reports advising to avoid the use of single agent aminoglycosides as definitive monotherapy.

Breakpoints not included in EUCAST:

Occasionally isolates may be identified where certain bug:drug combinations are not included within EUCAST. For these isolates, the Microbiology Laboratory uses additional guidance (CLSI) to determine likely susceptibility, which may include a report of 'Intermediate' susceptibility. The dosing guidance contained within this document can still be applied in these circumstances however such organisms should be discussed with Microbiology.

Clinical Practice:

So what does this all mean in clinical practice?

Where an organism is reported on the microbiology laboratory system as either 'S' or 'I', that drug can and should be considered as a valid option for treatment provided an appropriate dosing regimen is selected. Additional consideration must be given in the management of meningitis, and this should be discussed with Microbiology. Accurate sample collection and labelling is critical to ensure that appropriate advice and susceptibility reporting.

It is imperative that organisms reported as 'I' are not avoided. The overuse of newer or broader spectrum agents will further drive the development of antimicrobial resistance, risking our ability to manage such infections in the future.

The tables below offer guidance on regimens for increased exposure and are designed for use in neonates and children where sensitivities for an isolate are reported 'I'. They highlight the most commonly affected bug-drug combinations, however the dosing regimens can be applied to any isolate reported as 'I'. *Isolates reported as 'S' do not require increased exposure and should be dosed as per British National Formulary for Children (BNF-C)/West of Scotland (WoS) Neonatal monographs.*

AMIKACIN			
Drug class	Aminoglycoside		
Dose adjustments	Renal impairment – dose adjustment & close monitoring required Obesity - dose on adjusted ideal body weight		
Specific recommendations	Avoid monotherapy (EUCAST) unless isolated UTI **CF/NTM populations – dose as per BNF-C/NTM guidelines**		
INTRAVENOUS			
Neonates <32 CGA	Neonates ≥32 CGA - 28 days (CGA)	Children 1 month (CGA) – 12 years	Children >12 years
15mg/kg every 36 hours	15mg/kg every 24 hours	20mg/kg every 24 hours	15mg/kg every 24 hours
Check 'trough' level immediately prior to second dose. Aim level <5mg/L in normal renal function. If sufficient clearance re-check levels every 3 days or as per unit policy (neonates). For dosing in renal impairment contact Pharmacy for advice.			

AMOXICILLIN			
Drug class	Beta-lactam/Penicillin		
Dose adjustments	Renal impairment – dose adjustment may be required Hepatic impairment – dose with caution, monitor closely		
Specific recommendations	**Meningitis dose as per BNF-C** **Group B streptococcus in neonates follow WoS monographs**		
INTRAVENOUS			
Neonates (<7days)	Neonate (7- 28days)	Children 1 month – 18 years	
		<40kg	40kg and over
50mg/kg every 12 hours	50mg/kg every 8 hours	50mg/kg (max 2 grams) every 4 hours	2 grams every 4 hours
ORAL			
Neonates (7 days – 28 days)	Child 1 month – 4 years	Child 5 years- 11 years	Child 12 years – 18 years
30mg/kg (max 125mg) 3 x day	30mg/kg (max 500mg) 3 x day	30mg/kg (max 1 gram) 3 x day	1 gram 3 x day
For the treatment of organisms reported amoxicillin R, but co-amoxiclav S or I, amoxicillin may be added in combination with co-amoxiclav to increase the amoxicillin component of therapy.			

AZTREONAM				
Drug class	Monocyclic beta lactam (monobactam)			
Dose adjustments	Renal impairment – dose adjustment required Hepatic impairment – dose adjustment may be required, review as per SmPC			
Specific recommendations	**CF populations – dose as per BNF-C**			
INTRAVENOUS				
Neonates (<7 days)	Neonates ≥ 7days – 28 days WEIGHING< 2kg	Neonates ≥ 7days – 28 days WEIGHING ≥2kg	Children 1 month – <12 years	Child 12 – 17 years
30mg/kg every 12 hours	30mg/kg every 6 hours	30mg/kg every 6 hours	50mg/kg (max 2 grams) every 6 hours	2 grams every 6 hours

Administer by IV infusion over 30-60 minutes. For neonates >7days and >2kg, dose can be increased to 50mg/kg in critical illness

CEFOTAXIME			
Drug class	Beta-lactam/Cephalosporin		
Dose adjustments	Renal impairment – dose adjustment may be required. Hepatic impairment – monitor closely in severe impairment		
Specific recommendations			
INTRAVENOUS			
Neonates (<7 days)	Neonates 7 –20 days	Neonate 21 – 28 days	Child > 1 month
50mg/kg every 12 hours	50mg/kg every 8 hours	50mg/kg every 6 hours	50mg/kg (max 3 grams) every 6 hours
Administer by IV infusion over 30 – 60 minutes			

CEFTRIAXONE	
Drug class	Beta-lactam/Cephalosporin
Dose adjustments	Renal impairment – dose adjustment may be required. Hepatic impairment – monitor closely in severe impairment
Specific recommendations	
INTRAVENOUS	
Neonates (< 1 months post term CGA)	Child > 1 month (post term, CGA)
Not recommended	100mg/kg (max 4 grams) every 24 hours
Administer by IV infusion over 30 - 60 minutes. For doses >2 gram consider giving as 2 divided doses. Avoid co-administration of IV calcium containing solutions.	

CEFTAZIDIME			
Drug class	Beta-lactam/Cephalosporin		
Dose adjustments	Renal impairment – dose adjustment required. Hepatic impairment – monitor closely in severe impairment		
Specific recommendations	**Not suitable for the treatment of meningitis** **CF populations – dose as per BNF-C**		
INTRAVENOUS			
Neonates (<7 days)	Neonates 7 –20 days	Neonate 21 – 28 days	Child > 1 month
50mg/kg every 24 hours	50mg/kg every 12 hours	50mg/kg every 8 hours	50mg/kg (max 2 grams) every 8 hours
Administer by IV infusion over 30 minutes.			

CEFUROXIME			
Drug class	Beta-lactam/Cephalosporin		
Dose adjustments	Renal impairment – dose adjustment required		
Specific recommendations			
INTRAVENOUS			
Neonates (<7 days)	Neonates 7 –20 days	Neonate 21 – 28 days	Child > 1month – 18 years
50mg/kg every 12 hours	50mg/kg every 8 hours	50mg/kg every 6 hours	60mg/kg (max 1.5 grams) every 6 hours
Administer by IV infusion over 30- 60 minutes.			

CIPROFLOXACIN		
Drug class	Fluoroquinolone	
Dose adjustments	Renal impairment – dose adjustment may be required.	
Specific recommendations	Baseline ECG recommended – risk of QTc prolongation Monitor for toxicity – dose adjustment may be required in obesity	
INTRAVENOUS		
Neonates	Child > 1month (up to 40kg)	Child > 1month (40kg and over)
10mg/kg every 12 hours	10mg/kg (max 400mg) every 8 hours	400mg every 8 hours
The enteral bioavailability of ciprofloxacin is excellent. Reserve IV ciprofloxacin for patients where enteral absorption or delivery is compromised.		
ENTERAL		
Neonates	Child > 1month (up to 35kg)	Child > 1month (35kg and over)
15mg/kg every 12 hours	20mg/kg (max 750mg) every 12 hours	750mg every 12 hours
Absorption may be affected by administration via enteral feeding tubes. Monitor closely for signs of treatment response/failure. Avoid concomitant administration of multivalent cation containing drugs, mineral supplements, phosphate binders, sucralfate or antacids* (*not H2 antagonists) due to reduced absorption of ciprofloxacin. Avoid concomitant administration of dairy products or mineral-fortified drinks due to reduced absorption. Fluoroquinolones are associated with rare but disabling or potentially life-threatening adverse effects including adverse effects on the musculoskeletal and nervous system, heart valve regurgitation, aortic aneurysm and dissection. See Ciprofloxacin SmPC for further details on interaction and MHRA Drug Safety Updates March 2019 & Dec 2020 for further details on adverse events.		

CO-AMOXICLAV

Drug class	Beta-lactam/Penicillin
Dose adjustments	Renal impairment – dose adjustment may be required Hepatic impairment – dose with caution, close monitoring required
Specific recommendations	For *haemophilus influenza,* may be required in combination with amoxicillin to increase exposure to the penicillin component.

INTRAVENOUS

Neonates	Child 1 – 2 months	Child > 2month – 18 years
30mg/kg every 12 hours	30mg/kg every 8 hours	30mg/kg (max 1.2 grams) every 8 hours

ENTERAL

Neonates 0-27 days	Child 1-2 months	Child 2 – 23 months	Child 2- < 6 years (13-21kg)	Child 6- 12 years (22-40kg)	Child ≥12 years (≥ 41kg)
Use 125/31 suspension		**Use 400/57 suspension**		**Use 400/57 suspension**	
0.25ml/kg every 8 hours	0.5ml/kg every 8 hours	0.3ml/kg every 12 hours	5ml every 12 hours	10ml every 12 hours	10ml every 8 hours
				OR use 500/125 tabs	
				1 tab every 8 hours	1 tab every 8 hours (+ 1 x 250mg amoxicillin*)

*For ≥12 years and ≥41kg the penicillin exposure is increased by giving in combination with 1 x 250mg amoxicillin caps.

CO-TRIMOXAZOLE

Drug class	Sulphonamide:diaminopyrimidine combination (5:1)
Dose adjustments	Renal impairment – dose adjustment required. Severe hepatic impairment – close monitoring required
Specific recommendations	**Pneumocystis jirovecii (PCP) infection – refer to BNF-C** **G6PD deficiency – caution, risk of severe haemolysis** **Respiratory infection in Cystic Fibrosis – treat as per PCP infection**

INTRAVENOUS

Neonates	Child > 6 weeks – 17 years
Not recommended in < 6 weeks and until at least 4 weeks post term	27mg/kg every 12 hours *Increasing to 45mg/kg every 12 hours in complex infection or critical illness.*

Not recommended in infants <6 weeks age due to the risk of kernicterus, unless for treatment or prophylaxis of PCP.
Co-trimoxazole can cause bone marrow suppression – monitor FBC in prolonged treatment.

ENTERAL

Neonates	Child > 6 weeks – 18 years	
Not recommended in < 6 weeks	*Urinary tract infection*	24mg/kg (max 960mg) every 12 hours
	All other sites of infection	24mg/kg (max 1440mg) every 12 hours

For prophylaxis/treatment of PCP refer to relevant protocol and/or discuss with Pharmacy

GENTAMICIN		
Drug class	Aminoglycoside	
Dose adjustments	Renal impairment – dose adjustment & close monitoring required Obesity - dose on adjusted ideal body weight	
Specific recommendations	Avoid monotherapy (EUCAST) unless isolated UTI **For neonatal sepsis of unknown origin, follow WoS Neonatal monographs**	
INTRAVENOUS		
Neonates <32 wks CGA	Neonates ≥32wks - CGA -28 days	Children >1 month (CGA)
5mg/kg every 48 hours	5mg/kg every 24 hours	7mg/kg every 24 hours
Check 'trough' level prior to second dose. Aim level <1mg/L (children) or Level of <2mg/L (neonates). If sufficient clearance re-check levels every 3 days or as per unit policy (neonates) – aim for levels as above.		

MEROPENEM		
Drug class	Beta-lactam/Carbapenem	
Dose adjustments	Renal impairment – dose adjustment required. Hepatic impairment – close monitoring	
Specific recommendations	**For neonatal meningitis/sepsis of unknown origin, follow WoS Neonatal monographs**	
INTRAVENOUS		
Neonates <7 days	Neonates ≥7 days – child <50kg	Children ≥50kg
40mg/kg every 12 hours **as extended 3 hour infusion***	40mg/kg every 8 hours **as extended 3 hour infusion***	2 grams every 8 hours **as extended 3 hour infusion***
*Extended infusion times of 3 hours are recommended by EUCAST as a function of overall increased exposure, due to the pK/pD properties of meropenem. Extended infusions are not always practical however are strongly recommended in deep-seated infection and critically ill patients.		

PIPERACILLIN-TAZOBACTAM	
Drug class	Beta lactam/Penicillin + beta lactamase inhibitor
Dose adjustments	Renal impairment – dose adjustment required Hepatic impairment – close monitoring, no dose adjustment
Specific recommendations	**For neonatal sepsis of unknown origin, follow WoS Neonatal monographs**
INTRAVENOUS	
Neonates <28 days	Child 1 month – 18 years
90mg/kg every 8 hours **as extended 3 hour infusion****	90mg/kg* (max 4.5 grams) every 6 hours **as extended 3 hour infusion****
*Within RHC, doses should be rounded to the nearest dose-band as per RHC Piperacillin-tazobactam dose banding table to allow for CIVAS preparation in the Aseptic Services Unit. Dose banding is not applicable to neonates/neonatal units. **Extended infusion times of 3 hours are recommended by EUCAST as a function of overall increased exposure, due to the	

pK/pD properties of piperacillin-tazobactam. Extended infusions are not always practical however are strongly recommended in deep-seated infection and critically ill patients.

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