Doncaster and Bassetlaw Teaching Hospitals
NHS Foundation Trust

High Dose Antimicrobial Guideline

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Scope and background

This antimicrobial dosing guidance is for reported organisms that are susceptible to an antimicrobial, but only at the highest dose appropriate for that patient[1]. This will be documented on ICE Microbiology reports as: *'I= Susceptible, increased exposure'. The selected antibiotic should be prescribed at the highest safe dose (renal/liver adjusted) as outlined in this guideline.*

Antimicrobials listed within this high dose guideline include:

Please be aware that the risk of neuromuscular excitability or convulsions may be increased when using higher doses of penicillins in patients with renal impairment, especially where there is a history of convulsions.

Doses may need adjusting depending on patient factors such as renal and liver function (first dose especially in septic patients does not need adjusting). See individual drug sections below for further guidance. Please note that doses may need to be adjusted for extreme body weights, however this will need to be reviewed on an individual patient basis. If further advice required, please contact the Antimicrobial pharmacist or Consultant in Infection.

* Indicates that renal dosing advice has been adapted from the Renal Drug Database or other unlicensed sources and differs from the information in the product license. Therefore the patient should be informed that the recommended dose is off-license.

Amoxicillin PO for H.influenzae[2,3]

High oral dose	1g PO 8-hourly
High dose in renal impairment eGFR <10ml/min	500mg PO 8-hourly
PD/ HD/ HDF/High Flux	Dose as in GFR less than 10ml/min
High dose in hepatic impairment	Caution and monitor hepatic function

Azithromycin orally for Neisseria gonorrhoea[4,5,6]

High oral dose	**2g PO as a single dose**
High dose in renal impairment eGFR <10ml/min	Discuss with Microbiology
PD/ HD/ HDF/High Flux	Discuss with Microbiology
High dose in hepatic impairment	Avoid in severe liver disease

Aztreonam for Pseudomonas[7,8]		
High dose		**2g IV 6-hourly**
High dose in renal impairment	***eGFR 10 - 30***	2g IV loading dose, then 50% of the appropriate dose
	Less than 10	2g IV loading dose, then 25% of the appropriate dose
	PD	Dose as in GFR less than 10ml/min. Not dialysed.
	HD/HDF/High Flux	Dose as in GFR less than 10ml/min. Dialysed; give after dialysis.
High dose in hepatic impairment		A dose reduction of 20-25% is recommended for longer course for patients with chronic liver disease with cirrhosis, especially in cases of alcoholic cirrhosis and when renal function is also impaired.

Ceftazidime for Pseudomonas[9,10]		
High dose		**2g IV 8-hourly**
High dose in renal impairment	***eGFR 31 - 50***	2g IV12-hourly
	eGFR 16 - 30	2g IV 24-hourly
	eGFR 6 - 15	1g IV 24-hourly
	eGFR <5	1g IV 48-hourly
	HD	1g IV 48-hourly or post dialysis. Dialysed; give after dialysis
	HDF/High Flux	2g IV 48-hourly or post dialysis. Dialysed; give after dialysis
	PD	1g IV 24-hourly. Dialysed; give after dialysis
High dose in hepatic impairment		No dose adjustment required for mild to moderate hepatic dysfunction. Caution in using high doses in severe hepatic impairment.

Cefuroxime for Enterobacterales[11,12]		
High dose		**1.5g IV 8-hourly**
High dose in renal impairment	eGFR 10 - 20	1.5g IV 12-hourly
	eGFR < 10	1.5g IV 24-hourly
	HD/HDF/High Flux/CAPD	Dose as in GFR less than 10ml/min. Dialysed; give after dialysis.
High dose in hepatic impairment		No dose adjustment required

Ciprofloxacin orally for Pseudomonas or Staphylococci[13,14]

Only to be used where no appropriate alternative. Please be aware of the EMA and MHRA warnings about fluoroquinolone use:

-Risk of muscle, tendon and nervous system side effects. Please advise patients of the risk before prescribing and advise them to seek medical advice if they occur. Factors increasing the risk can be found in guidance here: EMA and MHRA

- Aortic aneurysm. Fluoroquinolones may increase risk of aortic aneurysm and dissection, particularly in older people. Factors increasing the risk and further information can be found here.

- Risk of psychiatric reactions with fluoroquinolones, including depression and psychiatric reactions, which may potentially lead to thoughts of suicide or suicide attempts. Further information can be found here

All patients should be informed of the above risks (verbally and in writing – see PIL here), and give consent to go ahead with this treatment. The conversation must be documented in their medical record.

High oral dose		750mg PO 12-hourly
High dose in renal impairment	***eGFR 10 - 30***	500mg PO 12-hourly
	eGFR <10	250mg PO 12-hourly
	PD/ HD/ HDF/High Flux	Dose as in GFR less than 10ml/min.
High dose in hepatic impairment		No dose adjustment required

Co-amoxiclav orally for H. influenzae [15,16]

High oral dose		**Co-amoxiclav 750mg/125mg PO every 8 hours (dose made up of co-amoxiclav 500mg/125mg tablet plus amoxicillin 250mg capsule)**
High dose in renal impairment	**eGFR <10**	Co-amoxiclav 500mg/125mg PO every 8 hours.
	PD/ HD/ HDF/High Flux	Dose as in GFR less than 10ml/min. Dialysed.
High dose in hepatic impairment		Caution and monitor hepatic function

Co-trimoxazole for Stenotrophomonas maltophilia[17,18]

High dose		**1.44g (IV or PO) 12-hourly**
High dose in renal impairment	***eGFR 15 - 30***	Use 50% of dose
	Less than 15/ PD/ HD/ HDF/High Flux	Often avoided, to discuss with Microbiology if other antibiotic options available.
High dose in hepatic impairment		Avoid in severe liver disease.

Fluconazole

For the treatment of fungal infections, please refer to the SYB Antifungal guidelines for Adult Patients on the HIVE.
Where an organism is reported as '*I= Susceptible, increased exposure, prescribe the highest safe dose with renal/liver adjustment.* Please contact Consultant in Infection or Antimicrobial Pharmacist if further advice needed.

Levofloxacin for Streptococcus pneumoniae[19,20]

Only to be used where no appropriate alternative. Please be aware of the EMA and MHRA warnings about fluoroquinolone use:
-Risk of muscle, tendon and nervous system side effects. Please advise patients of the risk before prescribing and advise them to seek medical advice if they occur. Factors increasing the risk can be found in guidance here: EMA and MHRA
- Aortic aneurysm. Fluoroquinolones may increase risk of aortic aneurysm and dissection, particularly in older people. Factors increasing the risk and further information can be found here.
- Risk of psychiatric reactions with fluoroquinolones, including depression and psychiatric reactions, which may potentially lead to thoughts of suicide or suicide attempts. Further information can be found here

All patients should be informed of the above risks (verbally and in writing – see PIL here), and give consent to go ahead with this treatment. The conversation must be documented in their medical record.

High dose		**500mg IV or PO 12 hourly**
High dose in renal impairment	***eGFR 20 - 50***	Initial dose 500mg (IV or PO) then 250mg 12 hourly
	eGFR 10 - 19	Initial dose 500mg (IV or PO) then125mg 12 hourly
	eGFR <10	Initial dose 500mg (IV or PO) then125mg 24 hourly
	HD/HDF/High Flux/CAPD	Dose as in GFR less than 10ml/min.
High dose in hepatic impairment		No dose adjustment required

Piperacillin/tazobactam for Pseudomonas[21,22]

High dose		4.5g IV 6-hourly
High dose in renal impairment	***eGFR 20 - 40***	4.5g IV 8-hourly
	eGFR < 20	4.5g IV 12-hourly
	HD*/HDF/High Flux/CAPD	Dose as in GFR less than 20ml/min.
High dose in hepatic impairment		No dose adjustment required

***Note, the manufacturer recommends that for patients on haemodialysis, one additional dose of piperacillin/tazobactam 2g/0.25g should be administered following each dialysis period, because haemodialysis removes 30-50% of piperacillin in 4 hours.**

Temocillin[23,24,25]

High dose		**2g IV 8-hourly**
High dose in renal impairment	***eGFR 41 - 60***	2g IV 12-hourly
	eGFR 20 - 40	2g IV stat, then 1g IV 12-hourly
	eGFR <20	2g IV stat, then 1g IV 24-hourly
	HD/HDF/High Flux/CAPD	Discuss with Consultant in Infection as alternative antibiotic therapy may be preferable. During OOH, a stat 2g dose can be given, but then discuss with Infection team or renal pharmacist the next working day.
High dose in hepatic impairment		No dose adjustment required.

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