Dosing and Therapeutic Drug Monitoring Amikacin Flucytosine and Teicoplanin Antibiotic Guidelines

<table>
<thead>
<tr>
<th>Lead Author:</th>
<th>Antibiotic Steering Group</th>
</tr>
</thead>
<tbody>
<tr>
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</tr>
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<td>Division/ Department:</td>
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<tr>
<td>Applies to:</td>
<td>Salford Royal Care Organisation</td>
</tr>
<tr>
<td>Approving Committee</td>
<td>Medicines Management Group</td>
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<tr>
<td>Date approved:</td>
<td>02/07/2020</td>
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<td>July 2025</td>
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It is your responsibility to check on the intranet that this printed copy is the latest version.
1. Overview (What is this guideline about?)

This document provides guidance on the dosing and required monitoring for three narrow therapeutic index antimicrobial agents - amikacin, flucytosine and teicoplanin.

2. Scope (Where will this document be used?)

This policy applies to all clinical staff involved in the prescribing of antimicrobials.

Associated Documents

- 144TD(C)25(A5) - Issue No 3.1 - Antimicrobial Stewardship Policy

- 163TD(C)(33) – Issue No. 14 - Medicines Policy

3. Background (Why is this document important?)

Antimicrobial agents are among the most commonly prescribed drugs and account for 20% of the hospital pharmacy budget. Unfortunately, the benefits of antibiotics to individual patients are compromised by the development of bacterial drug resistance. Resistance is a natural and inevitable result of exposing bacteria to antimicrobials.

Good antimicrobial prescribing will help to reduce the rate at which antibiotic resistance emerges and spreads. It will also minimise the many side effects associated with antibiotic prescribing, such as Clostridium difficile infection. It should be borne in mind that antibiotics are not needed for simple coughs and colds. In some clinical situations, where infection is one of several possibilities and the patient is not showing signs of systemic sepsis, a wait and see approach to antibiotic prescribing is often justified while relevant cultures are performed.

This document provides treatment guidelines for the most common situations in which antibiotic treatment is required. The products and regimens listed here have been selected by the Trust's Medicines Management Group on the basis of published evidence. Doses assume a weight of 60-80kg with normal renal and hepatic function. Adjustments may be needed for the treatment of some patients.

This document provides treatment guidelines for the appropriate use of antibiotics. The recommendations that follow are for empirical therapy and do not cover all clinical circumstances. Alternative antimicrobial therapy may be needed in up to 20% of cases. Alternative recommendations will be made by the microbiologist in consultation with the clinical team.

This document refers to the treatment of adult patients (unless otherwise stated).
Please refer to up to date BNF/SPC for a full list of cautions, contra-indications, interactions and adverse effects of individual drugs

4. What is new in this version?

- Amikacin section updated with links to ideal and adjusted body weight MD-calc calculator.
- Flucytosine monitoring section changed to table format to make it more readable. Link to peritonitis guideline in dosing section removed as that guideline no longer contains dosing advice for flucytosine. Safety advice added regarding use in dihydroptpyrimidine dehydrogenase (DPD) deficiency.
- Teicoplanin:
  - For severe S. Aureus/MRSA, deep seated infections and infective endocarditis: Increase the loading dose to 12mg/kg every 12 hours for 5 doses and the maintenance to 12mg/kg every 24 hours.
  - For serious Gram positive infections e.g. SSTI, pneumonia, UTI: Keep the current loading dose of 6mg/kg every 12 hours for 3 doses and the maintenance dose of 6mg/kg every 24 hours.
  - Increase the maximum single initial dose to be used from 1g to 1.2g as this has been used in HOPT for some time with no reported issues.
  - Adjustment to the renal dosing recommendations as per SPC.
  - Recommendation to check serum levels of teicoplanin weekly as per SPC.

5. Guideline

5.1 Amikacin

Amikacin is a semisynthetic aminoglycoside that is generally reserved for the treatment of severe infections caused by susceptible bacteria that are resistant to gentamicin. As with gentamicin, there is a risk of nephrotoxicity and ototoxicity during amikacin treatment and therefore doses should be calculated and monitoring carried out as described below.

Amikacin should ONLY be used on the advice of a microbiologist.

5.1.1. Dosing

Once Daily regimen: 15mg/kg 24 hourly

(should be calculated using ideal body weight (IBW) or adjusted body weight (ABW) if patient is more than 20% over their IBW).

The total daily dose should not exceed 1.5 g and the total cumulative dose should not exceed 15g.

IBW and ABW can be determined using an online calculator: https://www.mdcalc.com/ideal-body-weight-adjusted-body-weight
or by using the equations below.

**Ideal Body Weight (IBW)** may be calculated from:
- **Males:** $50\text{Kg} + 2.3\text{Kg}$ for every inch over 5 Feet
- **Females:** $45.4\text{Kg} + 2.3\text{Kg}$ for every inch over 5 Feet

**Adjusted body weight (ABW)** may be calculated from:

$$\text{ABW} = \text{Ideal body weight (IBW)} + 40\% \text{ of excess body weight (EBW)}$$

$$\text{Excess Body Weight (EBW)} = \text{actual body weight} - \text{ideal body weight}$$

For patients with endocarditis, febrile neutropenia or meningitis, a twice daily regimen should be used. Please contact pharmacy for further advice.

**Renal impairment**

For patients with $\text{CrCl} < 60\text{mls/min}$ there is a greater risk of toxicity with once daily dosing due to a protracted exposure to high trough levels. The following dosing regime should be used, based on calculated creatinine clearance (CrCl). CrCl may be calculated manually using the Cockcroft and Gault equation or by using an online calculator: [https://www.mdcalc.com/creatinine-clearance-cockcroft-gault-equation](https://www.mdcalc.com/creatinine-clearance-cockcroft-gault-equation)

Please speak to pharmacy for further advice on dosing.

<table>
<thead>
<tr>
<th>Calculated CrCl (ml/min)</th>
<th>Recommended dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>40-59</td>
<td>15mg/kg every 36 hours</td>
</tr>
<tr>
<td>20-39</td>
<td>15mg/kg every 48 hours</td>
</tr>
<tr>
<td>&lt;20</td>
<td>15mg/kg stat then re-dose when level &lt;5</td>
</tr>
</tbody>
</table>

**5.1.2. Monitoring**

**Once Daily regimen:**

A level should be taken **before the second dose** of amikacin. 

*The levels are sent to the Antimicrobial Reference Laboratory in Bristol (bloods are only processed Monday to Friday) and therefore the dose should NOT be withheld whilst awaiting the results.*

Pre dose level should be <5mg/L

If the trough level is satisfactory, continue Once Daily regimen, repeating levels twice weekly.
If the trough level is >5mg/L, recheck renal function and withhold any further doses until discussed with pharmacy and/or microbiology within normal working hours.

Creatinine and eGFR should also be monitored daily during treatment and dosing adjusted accordingly. If an Acute Kidney Injury occurs during treatment, please discuss with microbiology and/or pharmacy.

Multiple Daily Dose regimen:

Pre and Post dose levels should be taken around the third dose of amikacin.

The levels are sent to the Antimicrobial Reference Laboratory in Bristol (bloods are only processed Monday to Friday) and therefore the dose should NOT be withheld whilst awaiting the results.

5.2. Flucytosine

5.2.1. Dosing

In patients with CrCl>40mls/min, the usual dose is 100 - 200mg/kg daily in four divided doses.

MHRA and EMA safety alert:

Treatment with flucytosine is contraindicated in patients with known complete dihydropyrimidine dehydrogenase (DPD) deficiency, due to the risk of life-threatening toxicity.

• Patients with a partial DPD deficiency are also at increased risk of severe toxicity.
• Pre-treatment testing for DPD deficiency is however not required in order to avoid delay in starting flucytosine treatment.
• Determination of DPD activity may be considered where drug toxicity is confirmed or suspected.
• In case of drug toxicity (stomatitis, mucosal inflammation, diarrhoea, neutropenia, neurotoxicity), consideration should be given to stopping treatment with flucytosine.

5.2.2. Monitoring

<table>
<thead>
<tr>
<th>Route</th>
<th>Levels required</th>
<th>Timing of sample</th>
<th>Target level</th>
<th>Additional information</th>
</tr>
</thead>
<tbody>
<tr>
<td>PO</td>
<td>Pre-dose</td>
<td>Just before dose given</td>
<td>30-40mg/l</td>
<td>Levels&gt;100mg/l are potentially toxic.</td>
</tr>
<tr>
<td></td>
<td>Post-dose</td>
<td>2 hours after dose given</td>
<td>70-80mg/l</td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>Pre-dose</td>
<td>Just before dose given</td>
<td>30-40mg/l</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Post-dose</td>
<td>30 minutes after the end</td>
<td>70-80mg/l</td>
<td></td>
</tr>
</tbody>
</table>
Monitoring flucytosine is useful in all patients; essential if renal function impaired or if used in combination with amphotericin. Levels should be determined twice weekly, more frequently if renal function is changing.

Both a pre and a post-dose sample should be taken for most effective clinical management.

**Laboratory Services**

Levels must be received in the laboratory **before 9am** for same day analysis.

An on call service is available during weekends for **emergency use** only. Routine levels will **not** be processed out of hours.

### 5.3. Teicoplanin

Teicoplanin is a lipoglycopeptide antibacterial that may be used as an alternative to vancomycin in the treatment or prophylaxis of serious staphylococcal or other Gram-positive infections where other drugs cannot be used. It is a restricted antibiotic and must ONLY be prescribed on the advice of a microbiologist. Vancomycin should be used first line if a glycopeptide is required.

#### 5.3.1. Dosing and monitoring

*For dosing and monitoring of patients going home on IV teicoplanin for the treatment of cellulitis, please see the Pathway for Home IV Therapy for Cellulitis on the intranet.*

Teicoplanin is dosed according to the indication (as higher doses are needed in severe or deep seated infections), the patients Actual Body Weight* and their renal function. Recommended loading and maintenance doses are shown in Table 1.

Therapeutic drug monitoring is indicated in severe sepsis, MRSA infection, deep-seated staphylococcal and bone and joint infection. It is also indicated in cases of unexpected therapeutic failure and in the elderly or those with renal impairment.

- The first assay should be sent after 5 days treatment.
- Teicoplanin levels are sent to an external laboratory and take 1-3 days to return. They are not routinely tested at weekend so should ideally be sent earlier in the week (i.e. Mon-Wed) to avoid delays. If samples have to be sent after midday Thursday then please d/w microbiology department first.
• Please note that teicoplanin binds to glass and plastics and there may be a loss of drug if a small amount of blood is placed in a large tube. Therefore, please fill the tube to ¾ of its capacity.

• During maintenance treatment, teicoplanin levels should be performed once a week to ensure that concentrations are stable.

The relationship between toxicity and high levels is not well established, although there are reports of haematological toxicity being more common at levels >60mg/L.

### Table 1

<table>
<thead>
<tr>
<th>Indication</th>
<th>Loading dose*</th>
<th>Maintenance dose* (for patients with CrCl&gt;80mls/min</th>
<th>Target trough concentration during maintenance therapy (measured by FPIA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serious gram positive infections e.g. Complicated skin &amp; soft tissue infection*, Pneumonia, Complicated UTI</td>
<td>6mg/kg every 12 hours for 3 doses</td>
<td>6mg/kg every 24 hours</td>
<td>&gt;15mg/L</td>
</tr>
<tr>
<td>Severe S.aureus/MRSA or Deep seated infections such as osteomyelitis</td>
<td>12mg/kg every 12 hours for 5 doses</td>
<td>12mg/kg every 24 hours</td>
<td>&gt;20mg/L</td>
</tr>
<tr>
<td>Infective endocarditis</td>
<td>12mg/kg every 12 hours for 5 doses</td>
<td>12mg/kg every 24 hours</td>
<td>&gt;30mg/L</td>
</tr>
</tbody>
</table>

*NB: Maximum single dose of 1.2g to be used unless it is increased in response to plasma levels. 
*Higher doses may occasionally be recommended on the advice of a microbiologist.*

*Note dose of teicoplanin should be rounded to the nearest 200mg.*

### Renal impairment

Doses of teicoplanin should be adjusted in patients with renal impairment, though reduction is not required until the fourth day of treatment.

CrCl 30 - 80mls/min – dose as per Table 1 until day 4 and then give the maintenance dose every 48 hours.

CrCl<30mls/min- dose as per Table 1 until day 4 and then give the maintenance dose every 72 hours.
6. Roles and responsibilities

All clinical staff involved in the prescribing of antimicrobials to adhere to this policy including full documentation on EPMAR as detailed.

7. Monitoring document effectiveness

Key standards:

- Document the Indication/rationale for antimicrobial therapy, including clinical criteria relevant to this.
- Review and document the patient’s allergy status
- Ensure the choice of antibiotic complies with the antibiotic guidelines and you have documented any clinical criteria relevant to the choice of agent.
- Document a management plan including a stop or review date.
- Where relevant, consider drainage of pus or surgical

Method: Audits of compliance with the guideline will be conducted on a regular basis as part of the Antibiotic Point Prevalence study.

Team responsible for monitoring: Antibiotic audits are carried out by the Pharmacy team.

Frequency of monitoring: Monthly

Process for reviewing results and ensuring improvements in performance: Audit results are monitored by the Antibiotic Steering Group and results fed back to the relevant directorates where appropriate.

8. Abbreviations and definitions

BNF – British National Formulary
CAP – Community-acquired pneumonia
EPMAR – Electronic prescribing medication administration record
IV - Intravenous
MHRA - Medicines and Healthcare products Regulatory Agency

9. References


10. Appendices

Nil

11. Document Control Information

All sections must be completed by the author prior to submission for approval

<table>
<thead>
<tr>
<th>Lead Author:</th>
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</tr>
</tbody>
</table>

Consultation
List the persons or groups who have contributed to this guideline. (please state which Care Organisation)

<table>
<thead>
<tr>
<th>Name of person or group</th>
<th>Role / Department / Committee (Care Org)</th>
<th>Date</th>
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<tbody>
<tr>
<td>Consultant Microbiologists</td>
<td>SCO</td>
<td>Feb 2020</td>
</tr>
<tr>
<td>Antibiotic Steering Group</td>
<td>SCO</td>
<td>Feb 2020</td>
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Endorsement
List the persons or groups who have seen given their support to this guideline. (please state which Care Organisation)

<table>
<thead>
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<th>Name of person or group</th>
<th>Role / Department / Committee (Care Org)</th>
<th>Date</th>
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<tbody>
<tr>
<td>Elizabeth Trautt</td>
<td>Antibiotic Steering Group Chair SCO</td>
<td>May 2020</td>
</tr>
<tr>
<td>Alex Peel</td>
<td>Antibiotic Steering Group Chair SCO</td>
<td>Nov 2015</td>
</tr>
<tr>
<td>John MacDonald</td>
<td>Medicines Management Group Chair SCO</td>
<td>Mar 2015, Dec 2012</td>
</tr>
<tr>
<td>Paul Chadwick</td>
<td>Antibiotic Steering Group Chair SCO</td>
<td>Dec 2012, Jul 2010</td>
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</tbody>
</table>

Keywords / phrases:
Antibiotics, Infection, teicoplanin, flucytosine, amikacin, antibiotic, aminoglycoside, glycopeptide, monitor, TDM

Communication plan:
State below how the practice in this document will be rolled out across the organisation and embedded in practice

Document review arrangements:
This document will be reviewed by the author, or a nominated person, at least once every three years or earlier should a change in legislation, best practice or other change in circumstance dictate.
12. Equality Impact Assessment (EqIA) screening tool

Legislation requires that our documents consider the potential to affect groups differently, and eliminate or minimise this where possible. This process helps to reduce health inequalities by identifying where steps can be taken to ensure the same access, experience and outcomes are achieved across all groups of people. This may require you to do things differently for some groups to reduce any potential differences.

<table>
<thead>
<tr>
<th>1a) Have you undertaken any consultation/involvement with service users, staff or other groups in relation to this document?</th>
<th>Yes</th>
<th>Please state: Email distribution to microbiology consultant staff for comments. Discussions at Antibiotic Steering Group and Medicines Management Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>1b) Have any amendments been made as a result?</td>
<td>Yes – see changes to policy section</td>
<td></td>
</tr>
<tr>
<td>2) Does this guideline have the potential to affect any of the groups below differently or negatively?</td>
<td>This may be linked to access, how the process/procedure is experienced, and/or intended outcomes. Prompts for consideration are provided, but are not an exhaustive list.</td>
<td></td>
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<thead>
<tr>
<th>Protected Group</th>
<th>Yes</th>
<th>No</th>
<th>Unsure</th>
<th>Reasons for decision</th>
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<tbody>
<tr>
<td>Age (e.g. are specific age groups excluded? Would the same process affect age groups in different ways?)</td>
<td></td>
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<td>X</td>
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<td>Sex (e.g. is gender neutral language used in the way the guideline or information leaflet is written?)</td>
<td></td>
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<td>X</td>
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<tr>
<td>Race (e.g. any specific needs identified for certain groups such as dress, diet, individual care needs? Are interpretation and translation services required and do staff know how to book these?)</td>
<td></td>
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<tr>
<td>Religion &amp; Belief (e.g. Jehovah Witness stance on blood transfusions; dietary needs that may conflict with medication offered.)</td>
<td></td>
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<td>Sexual orientation (e.g. is inclusive language used? Are there different access/prevalence rates?)</td>
<td></td>
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<td>X</td>
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<tr>
<td>Pregnancy &amp; Maternity (e.g. are procedures suitable for pregnant and/or breastfeeding women?)</td>
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<td>Marital status/civil partnership (e.g. would there be any difference because the individual is/is not married/in a civil</td>
<td></td>
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Gender Reassignment (e.g. are there particular tests related to gender? Is confidentiality of the patient or staff member maintained?)  X

Human Rights (e.g. does it uphold the principles of Fairness, Respect, Equality, Dignity and Autonomy?)  X

Carers (e.g. is sufficient notice built in so can take time off work to attend appointment?)  X

Socio/economic (e.g. would there be any requirement or expectation that may not be able to be met by those on low or limited income, such as costs incurred?)  X

Disability (e.g. are information/questionnaires/consent forms available in different formats upon request? Are waiting areas suitable?) Includes hearing and/or visual impairments, physical disability, neurodevelopmental impairments e.g. autism, mental health conditions, and long term conditions e.g. cancer.  X

Are there any adjustments that need to be made to ensure that people with disabilities have the same access to and outcomes from the service or employment activities as those without disabilities? (e.g. allow extra time for appointments, allow advocates to be present in the room, having access to visual aids, removing requirement to wait in unsuitable environments, etc.)  X

3) Where you have identified that there are potential differences, what steps have you taken to mitigate these?

Not applicable

4) Where you have identified adjustments would need to be made for those with disabilities, what action has been taken?

Not applicable

5) Where the policy, procedure, guidelines, patient information leaflet or project impacts on patients how have you ensured that you have met the Accessible Information Standard – please state below:

...................................................................................................................................................................................................................................................................................

EDI Team/Champion only: does the above ensure compliance with Accessible Information Standard

 o Yes
 o No

If no what additional mitigation is required:

Will this guideline require a full impact assessment?  No

Please state your rationale for the decision: Update to existing policy and changes will not affect any protected groups differently

(a full impact assessment will be required if you are unsure of the potential to affect a group differently, or if you believe there is a potential for it to affect a group differently and do not know how to mitigate against this - Please contact the Inclusion and Equality team for advice on equality@pat.nhs.uk)

Author: Sue Wei Chong  Date: 16/6/2020