

ANTIBIOTIC GUIDELINES FOR THE EMPIRICAL TREATMENT OF SEPSIS IN IMMUNOCOMPETENT ADULTS

Version	<ul style="list-style-type: none">• 3.0
Date ratified	<ul style="list-style-type: none">• March 2009
Review date	<ul style="list-style-type: none">• March 2011
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Consultation	<ul style="list-style-type: none">• Nottingham <u>Antimicrobial</u> Guidelines Committee members
Evidence base	<ul style="list-style-type: none">• Local microbiological sensitivity surveillance and local audit of ESBL positive <i>E. coli</i> bacteraemias• Surviving sepsis campaign• Recommended best practice based on clinical experience of guideline developers
Changes from previous Guideline	<ul style="list-style-type: none">• Algorithm for treatment of sepsis based on risk of multi-resistant Gram negative infection
Inclusion criteria	<ul style="list-style-type: none">• Immuno-competent adult patients with sepsis
Exclusion criteria	<ul style="list-style-type: none">• Haematology and oncology patients, patients with neutropenic sepsis (see separate guidance)
Distribution	<ul style="list-style-type: none">• This guideline will be available on the Clinical Effectiveness Department Intranet page and the antibiotics guidelines websites: http://nuhnet/diagnostics_clinical_support/antibiotics
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This guideline has been registered with the Trust. Clinical guidelines are guidelines only. The interpretation and application of clinical guidelines will remain the responsibility of the individual clinician. If in doubt contact a senior colleague. Caution is advised when using guidelines after a review date.

ANTIBIOTIC GUIDELINES FOR THE EMPIRICAL TREATMENT OF SEPSIS IN IMMUNOCOMPETENT ADULTS

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Vancomycin and Gentamicin dosing / monitoring and calculation of GFR.

These guidelines detail the empirical antibiotic treatment of sepsis in immunocompetent adults. Please see separate guidelines for the treatment of neutropenic sepsis at:

http://nuhnet/diagnostics_clinical_support/antibiotics

Neutropenic patients should be discussed with a senior member of the oncology or haematology team on-call.

General Guidance

In cases of sepsis in immunocompetent adults in whom the diagnosis is unknown, empirical therapy based upon the likeliest of sources of bacteraemia is necessary. If the source of sepsis is unknown please refer to the algorithm on page 7.

Appropriate microbiological specimens should always be taken before starting antibiotics. This should include two sets (four bottles) of blood cultures, each set taken from separate sites (20ml/set). Blood cultures should also be taken from all intravascular devices present, including central lines and Hickman lines and labelled stating which line they were taken from.

Appropriate antibiotic therapy should be administered, within one hour for inpatients and within three hours of the time of presentation for patients being admitted.

Recent microbiology results should be reviewed to identify if the patient is at risk of sepsis with a more resistant organism, which may not respond to standard first line therapy.

Antibiotics are only part of the management of a patient with an infection. Further details about the management and investigation of sepsis can be found at the Surviving sepsis campaign website <http://www.survivingsepsis.org/>

Current trends in Antibiotic Resistance

MRSA and Serious Infection

At present in Nottingham about 20% of *Staphylococcus aureus* bacteraemias and septicaemias in adult patients are due to meticillin resistant *S. aureus* i.e. MRSA; which will not be sensitive to the agents frequently used for *S. aureus* sepsis, e.g. flucloxacillin and cefuroxime.

MRSA infection is more likely in current inpatients, but patients admitted from the community are at risk of MRSA infection if they have any of the risk factors listed below:

- Recent treatment as an inpatient in the last 6 months or as an outpatient with an indwelling line
- Previous MRSA infection or colonisation
- Long-term urinary catheter
- Resident of a nursing or residential home with breaks in their skin e.g. leg ulcers

Initial antibiotic treatment of sepsis of unknown aetiology or severe staphylococcal infections should therefore be altered to cover the possibility of MRSA in a patient who has any of these risk factors for MRSA infection. Further therapy should be adjusted in light of the microbiological culture and sensitivity results.

Multiresistant Gram Negative Bacilli (MRGNB)

Recent local, national and international surveillance has identified a worrying increase in multiple resistance to antibiotics in Gram-negative bacilli; particularly gentamicin, quinolone and cephalosporin resistant *E. coli*; with up to 10% resistant to gentamicin and 3rd generation cephalosporins (ESBL positive), and 19% resistant to ciprofloxacin. This is of concern as *E. coli* is the most common cause of community and hospital acquired Gram-negative sepsis.

Local surveillance has identified the following risk factors for ESBL positive *E. coli* or multi-resistant Gram negative sepsis:

- Previous history of isolation of ESBL positive *E. coli* or Multiresistant Gram negative organisms

OR

- Recurrent urinary or biliary tract infections (≥ 3 in last year)
- Sepsis despite current or recent (within the last week) treatment with broad-spectrum antibiotics e.g. co-amoxiclav, cefuroxime or quinolones (ciprofloxacin, levofloxacin)

To enable effective management of these patients, it is therefore important that appropriate specimens (including blood cultures) are taken and their previous microbiology reviewed.

Guidance on Initial Antibiotic Therapy by Body Site

All doses that are recommended in this guide are for those with normal renal function – please check doses if renal impairment on antibiotic website http://nuhnet/diagnostics_clinical_support/antibiotics

ABDOMINAL/BILIARY INFECTION

(See note regarding multi-resistant Gram negative bacilli (MRGNB) on page 4)

E.g. perforation of abdominal / gynaecological viscus – which is usually polymicrobial:

Co-amoxiclav IV 1.2 g tds

Or

If rash with penicillins Cefuroxime IV 1.5g tds (Not to be used in serious penicillin allergy, e.g. urticarial rash within the first 72 hours, anaphylaxis or angioedema)+ **Metronidazole IV 500mg tds**

If the patient has severe sepsis or the blood pressure fails to respond to initial fluid bolus:

+ **Gentamicin IV 5 mg/kg** (if normal renal function) as a single dose (max 500mg)

[See dosing advice in renal impairment page 13-15]

Further therapy

Review need for IV antibiotics at 48 hours with microbiology results see IV-PO switch guideline on antibiotics website.

Total duration of IV+PO therapy 7 days

OR if risk of MRGNB (see page 4)

Meropenem IV 1g tds (review antibiotics with microbiology within 48 hours)

(Not to be used in serious penicillin allergy, e.g. anaphylaxis, contact Microbiology for further advice)

If the patient has severe sepsis or the blood pressure fails to respond to initial fluid bolus:

+ **Gentamicin IV 5 mg/kg** (if normal renal function) as a single dose (max 500mg)

[See dosing advice in renal impairment page 13-15]

BONE AND JOINT INFECTION

Joint aspiration and or deep bone specimens for Gram stain and culture (prior to treatment if possible) are mandatory to establish the diagnosis and further management. If unable to obtain a specimen contact the on-call rheumatologist or orthopaedic surgeon.

Flucloxacillin IV 2g qds

(covers both Meticillin sensitive *S. aureus* and streptococcal infections)

Penicillin-allergy:

Clindamycin IV 600mg qds (change to oral when medically stable)

or

Cefuroxime IV 1.5g tds

(Not to be used in serious penicillin allergy, e.g. urticarial rash within the first 72 hours, anaphylaxis or angioedema)

If MRSA infection is a possibility (see page 3)

Vancomycin IV 1g bd

(If mild renal impairment or age >65 years, reduce frequency to 1g od, monitor levels - see page 12)

+ **Cefuroxime** IV 1.5 g tds (Not to be used in serious penicillin allergy, e.g. anaphylaxis)

If suspected/proven Gram negative infection (elderly patients and/or immunocompromised):

Cefuroxime IV 1.5g tds

(Not to be used in serious penicillin allergy, e.g. anaphylaxis)

If risk of MRGNB (see page 4) discuss treatment with the on call medical microbiologist

If suspected/proven gonococcal infection:

Ceftriaxone IV 1g od

(Not to be used in serious penicillin allergy, e.g. anaphylaxis)

Further therapy

Further therapy should be discussed with a medical microbiologist as antibiotic choice will need to be modified following the results of the Gram stain and culture. Staphylococcal bone and joint infections are commonly treated with more than one agent. If infection is confirmed the treatment is usually given for a total of 4-6 weeks of which 2 weeks is given IV.

CELLULITIS

Therapy is usually directed at *Streptococcus pyogenes* (group A β -haemolytic streptococcus) and *S. aureus*

When there are no signs of systemic upset, sepsis, or rapidly progressing cellulitis:

Flucloxacillin PO 500mg-1g qds or if penicillin allergy Clarithromycin PO 500mg bd (not if known/likely MRSA infection)

When more severe or failed adequate doses of oral flucloxacillin:

Community acquired

Flucloxacillin IV 2g qds (covers both *S. aureus* and *S. pyogenes*).

Changing to oral flucloxacillin when cellulitis receding and systemically stable

Review need for IV antibiotics at 48 hours with microbiology results see IV-PO switch guideline on antibiotics website, usual total length of treatment 5-7 days.

Penicillin allergy:

Clindamycin PO 450-600mg qds or IV 600mg qds if vomiting/ severe sepsis (change to oral when medically stable)

Hospital acquired or where MRSA is a possibility (see page 2)

Vancomycin IV 1g bd

(If mild renal impairment or age >65 years, reduce frequency to 1g od, monitor levels - see page 12)

If rapidly progressive cellulitis with shock, please discuss with a medical microbiologist as the possibility of deeper infection, particularly **necrotising fasciitis** should be considered, which is a *medical and surgical emergency* and modification of the antibiotic therapy maybe required.

Unresponsive infection may be due to another diagnosis eg varicose eczema, where a dermatology opinion may be appropriate.

INFECTIVE ENDOCARDITIS

It is essential to collect three sets of blood cultures, from separate sites (20ml per set) before treatment.

NOTE: All therapy and investigation of cases of endocarditis or possible endocarditis should be discussed with Microbiology/Infectious Diseases. Therapy is determined by positive microbiology results. If the patient fulfils the Dukes criteria for diagnosis but cultures are negative therapy is directed to the likely causative organisms as advised by microbiology. Please see separate guidance available on the antibiotic website: http://nuhnet/diagnostics_clinical_support/antibiotics

LINE INFECTION

- **PERIPHERAL CANNULA (VENFLON) SITE**

Usually due to *S. aureus* sepsis, 20% of which are resistant to flucloxacillin i.e. MRSA.

Remove the cannula

If pus at site of an old venflon site, or mild erythema, but no signs of sepsis, take blood cultures and swab any pus:

Doxycycline PO 100 mg bd for one day then 100mg od for 6 days, which is active against most MRSA and MSSA.

Monitor line site closely to check response to treatment.

Any signs of severe infection, or spreading cellulitis:

Vancomycin IV 1g bd

(If mild renal impairment or age >65 years, reduce frequency to 1g od, monitor levels - see page 12)

Change to IV **Flucloxacillin 1-2 g qds** if MSSA is isolated.
Review need for IV antibiotics at 48 hours with microbiology results see IV-PO switch guideline on antibiotics website.

If meets criteria for oral switch and negative blood cultures PO

Flucloxacillin 500mg-1g qds.

Total duration of IV+PO therapy 7 days, 14 days if positive blood cultures

- **CENTRAL LINES (for haemodialysis, TPN and haematology lines see separate specialty guidance)**

Exit site infection (without sepsis)

If pain around exit site, purulent discharge or erythema / Induration around exit site, take blood cultures through the line and peripherally and swab any pus.

For temporary central lines

Remove line

Vancomycin IV 1g bd (If mild renal impairment or age >65 years, reduce frequency to 1g od, monitor levels - see page 12). Review need for vancomycin at 48 hours with clinical response and blood culture results.

Line-associated bacteraemia due to *S. aureus* should be treated with a minimum of 14 days antibiotic therapy after line removal.

Change to **Flucloxacillin** IV 1-2g qds if MSSA is isolated and not allergic.

Central-line associated bacteraemia due to Coagulase negative staphylococci may respond to antibiotics without line removal, but relapse is common.

Tunnelled line exit site infection

Assess tunnelled track for erythema, tenderness or induration and if present see guideline below on tunnel-track infections.

Doxycycline 100mg PO BD (1st day) then OD for 14 days

or **Flucloxacillin** 500mg-1g qds if known MSSA and not allergic for 14 days

Tunnelled line track infections (Hickman lines and other tunnelled lines)

Remove line if possible

Vancomycin IV 1g bd (If mild renal impairment or age >65 years, reduce frequency to 1g od, monitor levels - see page 12).

Change to **Flucloxacillin** IV 1-2g qds if meticillin sensitive *S. aureus* is isolated and not allergic.

Review antibiotics with culture results

If difficult infection, discuss with microbiology regarding the addition of a second agent.

Line-associated bacteraemia due to *S. aureus* should be treated by a minimum of 14 days antibiotic therapy after line removal

For Central Line-associated Sepsis

Remove line if possible

Vancomycin IV 1g bd (If mild renal impairment or age >65 years, reduce frequency to 1g od, monitor levels - see page 12).

If the patient has severe sepsis or the blood pressure fails to respond to initial fluid bolus:

+ **Gentamicin** IV 5 mg/kg (if normal renal function) as a single dose (max 500mg)

[See dosing advice in renal impairment page 13-15]

Review antibiotic choice with culture results

Change to **flucloxacillin** IV 1-2g qds if MSSA is isolated.

MENINGITIS See separate guidelines.

PNEUMONIA See separate guidelines.

UROSEPSIS

(See note regarding multi-resistant gram negative bacilli on page 4)

Pyelonephritis is usually due to Gram negative bacilli:

Co-amoxiclav IV 1.2 g tds

Or

If rash with penicillins

Cefuroxime IV 1.5g tds (Not to be used in serious penicillin allergy, e.g. urticarial rash within the first 72 hours, anaphylaxis or angioedema)

If the patient has severe sepsis or the blood pressure fails to respond to initial fluid bolus:

+ **Gentamicin** IV 5 mg/kg (if normal renal function) as a single dose (max 500mg)

[See dosing advice in renal impairment page 13-15]

Further therapy

Review need for IV antibiotics at 48 hours with microbiology results see IV-PO switch guideline on antibiotics website.

Total duration of IV+PO therapy 7-10 days

OR

OR if risk of MRGNB (see page 4)

Meropenem IV 1g tds (review antibiotics with microbiology within 48 hours)

(Not to be used in serious penicillin allergy, e.g. urticarial rash within the first 72 hours, anaphylaxis or angioedema, please discuss with a medical microbiologist)

If the patient has severe sepsis or the blood pressure fails to respond to initial fluid bolus:

+ **Gentamicin** IV 5 mg/kg (if normal renal function) as a single dose (max 500mg)

[See dosing advice in renal impairment page 13-15]

OR

if patient has a severe allergy to penicillins (e.g. urticarial rash within the first 72 hours, anaphylaxis or angioedema):

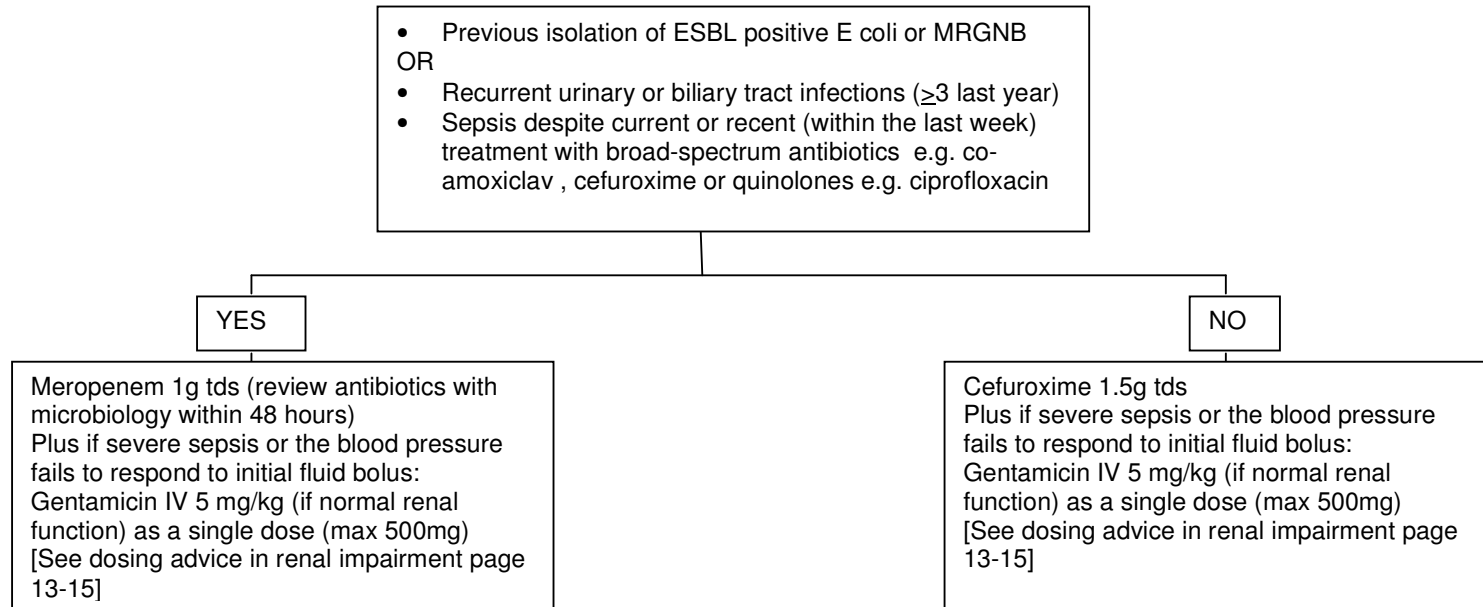
Ciprofloxacin PO 500mg bd, or if vomiting IV 400mg bd, after discussion with duty medical microbiologist

If the patient has severe sepsis or the blood pressure fails to respond to initial fluid bolus:

+ **Gentamicin** IV 5 mg/kg (if normal renal function) as a single dose (max 500mg)

[See dosing advice in renal impairment page 13-15]

Guidelines for Empirical Treatment of Suspected Sepsis of Unknown Origin



When taking blood cultures, two sets of blood cultures should be sent. Each set (two bottles) should be taken from separate venepuncture sites. In hours, the samples should be sent straight to microbiology. Out of hours, samples should be taken to the incubator on A floor at QMC or the incubator at pathology reception at City. They must **not** be sent by tube system.

If in doubt discuss or if patient has a severe allergy to penicillins (e.g. urticarial rash within the first 72 hours, anaphylaxis or angioedema) with a **medical microbiologist/ on-call infectious disease consultant**

VANCOMYCIN DOSING AND MONITORING

Vancomycin is used parenterally for the treatment of resistant Gram-positive infections. Serum monitoring of pre-dose levels is essential to ensure therapeutic levels are achieved without renal toxicity.

The normal dose is 1g bd infused over 2 hours.

If mild renal impairment or age >65 years, frequency reduced to 1g od.

For moderate or severe renal impairment please see separate guidance

CrCl (ml/min)	Vancomycin Dose
20 – 50 (or >65 yrs if Crcl >50ml/min)	1g od. Check pre dose level before third dose.
10 – 20	1g every 48 hours. Check pre dose level before second dose.
<10	1g stat (or 15mg/kg up to max 2g). Check level after 4-5 days. ONLY re-dose when level <12mg/L. If deep seated infection when <15mg/L.

Ensure patients have a fluid balance chart and urine output is monitored

Monitoring of levels

- A **pre-dose** sample (red topped sample sent to microbiology) should be taken **before** the **third** or **fourth** dose. Recommended pre-dose levels for deep seated infection – bone/joint/pneumonia/endocarditis are 10-15mg/L, with other infections levels of 5-15mg/L are acceptable.
- Give time of last dose and time sample taken, details of dose and latest creatinine on the sample request form (without which the result cannot be interpreted)
 - The dose **can be given** after the pre-dose level is taken if the serum creatinine is stable with good urine output
 - It is not necessary to do a post dose level
 - Try and time the dose so it is convenient for levels
 - Results will be available on the results reporting system on the day that the sample is received.

ONCE DAILY GENTAMICIN DOSING AND MONITORING

Gentamicin is an effective antibiotic for treating many infections, especially those arising from the gastrointestinal and urinary tract or hospital-acquired pneumonia. Recent studies have shown that gentamicin can be given as a single dose rather than in divided doses. This is easier for the ward staff, requires fewer levels to be taken, and appears to be less nephrotoxic. (The effect on ototoxicity is still unclear.)

This regimen is ideal for short courses e.g. 5 days. Longer courses will need conventional dosing. N.B. it is not appropriate for some patient groups either because of lack of published data, or risk of accumulation and toxicity.

Not to be used in:

- Children, (Neonates follow separate cross-town NNU guidelines)
- Pregnancy
- Situations where gentamicin is added for synergistic effect e.g. Endocarditis, Listeriosis.
- Ascites
- Major burns (>20% surface area)

Dosage:

- Use 5mg/kg/dose (up to a maximum of 500mg)
- Round the dose up or down to the nearest 40mg increment e.g. 320mg or 360mg
- Dose obese patients using the Gentamicin dosing calculator on the antibiotic website (http://nuhnet/diagnostics_clinical_support/antibiotics)
- Give as an **infusion** over 60 minutes (in 100ml NaCl 0.9% or Dex 5%).
- In patients with **established renal impairment** (ie CrCl <40ml/min) the dose must be reduced see below
- Many elderly patients have a CrCl below 50ml/min, which, because of reduced muscle mass, may not be indicated by a raised creatinine level. It is therefore prudent to assume at least **mild** renal impairment when prescribing for this patient group.

ONCE DAILY GENTAMICIN DOSING IN ESTABLISHED RENAL IMPAIRMENT

CrCl 10 –40ml/min	CrCl <10 (severe)
3mg/kg stat (max 300mg) Check levels 18–24 hours after first dose. Redose only when levels < 1 mg/L	2 mg/kg stat (max 200mg) Redose according to levels Close monitoring of blood levels recommended and dose adjustment as necessary

Calculation of Creatinine Clearance

The Cockcroft-Gault equation (below) should be used to calculate creatinine clearance and gives an estimate of kidney function for the purposes of drug dosing in renal impairment. **Cockcroft-Gault CrCl estimates should be used for drug dosing rather than the automated MDRD eGFR produced by the clinical chemistry laboratory available on NOTIS/HISS. There can be a significant difference between the results of the two calculations.**

The Cockcroft-Gault equation is used to calculate creatinine clearance as an **estimate** of GFR (ml/min):

$$\text{CrCl (ml/min)} = \frac{\text{F x (140-age) x weight (kg)}}{\text{Serum creatinine (micromol/L)}}$$

where F = 1.23 (male) = 1.04 (female)

Where F = 1.23 (male), F = 1.04 (female)

- If patient is anuric, morbidly obese or in acute renal failure (ARF), this equation will NOT give a true reflection of creatinine clearance.
- Anuric and oliguric (<500ml/day) patients can be assumed to have a CrCl < 10ml/min (severe renal impairment)

A **Creatinine Clearance Calculator** is available on the Nottingham Hospitals antibiotic website: http://nuhnet/diagnostics_cinical_support/antibiotics

Monitoring of Gentamicin levels and renal function

- Take a **trough level 18-24 hours** (red-topped sample to microbiology) after the **first** dose, the ideal trough is less than 1.0mg/L
- Give time of last dose and time taken, details of dose and latest creatinine on the sample request form (without which the results cannot be interpreted).
- **For a result to be returned the same day, samples must be at path lab reception before 3.30pm on weekdays and before 10am on weekends.**
- In a patient **<65 years**, if the **serum creatinine is normal with good urine output give the second dose** without waiting for the result.
- In a patient **>65 years old** or with **abnormal renal function, await the result before giving a second dose** and obtain advice from the medical microbiologist if the pre dose is level is >1.0 mg/l
- When the first dose of gentamicin has been given in the evening/night, the level should be taken by 3.00pm the following day if this falls within the 18-24 hour window, and sent for analysis immediately. If this is not possible the doctor must decide whether the second dose of gentamicin is given

before the level is known. As a general guide, for patients over 65 years or with impaired renal function, the level and dose may be delayed until the next morning.

- It is **not** necessary to do a post dose level
- Results will be available on results reporting system on the day that the sample is received.
- Renal function should be checked at least three times a week and levels should be checked twice weekly during a treatment course.
- If renal function deteriorates then renal function should be checked daily and gentamicin levels closely monitored. A dose reduction may be required.
- All patients prescribed more than one dose of Gentamicin should have a fluid balance chart completed and urine output should be closely monitored.