Henry Paw and
Rob Shulman

Handbook of Drugs in Intensive Care

An A-Z Guide

Sixth Edition

CAMBRIDGE Medicine

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This book is dedicated to Georgina Paw

Contents

Introduction

Since the publication of the fifth edition in 2013 and a reprint in 2014, there have been several new drugs introduced to the critical care setting. This book has now been extensively updated. The main purpose of the book is to provide a practical guide that explains how to use drugs safely and effectively in a critical care setting. Doctors, nurses, pharmacists and other healthcare professionals caring for the critically ill patient will find it useful. It is not intended to list every conceivable complication and problem that can occur with a drug but to concentrate on those the clinician is likely to encounter. The book should be seen as complementary to, rather than replacing, the standard textbooks.

The book is composed of two main sections. The A–Z guide is the major part and is arranged alphabetically by the non-proprietary name of the drug. This format has made it easier for the user to find a particular drug when in a hurry. The discussion on an individual drug is restricted to its use in the critically ill adult patient. The second part is comprised of short notes on relevant intensive care topics. Inside the back cover is a fold-out chart showing drug compatibility for IV administration.

While every effort has been made to check drug dosages based on a 70 kg adult and information about every drug, it is possible that errors may have crept in. We would therefore ask readers to check the information if it seems incorrect. In addition, we would be pleased to hear from any readers with suggestions about how this book can be improved. Comments should be sent via e-mail to: henry.paw@york.nhs.uk.

HGWP
RS

How to Use this Book

European law (directive 92/27/EEC) requires the use of the Recommended International Non-proprietary Name (rINN) in place of the British Approved Name (BAN). For a small number of drugs these names are different. The Department of Health requires the use of BAN to cease and be replaced by rINN, with the exceptions of adrenaline and noradrenaline. For these two drugs both their BAN and rINN will continue to be used.

The format of this book was chosen to make it more 'user friendly' – allowing the information to be readily available to the reader in times of need. For each drug there is a brief introduction, followed by the following categories:

Uses

This is the indication for the drug's use in the critically ill. There will be some unlicensed use included and this will be indicated in brackets.

Contraindications

This includes conditions or circumstances in which the drug should not be used – the contraindications. For every drug, this includes known hypersensitivity to the particular drug or its constituents.

Administration

This includes the route and dosage for a 70 kg adult. For obese patients, the text states which weight should be used for weight-based dosing calculation, where this information is known. Lean body weight tables are provided in Appendix D. It also advises on dilutions and situations where dosage may have to be modified. To make up a dilution, the instruction 'made up to 50 ml with 0.9% sodium chloride' means that the final volume is 50 ml. In contrast, the instruction 'to dilute with 50 ml 0.9% sodium chloride' could result in a total volume >50 ml. It is recommended that no drug should be stored for >24 hours after reconstitution or dilution.

How not to use . . .

This describes administration techniques or solutions for dilution which are not recommended.

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Adverse effects

These are effects other than those desired.

Cautions

Warns of situations when the use of the drug is not contraindicated but needs to be carefully watched. This will include key drug–drug interactions.

Organ failure

Highlights any specific problems that may occur when using the drug in a particular organ failure.

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Common Abbreviations

ACE-I	angiotensin converting enzyme inhibitor
ACh	acetylcholine
ACT	activated clotting time
AF	atrial fibrillation
APTT	activated partial thromboplastin time
ARDS	acute respiratory distress syndrome
AUC	area under the curve
AV	atrioventricular
BP	blood pressure
CABG	coronary artery bypass graft
cAMP	cyclic adenosine monophosphate (AMP)
CC	creatinine clearance
CMV	cytomegalovirus
CNS	central nervous system
CO	cardiac output
COPD	chronic obstructive pulmonary disease
CPR	cardiopulmonary resuscitation
CSF	cerebrospinal fluid
CT	computerized tomography
CVP	central venous pressure
CVVH	continuous veno-venous haemofiltration
d	day
DIC	disseminated intravascular coagulation
DOAC	direct oral anticoagulant
DVT	deep vein thrombosis
ECG	electrocardiogram
EBV	Epstein Barr virus
EEG	electroencephalogram
EMD	electromechanical dissociation
$ETCO_2$	end-tidal carbon dioxide concentration
FBC	full blood count
FFP	fresh frozen plasma

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g	gram
GFR	glomerular filtration rate
HIT	heparin-induced thrombocytopenia
HOCM	hypertrophic obstructive cardiomyopathy
h	hour
HR	heart rate
ICP	intracranial pressure
ICU	intensive care unit
IM	intramuscular
INR	international normalized ratio
IOP	intraocular pressure
IPPV	intermittent positive pressure ventilation
IV	intravenous
K^+	potassium
kg	kilogram
l	litre
LFT	liver function tests
LMWH	low molecular weight heparin
MAOI	monoamine oxidase inhibitor
mg	milligram
µg	microgram
MI	myocardial infarction
MIC	minimum inhibitory concentration
min	minute
ml	millilitre
MRSA	methicillin-resistant *Staphylococcus aureus*
NG	nasogastric
ng	nanogram
NIV	non-invasive ventilation
NJ	nasojejunal
NOAC	novel oral anticoagulant
nocte	at night
NSAID	non-steroidal anti-inflammatory drug
$PaCO_2$	partial pressure of carbon dioxide in arterial blood
PaO_2	partial pressure of oxygen in arterial blood
PCA	patient controlled analgesia
PCWP	pulmonary capillary wedge pressure

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PD	peritoneal dialysis
PE	pulmonary embolism
PEA	pulseless electrical activity
PEG	percutaneous endoscopic gastrostomy
PEJ	percutaneous endoscopic jejunostomy
PO	*per orum* (by mouth)
PPI	proton pump inhibitor
PR	*per rectum* (rectal route)
PRN	pro re nata (as required)
PT	prothrombin time
PVC	polyvinyl chloride
PVD	peripheral vascular disease
RR	respiration rate
s	second
SC	subcutaneous
SIRS	systemic inflammatory response syndrome
SL	sublingual
SSRI	selective serotonin re-uptake inhibitor
STEMI	ST-segment elevation myocardial infarction
SVR	systemic vascular resistance
SVT	supraventricular tachycardia
TFT	thyroid function tests
TNF	tumour necrosis factor
TPN	total parenteral nutrition
TSH	thyroid stimulating hormone
U&E	urea and electrolytes
VF	ventricular fibrillation
VRE	vancomycin-resistant *Enterococcus faecium*
VT	ventricular tachycardia
WFI	water for injection
WPW syndrome	Wolff–Parkinson–White syndrome

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I would like to thank my ICU colleagues from whom I have sought advice during the preparation of this edition. HP.

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Drugs: An A–Z Guide

Chapter

A

Acetazolamide

Acetazolamide is a carbonic anhydrase inhibitor normally used to reduce intraocular pressure in glaucoma. Metabolic alkalosis may be partially corrected by the use of acetazolamide. The most common cause of metabolic alkalosis on the ICU is usually the result of furosemide administration.

Uses

Metabolic alkalosis (unlicensed)

Contraindications

Hypokalaemia
Hyponatraemia
Hyperchloraemic acidosis
Severe liver failure
Renal failure
Sulphonamide hypersensitivity

Administration

- IV: 250–500 mg, given over 3–5 minutes every 8 hours

Reconstitute with 5 ml WFI
Monitor: FBC, U&E and acid/base balance

How not to use acetazolamide

IM injection – painful
Not for prolonged use

Adverse effects

Metabolic acidosis
Electrolyte disturbances (hypokalaemia and hyponatraemia)
Blood disorders
Abnormal LFT

Cautions

Avoid extravasation at injection site (risk of necrosis)
Avoid prolonged use (risk of adverse effects)
Concurrent use with phenytoin (↑ serum level of phenytoin)

Organ failure

Renal: avoid if possible (metabolic acidosis)

CC (ml/min)	Dose (mg)	Interval (h)
20–50	250	Up to 6
10–20	250	Up to 12
<10	250	24

Hepatic: avoid (abnormal LFT)

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Acetylcysteine (Parvolex)

Acetylcysteine is an effective antidote to paracetamol if administered within 8 hours after an overdose. Although the protective effect diminishes progressively as the overdose–treatment interval increases, acetylcysteine can still be of benefit up to 24 hours after the overdose. In paracetamol overdose the hepatotoxicity is due to formation of a toxic metabolite. Hepatic reduced glutathione inactivates the toxic metabolite by conjugation, but glutathione stores are depleted with hepatotoxic doses of paracetamol. Acetylcysteine, being a sulphydryl (SH) group donor, protects the liver, probably by restoring depleted hepatic reduced glutathione or by acting as an alternative substrate for the toxic metabolite.

Acetylcysteine may have significant cytoprotective effects. The cellular damage associated with sepsis, trauma, burns, pancreatitis, hepatic failure and tissue reperfusion following acute MI may be mediated by the formation and release of large quantities of free radicals that overwhelm and deplete endogenous antioxidants (e.g. glutathione). Acetylcysteine is a scavenger of oxygen free radicals. In addition, acetylcysteine is a glutathione precursor, capable of replenishing depleted intracellular glutathione and, in theory, augmenting antioxidant defences (p. 354).

Acetylcysteine can be used to reduce the nephrotoxic effects of IV contrast media. Possible mechanisms include scavenging a variety of oxygen-derived free radicals and the improvement of endothelium-dependent vasodilation.

Nebulized acetylcysteine can be used as a mucolytic agent. It reduces sputum viscosity by disrupting the disulphide bonds in the mucus glycoproteins and enhances mucociliary clearance, thus facilitating easier expectoration.

Uses

Paracetamol overdose

Antioxidant (unlicensed)

Prevent IV contrast-induced nephropathy (unlicensed)

Reduce sputum viscosity and facilitate easier expectoration (unlicensed)

As a sulphydryl group donor to prevent the development of nitrate tolerance (unlicensed)

Administration

Paracetamol overdose:

- IV infusion: 150 mg/kg in 200 ml glucose 5% over 60 minutes, followed by 50 mg/kg in 500 ml glucose 5% over 4 hours, then 100 mg/kg in 1 l glucose 5% over the next 16 hours

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Weight (kg)	Initial	Second	Third
	150 mg/kg in 200 ml glucose 5% over 60 minutes	50 mg/kg in 500 ml glucose 5% over 4 hours	100 mg/kg in 1 l glucose 5% over 16 hours
	Parvolex (ml)	Parvolex (ml)	Parvolex (ml)
50	37.5	12.5	25
60	45.0	15.0	30
70	52.5	17.5	35
80	60.0	20.0	40
90	67.5	22.5	45
x	0.75*x*	0.25*x*	0.5*x*

For children >20 kg: same doses and regimen but in half the quantity of IV fluid
Treatment nomogram:

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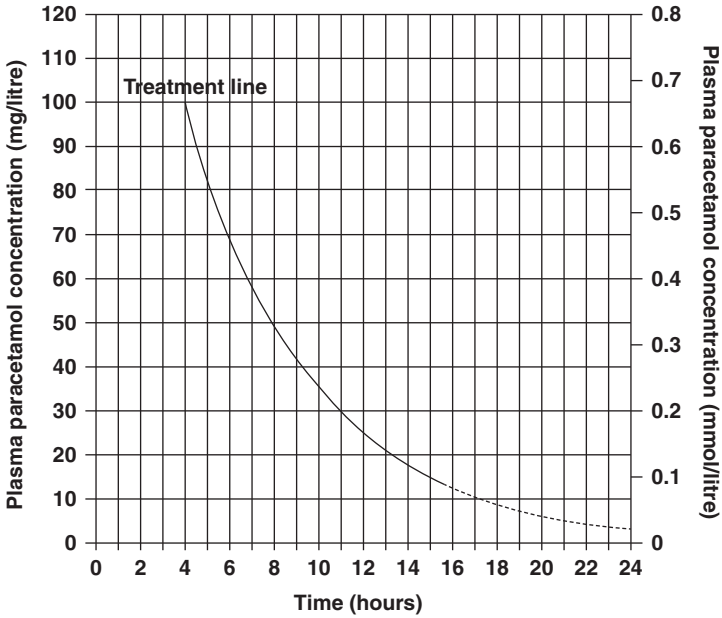

Patients whose plasma-paracetamol concentrations are on or above the **treatment line** should be treated with acetylcysteine by intravenous infusion.
The prognostic accuracy after 15 hours is uncertain, but a plasma-paracetamol concentration on or above the treatment line should be regarded as carrying a serious risk of liver damage.

Patients whose plasma concentrations fall on or above the treatment line should receive acetylcysteine. The prognostic value after 15 hours is uncertain, although a plasma paracetamol concentration on or above the treatment line is likely to carry a serious risk of liver damage. Use acetylcysteine for paracetamol overdose irrespective of the plasma paracetamol level if the overdose is staggered or there is doubt over the time of paracetamol ingestion, or paracetamol overdose with a timed plasma paracetamol concentration on or above a single treatment line joining points of 100 mg/l at 4 hours and 15 mg/l at 15 hours regardless of risk factors of hepatotoxicity.

Antioxidant:

- IV infusion: 75–100 mg/kg in 1 l glucose 5%, give over 24 hours (rate 40 ml/h)

Prevent IV contrast-induced nephropathy (not required for oral/enterally administered contrast):

- IV bolus 1,200 mg pre-contrast, then after 12 hours 1,200 mg PO/NG (or IV if nil-by-mouth) 12 hourly for 48 hours (there is also evidence for 600 mg as an alternate dose)

  Dilution: make up to 20 ml with glucose 5%

  If the oral capsules are not available, the IV formulation may be given orally

  To mask the bitter taste, dilute the injection to a concentration of 50 mg/ml with an acidic drink (e.g. orange juice, blackcurrant juice or cola)

  To be given in conjunction with IV sodium bicarbonate 1.26% at 3 ml/kg/h over 1 hour prior to IV contrast; continue at reduced rate of 1 ml/kg/h for 6 hours following contrast

Reduce sputum viscosity:

- Nebulized: 4 ml (800 mg) undiluted Parvolex (20%) driven by air, 8 hourly

  Administer before chest physiotherapy

How not to use acetylcysteine

Do not drive nebuliser with oxygen (oxygen inactivates acetylcysteine)

Adverse effects

Anaphylactoid reactions (nausea, vomiting, flushing, itching, rashes, bronchospasm, hypotension)

Fluid overload

Cautions

There are no contraindications to treatment of paracetamol overdose with acetylcysteine

Asthmatics (risk of bronchospasm)

Pulmonary oedema (worsens)

Each 10 ml ampoule contains Na^+ 12.8 mmol (↑ total body sodium)

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Aciclovir

Aciclovir interferes with herpes virus DNA polymerase, inhibiting viral DNA replication. Aciclovir is renally excreted and has a prolonged half-life in renal impairment.

Uses

Herpes simplex virus (HSV) infections:

- HSV encephalitis
- HSV genital, labial, peri-anal and rectal infections

Varicella zoster virus infections:

- Beneficial in the immunocompromised patients when given IV within 72 hours; prevents complications of pneumonitis, hepatitis or thrombocytopenia
- In patients with normal immunity, may be considered if the ophthalmic branch of the trigeminal nerve is involved

Contraindications

Not suitable for CMV or EBV infections

Administration

- IV: 5–10 mg/kg 8 hourly (*i.e. 5 mg/kg for herpes simplex, herpes zoster; 10 mg/kg for herpes zoster in immunocompromised, HSV encephalitis)
- In obesity, use ideal body weight for dosing

  Available in 250 mg/10 ml and 500 mg/20 ml ready-diluted or in 250 mg and 500 mg vials for reconstitution

  Reconstitute 250 mg vial with 10 ml WFI or sodium chloride 0.9% (25 mg/ml)

  Reconstitute 500 mg vial with 20 ml WFI or sodium chloride 0.9% (25 mg/ml)

  Take the reconstituted solution (25 mg/ml) and make up to 50 ml (for 250 mg vial) or 100 ml (for 500 mg vial) with sodium chloride 0.9% or glucose 5%, and give over 1 hour

  Ensure patient is well hydrated before treatment is administered

  If fluid-restricted, can give centrally via syringe pump undiluted (unlicensed)

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In renal impairment:

CC (ml/min)	Dose (mg/kg)*	Interval (h)
>50 or CVVH rate >3 l/h	5–10	8
25–50 or CVVH rate 1.5–3 l/h	5–10	12
10–25 or CVVH rate <1.5 l/h	5–10	24
<10	2.5–5	24

How not to use aciclovir

Rapid IV infusion (precipitation of drug in renal tubules leading to renal impairment)

Adverse effects

Phlebitis

Reversible renal failure

Elevated LFTs

CNS toxicity (tremors, confusion and fits)

Neuropsychiatric side effects – in renal failure may be due to accumulation of aciclovir metabolite, 9-carboxymethoxymethylguanine (CMMG)

Cautions

Concurrent use of methotrexate

Renal impairment (reduce dose)

Dehydration/hypovolaemia (renal impairment due to precipitation in renal tubules)

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Adenosine (Adenocor)

This endogenous nucleoside is safe and effective in ending >90% of re-entrant paroxysmal SVT. However, this is not the most common type of SVT in the critically ill patient. After an IV bolus effects are immediate (10–30 seconds), dose-related and transient (half-life <10 seconds; entirely eliminated from plasma in <1 minute, being degraded by vascular endothelium and erythrocytes). Its elimination is not affected by renal/hepatic disease. Adenosine works faster and is superior to verapamil. It may be used in cardiac failure, in hypotension and with beta-blockers, in all of which verapamil is contraindicated.

Uses

It has both therapeutic and diagnostic uses:

- Alternative to DC cardioversion in terminating paroxysmal SVT, including those associated with WPW syndrome
- Determining the origin of broad complex tachycardia; SVT responds, VT does not (predictive accuracy 92%; partly because VT may occasionally respond). Though adenosine does no harm in VT, verapamil may produce hypotension or cardiac arrest

Contraindications

Second- or third-degree heart block (unless pacemaker fitted)

Sick sinus syndrome (unless pacemaker fitted)

Asthma – may cause bronchospasm

Patients on dipyridamole (drastically prolongs the half-life and enhances the effects of adenosine – may lead to dangerously prolonged high-degree AV block)

Administration

- Rapid IV bolus: 3 mg over 1–2 seconds into a large vein, followed by rapid flushing with sodium chloride 0.9%
  If no effect within 2 minutes, give 6 mg

  If no effect within 2 minutes, give 12 mg

  If no effect, abandon adenosine

  Need continuous ECG monitoring

  More effective given via a central vein or into right atrium

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How not to use adenosine

Without continuous ECG monitor

Adverse effects

Flushing (18%), dyspnoea (12%) and chest discomfort are the commonest side effects but are well tolerated and invariably last <1 minute

If given to an asthmatic and bronchospasm occurs, this may last up to 30 minutes

Use aminophylline to reverse

Cautions

AF or atrial flutter with accessory pathway (↑ conduction down anomalous pathway may increase)

Early relapse of paroxysmal SVT is more common than with verapamil but usually responds to further doses

Adenosine's effect is enhanced and extended by dipyridamole – if essential to give with dipyridamole, reduce initial dose to 0.5–1 mg

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Adrenaline

Both α- and β-adrenergic receptors are stimulated. Low doses tend to produce predominantly β-effects while higher doses tend to produce predominantly α-effects. Stimulation of β_1-receptors in the heart increases the rate and force of contraction, resulting in an increase in cardiac output. Stimulation of α_1 -receptor causes peripheral vasoconstriction, which increases the systolic BP. Stimulation of β_2-receptors causes bronchodilatation and vasodilatation in certain vascular beds (skeletal muscles). Consequently, total systemic resistance may actually fall, explaining the decrease in diastolic BP that is sometimes seen. Vasoconstriction can be offset with a dilator such as glyceryl trinitrate.

Uses

Low cardiac output states

Bronchospasm

Cardiac arrest (p. 314)

Anaphylaxis (p. 321)

Contraindications

Before adequate intravascular volume replacement

Administration

Low cardiac output states:

- Dose: 0.01–0.30 (though up to 3 may be needed very occasionally) μg/kg/min IV infusion via a central vein
- Titrate dose according to HR, BP, cardiac output, presence of ectopic beats and urine output

Dosage chart (ml/h)

4 mg made up to 50 ml glucose 5%

Weight (kg)	Dose (μg/kg/min)				
	0.02	0.05	0.1	0.15	0.2
50	0.8	1.9	3.8	5.6	7.5
60	0.9	2.3	4.5	6.8	9.0
70	1.1	2.6	5.3	7.9	10.5

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(cont.)

Weight (kg)	Dose (μg/kg/min)				
	0.02	0.05	0.1	0.15	0.2
80	1.2	3.0	6.0	9.0	12
90	1.4	3.4	6.8	10.1	13.5
100	1.5	3.8	7.5	11.3	15.0
110	1.7	4.1	8.3	12.4	16.5
120	1.8	4.5	9.0	13.5	18.0

Bronchospasm

- 0.5–1 mg nebulized PRN
- 0.5–1 ml of 1:1,000 (0.5–1 mg) made up to 5 ml with sodium chloride 0.9%

Cardiac arrest (p. 314)

- IV bolus: 10 ml 1 in 10,000 solution (1 mg)

Anaphylaxis (p. 324)

- IV bolus: 0.5–1.0 ml 1 in 10,000 solution (50–100 μg), may be repeated PRN, according to BP

How not to use adrenaline

In the absence of haemodynamic monitoring:

- do not connect to CVP lumen used for monitoring pressure (surge of drug during flushing of line)
- incompatible with alkaline solutions, e.g. sodium bicarbonate, furosemide, phenytoin and enoximone

Adverse effects

Arrhythmia

Tachycardia

Hypertension

MI

Increased lactate levels

Cautions

Acute MI

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Alfentanil

It is an opioid 30 times more potent than morphine and its duration is shorter than that of fentanyl. The maximum effect occurs about 1 minute after IV injection. Duration of action following an IV bolus is between 5 and 10 minutes. Its distribution volume and lipophilicity are lower than fentanyl. It is ideal for infusion and may be the agent of choice in renal failure. The context-sensitive half-life may be prolonged following IV infusion. In patients with hepatic failure the elimination half-life may be markedly increased and a prolonged duration of action may be seen.

Uses

Patients receiving short-term ventilation

Contraindications

Airway obstruction

Concomitant use of MAOI

Administration

- IV bolus: 500 μg every 10 minutes as necessary
- IV infusion rate: 1–5 mg/h (up to 1 μg/kg/min)

Draw ampoules up neat to make infusion, i.e. 0.5 mg/ml or dilute to a convenient volume with glucose 5% or sodium chloride 0.9%

How not to use alfentanil

In combination with an opioid partial agonist, e.g. buprenorphine (antagonizes opioid effects)

Adverse effects

Respiratory depression and apnoea

Bradycardia

Nausea and vomiting

Delayed gastric emptying

Reduce intestinal mobility

Biliary spasm

Constipation

Urinary retention

Chest wall rigidity (may interfere with ventilation)

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Cautions

Enhanced sedative and respiratory depression from interaction with:

- benzodiazepines
- antidepressants
- antipsychotics

Avoid concomitant use of and for 2 weeks after MAOI discontinued (risk of CNS excitation or depression – hypertension, hyperpyrexia, convulsions and coma)

Head injury and neurosurgical patients (may exacerbate ↑ ICP as a result of ↑ $PaCO_2$)

Erythromycin (↓ clearance of alfentanil)

Organ failure

Respiratory: ↑ respiratory depression

Hepatic: enhanced and prolonged sedative effect

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Alteplase (Actilyse)

The use of thrombolytics is well established in MI and PE. They act by activating plasminogen to form plasmin, which degrades fibrin and so breaks up thrombi. Alteplase or recombinant tissue-type plasminogen activator (rt-PA) can be used in major PE associated with hypoxia and haemodynamic compromise. Whilst alteplase is more expensive than streptokinase, it is the preferred thrombolytic as it does not worsen hypotension. Severe bleeding is a potential adverse effect of alteplase and requires discontinuation of the thrombolytic and may require administration of coagulation factors and antifibrinolytic drugs (such as tranexamic acid).

Uses

Major PE

Acute MI

Acute stroke

Contraindications

Recent haemorrhage, trauma or surgery

Coagulation defects

Severe hypertension

Oesophageal varices

Severe liver disease

Acute pancreatitis

Administration

PE:

Ideally, APTT ratio should be <1.5 before thrombolysis starts, but do not delay if condition appears to be immediately life-threatening

IV alteplase: Stop all anticoagulants prior to starting thrombolysis

In stable, massive PE patients, give 10 mg IV bolus over 1–2 minutes, then 90 mg over 2 hours (maximum total dose 1.5 mg/kg if <65 kg)

For patients who are rapidly deteriorating and in whom cardiac arrest is imminent, or who have an in house cardiac arrest, give 50 mg IV bolus alteplase and reassess at 30 minutes

Start LMWH therapy if APTT ratio <2.5 and CC >30 ml/min at the DVT treatment dose; if APTT is >2.5 repeat every 4 hours until APTT <2.5 then start LMWH; if the patient was on anticoagulation pre-thrombolysis,

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initiate LMWH not before the next dose of the previous anticoagulant was due

Start warfarin on day 3 to 7 of LMWH and continue until INR in range for 2 consecutive days with not less than 5 days overlap

Dissolve in WFI to a concentration of 1 mg/ml (50 mg vial with 50 ml WFI)

Foaming may occur; this will dissipate after standing for a few minutes

Monitor: BP (treat if systolic BP >180 mmHg or diastolic BP >105 mmHg)

MI:

Accelerated regimen (initiated within 6 hours of symptom onset), 15 mg IV, then 50 mg IV infusion over 30 minutes, then 35 mg over 60 minutes (total dose 100 mg over 90 minutes); in patients <65 kg, 15 mg by IV, the IV infusion of 0.75 mg/kg over 30 minutes, then 0.5 mg/kg over 60 minutes (maximum total dose 100 mg over 90 minutes)

MI, initiated within 6–12 hours of symptom onset, 10 mg IV, followed by IV infusion of 50 mg over 60 minutes, then four infusions each of 10 mg over 30 minutes (total dose 100 mg over 3 hours; maximum 1.5 mg/kg in patients <65 kg)

Acute stroke:

Treatment must begin within 3 hours of symptom onset

IV: 900 μg/kg (max. 90 mg), initial 10% of dose by IV injection over 3 minutes, remainder by IV infusion over 60 minutes

Not recommended in the elderly over 80 years of age

Management of bleeding and thrombolysis

Bleeding may occur even when coagulation screening tests are normal. Monitor regularly for clinical signs of bleeding. If internal bleeding is suspected, consider whether the infusion of thrombolytic therapy should be stopped and investigations undertaken. If bleeding is local and minor, apply sustained local pressure. For more serious bleeding, stop the infusion of thrombolytic therapy and heparin (restore depleted fibrinogen, factors V and VIII within 12–24 hours). For severe, life-threatening bleeding, discontinue thrombolytic therapy and LMWH. Administer tranexamic acid IV 1 g over 15 minutes, repeated 8 hourly as necessary. Administer FFP and/or cryoprecipitate to replenish depleted clotting factors, depending on coagulation screen. Red cells should be infused as clinically indicated. For life-threatening haematoma (e.g. intracranial) consider measures either to evacuate or relieve pressure.

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How not to use alteplase

Not to be infused in glucose solution

Adverse effects

Nausea and vomiting

Bleeding

Cautions

Acute stroke (risk of cerebral bleed)

Diabetic retinopathy (risk of retinal bleeding)

Abdominal aortic aneurysm and enlarged left atrium with AF (risk of embolization)

Organ failure

Renal: risk of hyperkalaemia

Hepatic: avoid in severe liver failure

Acknowledgement: UCLH Foundation Trust PE Guideline

Aminophylline

Aminophylline is the ethylenediamine salt of theophylline. It is a non-specific inhibitor of phosphodiesterase, producing increased levels of cAMP. Increased cAMP levels result in:

- bronchodilation
- CNS stimulation
- positive inotropic and chronotropic effects
- diuresis

Theophylline has been claimed to reduce fatigue of diaphragmatic muscles

Uses

Prevention and treatment of bronchospasm

Contraindications

Uncontrolled arrhythmias

Hyperthyroidism

Administration

- Loading dose: 5 mg/kg IV, diluted in 100 ml sodium chloride 0.9% or glucose 5%, given over 30 minutes, followed by maintenance dose 0.1–0.8 mg/kg/h

  Dilute 500 mg (20 ml) aminophylline (25 mg/ml) in 480 ml sodium chloride 9% or glucose 5% to give a concentration of 1 mg/ml

  No loading dose if already on oral theophylline preparations (toxicity)

  Reduce maintenance dose (0.1–0.3 mg/kg/h) in the elderly and patients with congestive heart failure and liver disease

  Increase maintenance dose (0.8–1 mg/kg/h) in children (6 months to 16 years) and young adult smokers

  Monitor plasma level (p. 309)

  Therapeutic range 55–110 μmol/l or 10–20 mg/l. Take first level 4–6 hours after starting treatment

The injection can be administered nasogastrically (unlicensed). This may be useful as there is no liquid preparation of aminophylline or theophylline. To convert from IV to NG, keep the total daily dose the same, but divide into four equal doses. Aminophylline modified-release tablets are taken by mouth twice daily. Alternatively, if these are crushed up to go down a nasogastric tube then they will lose their slow-release characteristic and will need to be administered four times per day, keeping the total daily dose the same.

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Unlicensed indication: Methotrexate toxicity: aminophylline 25 mg/kg, 6 hourly IV (methotrexate increases adenosine, which is inhibited by aminophylline)

Dosage chart (ml/h)

Weight (kg)	Dose (mg/kg/h)									
	0.1	0.2	0.3	0.4	0.5	0.6	0.7	0.8	0.9	1
50	5	10	15	20	25	30	35	40	45	50
60	6	12	18	24	30	36	42	48	54	60
70	7	14	21	28	35	42	49	56	63	70
80	8	16	24	32	40	48	56	64	72	80
90	9	18	27	36	45	54	63	72	81	90
100	10	20	30	40	50	60	70	80	90	100
110	11	22	33	44	55	66	77	88	99	110
120	12	24	36	48	60	72	84	96	108	120
	• Elderly • Congestive heart failure • Liver disease			• Usual adult maintenance				• Children • Young adult smokers		

How not to use aminophylline

Rapid IV administration (hypotension, arrhythmias)

Adverse effects

Tachycardia

Arrhythmias

Convulsions

Cautions

Subject to enzyme inducers and inhibitors (p. 307)

Concurrent use of erythromycin and ciprofloxacin: reduce dose

Organ failure

Cardiac: prolonged half-life (reduce dose)

Hepatic: prolonged half-life (reduce dose)

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Amiodarone

Amiodarone has a broad spectrum of activity on the heart. In addition to having an anti-arrhythmic activity, it also has anti-anginal effects. This may result from its α- and β-adrenoceptor-blocking properties as well as from its calcium-channel-blocking effect in the coronary vessels. It causes minimal myocardial depression. It is therefore often a first-line drug in critical care situations. It has an extremely long half-life (15–105 days). Unlike oral amiodarone, IV administration usually acts relatively rapidly (20–30 minutes). Oral bioavailability is 50%, therefore 600 mg PO/NG is equivalent to 300 mg IV. Overlap the initial oral and IV therapy for 16 to 24 hours. An oral loading dose regimen is necessary even when the patient has been adequately 'loaded' intravenously. This is because amiodarone has a large volume of distribution (4,000 l) and a long half-life. The high initial plasma levels quickly dissipate as the drug binds to the peripheral lipophilic tissues. Thus a prolonged loading regimen is required. When the cause of the arrhythmia has resolved, e.g. sepsis, then amiodarone treatment can be stopped abruptly.

Uses

Good results with both ventricular and supraventricular arrhythmias, including those associated with WPW syndrome

Contraindications

Iodine sensitivity (amiodarone contains iodine)

Sinus bradycardia (risk of asystole)

Heart block (unless pacemaker fitted)

Administration

- Loading: 300 mg in 25–250 ml glucose 5% IV over 20–120 minutes, followed by 900 mg in 50–500 ml glucose 5% over 24 hours. If fluid-restricted, up to 900 mg can be diluted in 50 ml glucose 5% and administered centrally
- Maintenance: 600 mg IV daily for 7 days, then 400 mg IV daily for 7 days, then 200 mg IV daily

Administer IV via central line. A volumetric pump should be used as the droplet size of amiodarone may be reduced.

Must be diluted in glucose 5% (do not dilute in sodium chloride 0.9%)

Because phlebitis may occur, the drug should be given through a central venous line when possible. If peripheral administration is necessary, dilute dose in 500 ml glucose 5%. Concentrations >2 mg/ml must be given centrally

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Dilution to a concentration of less than 600 μg /ml is unstable. Solutions of <300 mg/500 ml glucose 5% should not be used

Continuous cardiac monitoring

- Oral: 200 mg 8 hourly for 7 days, then 200 mg 12 hourly for 7 days, then 200 mg daily

How not to use amiodarone

Incompatible with sodium chloride 0.9%

Avoid the use of peripheral vein (thrombophlebitis) unless well diluted

Adverse effects

Short-term

- Skin reactions common
- Vasodilation and hypotension or bradycardia after rapid infusion
- Corneal microdeposits (reversible on stopping)

Long-term

- Pulmonary fibrosis, alveolitis and pneumonitis (usually reversible on stopping)
- Liver dysfunction (asymptomatic ↑ in LFT common)
- Hypo- or hyperthyroidism (check TFT before starting drug)
- Peripheral neuropathy, myopathy and cerebellar dysfunction (reversible on stopping)

Cautions

Increased risk of bradycardia, AV block and myocardial depression with beta-blockers and calcium-channel antagonists

Potentiates the effect of digoxin, theophylline and warfarin – reduce dose

Organ failure

Hepatic: worsens

Renal: accumulation of iodine may ↑ risk of thyroid dysfunction

Amitriptyline

A tricyclic antidepressant with sedative properties. When given at night it will help to promote sleep. It may take up to 4 weeks before any beneficial antidepressant effect is seen. It is used less often now in depression due to the high rate of fatality in overdose.

Uses

Depression in patients requiring long-term ICU stay, particularly where sedation is required

Difficulty with sleep

Neuropathic pain (unlicensed indication)

Contraindications

Recent MI

Arrhythmia

Heart block

Severe liver disease

Administration

- Oral: depression 25–75 mg nocte

  Neuropathic pain 10–25 mg at night, increased if necessary up to 75 mg daily

How not to use amitriptyline

During the daytime (disturbs the normal sleep pattern)

Adverse effects

Antimuscarinic effects (dry mouth, blurred vision, urinary retention)

Arrhythmias

Postural hypotension

Confusion

Hyponatraemia

Cautions

Cardiac disease (risk of arrhythmias)

Hepatic failure

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Acute-angle glaucoma

Avoid long-term use if patient represents a suicide risk

Concurrent use of MAOI

Additive CNS depression with other sedative agents

May potentiate direct-acting sympathomimetic drugs

Prostatic hypertrophy–urinary retention (unless patient's bladder catheterized)

Organ failure

CNS: sedative effects increased

Hepatic: sedative effects increased

Amphotericin (Liposomal) – AmBisome

Amphotericin is active against most fungi and yeasts. It also has useful activity against protozoa, including *Leishmania* spp., *Naeglaria* and *Hartmanella*. AmBisome is a formulation of amphotericin, encapsulated in liposomes. This improves its tolerability and renders the drug less toxic to the kidney than the parent amphotericin compound (Fungizone), which has largely been superseded. Each vial contains 50 mg amphotericin.

Uses

Severe systemic fungal infections, as liposomal amphotericin a safer alternative to conventional amphotericin

Administration

- IV: initially 1 mg/kg daily, ↑ if necessary to 3 mg/kg daily

  Add 12 ml WFI to each 50 mg vial of liposomal amphotericin (4 mg/ ml)

  Shake vigorously for at least 15 seconds

  Calculate the amount of the 4 mg/ml solution required, i.e.:

  100 mg = 25 ml
  150 mg = 37.5 ml
  200 mg = 50 ml
  300 mg = 75 ml

  Using the 5 μm filter provided add the required volume of the 4 mg/ml solution to at least equal volume of glucose 5% (final concentration 2 mg/ml) and given over 30–60 minutes

  Although anaphylactic reactions are rare, before starting treatment an initial test dose of 1 mg should be given over 10 minutes, infusion stopped and patient observed for 30 minutes; continue infusion if no signs of anaphylactic reaction

  The diluted solution is stable for 24 hours

  Although nephrotoxic, no dose adjustment is required in haemofiltration, though a change in antifungal should be considered

  In renal dialysis patients, give AmBisome at the end of each dialysis

  Monitor: serum potassium and magnesium

How not to use liposomal amphotericin

Must not be given by rapid IV infusion (arrhythmias)

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Not compatible with sodium chloride

Do not mix with other drugs

There are two formulations of IV amphotericin and they are not interchangeable. Errors of this sort have caused lethal consequences or subtherapeutic doses.

Adverse effects

Prevalence and severity lower than with conventional amphotericin

Cautions

Kidney disease

Concurrent use of nephrotoxic drugs

Avoid concurrent administration of corticosteroids (except to treat febrile and anaphylactic reactions)

Diabetic patient: each vial contains 900 mg sucrose

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Amoxicillin

Amoxicillin has a spectrum of activity, which includes staphylococci, streptococci, most enterococci, *Listeria monocytogenes* and Gram-negative rods such as *Salmonella* spp., *Shigella* spp., *Escherichia coli, Haemophilus influenzae* and *Proteus* spp. It is not active against *Pseudomonas aeruginosa* and *Klebsiella* spp. However, due to acquired resistance, almost all staphylococci, 50% of *E. coli* and up to 15% of *H. influenzae* strains are now resistant. All penicillin-resistant pneumococci and enterococci have reduced susceptibility to amoxicillin.

Uses

Urinary tract infections

Respiratory tract infections

Invasive salmonellosis

Serious infections with *L. monocytogenes*, including meningitis

Contraindications

Penicillin hypersensitivity

Administration

- IV: 500 mg–1 g diluted in 10 ml WFI, 6–8 hourly over 3–5 minutes

Meningitis caused by *L. monocytogenes* (with gentamicin):

- IV: 2 g diluted in 10 ml WFI every 4 hours over 3–5 minutes; treat for 10–14 days

Infective endocarditis (with gentamicin): 2 g IV 4 hourly

In renal impairment:

CC (ml/min)	Dose (g) depending on severity of infection	Interval (h)
10–20	Usual dosing	Usual interval
<10	500 mg–1 g (max 6 g/d in endocarditis)	8

How not to use amoxicillin

Not for intrathecal use (encephalopathy)

Do not mix in the same syringe with an aminoglycoside (efficacy of aminoglycoside reduced)

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Adverse effects

Hypersensitivity

Skin rash increases in patients with infectious mononucleosis (90%), chronic lymphocytic leukaemia and HIV infections (discontinue drug)

Cautions

Severe renal impairment (reduce dose, rashes more common)

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Anidulafungin (Ecalta)

Anidulafungin (Ecalta) is an echinocandin, similar to caspofungin and micafungin. It covers a wide range of *Candida* species, causing invasive candidiasis (including *C. krusei* and *C. glabrata*) and is eliminated by non-enzymatic degradation to an inactive metabolite. The key distinguishing features compared to caspofungin are simplicity of dosing regimen, storage at room temperature, narrower clinical indication and fewer drug interactions.

Uses

Invasive candidiasis in adult non-neutropenic patients

Contraindications

Hypersensitivity to echinocandins

Administration

- IV: Load with 200 mg on day 1, followed by 100 mg daily thereafter for a minimum of 14 days
  Reconstitute each vial with 30 ml solvent provided, allowing up to 5 minutes for reconstitution

  Add the reconstituted solution to a bag of sodium chloride 0.9% or glucose 5%, i.e. 100 mg in 250 ml and 200 mg in 500 ml

  Administer at 3 ml/min

  Available in vials containing 100 mg with solvent containing ethanol anhydrous in WFI

How not to use anidulafungin

Do not use in children under 18 years as insufficient data

Adverse effects

Coagulopathy

Convulsion

Headache

Increased creatinine

Hypokalaemia

Elevated LFT

Flushing

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Diarrhoea, nausea and vomiting

Rash

Pruritus

Cautions

Hepatic failure worsening LFTs

Breastfeeding and pregnancy and high-risk groups, e.g. liver disease, epilepsy, alcoholism – diluent contains the equivalent of 6 g of ethanol/ 100 mg of anidulafungin

Fructose intolerance

Organ failure

Renal: no dose adjustment necessary, as negligible renal clearance

Hepatic: no dose adjustment, as not metabolized in liver

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Atracurium

Atracurium is a non-depolarising neuromuscular blocker that is broken down by Hofmann degradation and ester hydrolysis. The ampoules have to be stored in the fridge to prevent spontaneous degradation. Atracurium has an elimination half-life of 20 minutes. The principal metabolite is laudanosine, which can cause convulsions in dogs. Even with long-term infusions, the concentration of laudanosine is well below the seizure threshold (17 µg/ml). It is the agent of choice in renal and hepatic failure.

Uses

Muscle paralysis

Contraindications

Airway obstruction

To facilitate tracheal intubation in patients at risk of regurgitation

Administration

- IV bolus: 0.5 mg/kg, repeat with 0.15 mg/kg at 20–45-minute interval
- IV infusion: 0.2–0.78 mg/kg/h (up to 1.77 mg/kg/h)

Monitor with peripheral nerve stimulator

How not to use atracurium

As part of a rapid sequence induction

In the conscious patient

By persons not trained to intubate trachea

Adverse effects

Bradycardia

Hypotension

Cautions

Asthmatics (histamine release)

Breathing circuit (disconnection)

Prolonged use (disuse muscle atrophy)

Organ failure

Hepatic: increased concentration of laudanosine

Renal: increased concentration of laudanosine

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Atropine

The influence of atropine is most noticeable in healthy young adults in whom vagal tone is considerable. In infancy and old age, even large doses may fail to accelerate the heart.

Uses

Sinus bradycardia – will increase BP as a result

Reversal of muscarinic effects of anticholinesterases (neostigmine)

Organophosphate poisoning

Hypersalivation

Contraindications

Complete heart block

Tachycardia

Administration

Bradycardia: 0.3–1 mg IV bolus, up to 3 mg (total vagolytic dose), may be diluted with WFI

Reversal of muscarinic effects of anticholinesterase: 1.2 mg for every 2.5 mg neostigmine

Organophosphate poisoning: 1–2 mg initially, then further 1–2 mg every 30 min PRN

Hypersalivation: 1% atropine eye drops 1–2 drops sublingually twice to four times a day (unlicensed indication) – can cause hallucinations

How not to use atropine

Slow IV injection of doses <0.3 mg (bradycardia caused by medullary vagal stimulation)

Adverse effects

Drowsiness, confusion

Dry mouth

Blurred vision

Urinary retention

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Tachycardia

Pyrexia (suppression of sweating)

Atrial arrhythmias and atrioventricular dissociation (without significant cardiovascular symptoms)

Dose >5 mg results in restlessness and excitation, hallucinations, delirium and coma

Cautions

Elderly (↑ CNS side effects)

Child with pyrexia (further ↑ temperature)

Acute myocardial ischaemia (tachycardia may cause worsening)

Prostatic hypertrophy–urinary retention (unless patient's bladder catheterized)

Paradoxically, bradycardia may occur at low doses (<0.3 mg)

Acute-angle glaucoma (further ↑ IOP)

Pregnancy (fetal tachycardia)

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Aztreonam

Aztreonam is poorly absorbed orally, so can only be given parenterally or inhaled using a nebulizer (approved in the USA). It is active against infections caused by Gram-negative bacteria such as *Escherichia coli, Haemophilus influenzae, Klebsiella pneumoniae, Proteus mirabilis, Pseudomonas aeruginosa* and *Serratia marcescens.* This may include pneumonia, urinary tract infections and intra-abdominal infections. Aztreonam is largely ineffective against Gram-positive and anaerobic bacteria. It is inactivated by extended-spectrum beta-lactamase (ESBL).

Aztreonam is often used in people who are allergic to penicillin or where aminoglycosides are contraindicated. There is a low cross-reactivity between aztreonam and the other beta-lactam antibiotics (penicillins and cephalosporins). However, ceftazidime exhibits a higher risk of cross-reactivity with aztreonam due to a similar side chain.

Uses

Urinary tract infection

Pneumonia

Intra-abdominal infection

Contraindications

Ceftazidime hypersensitivity

Administration

- IV: 1–2 g diluted in 10 ml WFI, 6 hourly over 3–5 minutes, higher doses should be given for severe infections in 100 ml of glucose 5% or sodium chloride 0.9% and given over 30–60 minutes

  Prophylaxis: 600 mg 12 hourly

  Give at a rate not >300 mg/min

  Maximum daily dose: 8 g/d

In renal impairment:

CC (ml/min)	IV Dose (range depending on severity of infection)
>30 or CVVH rate >1.8 l/h	Normal dose
10–30 or CVVH rate 0.6–1.7 l/h	1–2 g loading dose then 50% of normal dose
<10	1–2 g loading dose then maintenance of 25% of appropriate normal dose

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How not to use aztreonam

Not for intrathecal use (encephalopathy)

Do not mix in the same syringe with an aminoglycoside (efficacy of aminoglycoside reduced)

Adverse effects

Injection site reactions (redness, discomfort)

Rash and hypersensitivity

Haemolytic anaemia

Eosinophilia

Transient neutropenia and thrombocytopenia

Raised serum transaminases and bilirubin

Toxic epidermal necrolysis (rare)

Convulsions (can occur in high dose or renal failure)

Cautions

Severe renal impairment (reduce dose, high doses may cause convulsions)

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Chapter

B

Benzylpenicillin

Benzylpenicillin can only be given parenterally. It is active against most streptococci but the majority of strains of *Staphylococcus aureus* are resistant due to penicillinase production. Resistance rates are increasing in *Streptococcus pneumoniae*, and benzylpenicillin should probably not be used for empiric treatment of meningitis unless local levels of resistance are extremely low. All strains of *Neisseria meningitidis* remain sensitive.

Uses

Infective endocarditis

Streptococcal infections including severe necrotising soft-tissue infections and severe pharyngeal infections

Pneumococcal infections – excluding empiric therapy of meningitis

Gas gangrene and prophylaxis in limb amputation

Meningococcal meningitis with sensitive organism

Tetanus

Post-splenectomy prophylaxis

Contraindications

Penicillin hypersensitivity

Administration

- IV: 600–1,200 mg diluted in 10 ml WFI, 6 hourly over 3–5 minutes, higher doses should be given for severe infections in 100 ml of glucose 5% or sodium chloride 0.9% and given over 30–60 minutes

  Infective endocarditis: 7.2 g/24 h (with gentamicin)

  Adult meningitis: 14.4 g/24 h

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Post-splenectomy prophylaxis: 600 mg 12 hourly

Give at a rate not >300 mg/min

In renal impairment:

CC (ml/min)	Dose (range depending on severity of infection)
10–20	600 mg–2.4 g every 6 hours
<10	600 mg–1.2 g every 6 hours

How not to use benzylpenicillin

Not for intrathecal use (encephalopathy)

Do not mix in the same syringe with an aminoglycoside (efficacy of aminoglycoside reduced)

Adverse effects

Hypersensitivity

Haemolytic anaemia

Transient neutropenia and thrombocytopenia

Convulsions (can occur in high dose or renal failure)

Cautions

Anaphylactic reactions frequent (1:100,000)

Severe renal impairment (reduce dose, high doses may cause convulsions)

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Beriplex

The coagulation factors II, VII, IX and X, which are synthesized in the liver with the help of vitamin K, are called the prothrombin complex. Beriplex contains the human coagulation factors II, VII, IX and X, and, in addition, the vitamin K-dependent coagulation inhibitors Protein C and Protein S.

Uses

Bleeding in acquired deficiency of prothrombin complex coagulation factors due to vitamin K antagonists (e.g. warfarin), when rapid correction of the deficiency is required

Contraindications

HIT

DIC – Beriplex may only be used after termination of the consumptive state

Administration

Beriplex is presented as a powder containing 250 units human prothrombin complex and is reconstituted in 10 ml WFI.

The dose will depend on the INR and is based on body weight up to but not exceeding 100 kg. For patients weighing more than 100 kg, the maximum single dose should not be exceeded. Administer the reconstituted solution IV, at a rate not more than 8 ml/min.

Pre-treatment INR	2.0–3.9	4.0–6.0	>6.0
Dose of reconstituted product (ml/kg)	1	1.4	2
Dose (units/kg)	25	35	50
Maximum single dose (units) >100 kg	2,500	3,500	5,000

If INR is not known, a dose of 25 units/kg is given, which can be supplemented with a second dose based on the INR if necessary.

The reversal of the vitamin K antagonist is commonly reached 30 minutes after the Beriplex injection. To prevent the need for repeat dosing, consider giving a simultaneous dose of vitamin K, which takes effect within 4–6 hours.

The coagulation status must be monitored regularly to avoid overdosing.

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How not to use Beriplex

Avoid repeated dosing with Beriplex by giving simultaneous dose of vitamin K

Adverse effects

Thromboembolic events (common)

Headache (common)

Pyrexia (common)

Hypersensitivity or allergic reactions (uncommon)

DIC

Cautions

Beriplex is prepared from human blood, so the possibility of transmitting infective agent cannot be totally excluded

Beriplex contains approximately 15 mmol per 100 ml of reconstituted solution

Because of the risk of thromboembolic complications, closely monitor patients with a history of coronary heart disease or myocardial ischaemia

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Bumetanide

A loop diuretic, similar to furosemide but 40 times more potent. Ototoxicity may be less with bumetanide than with furosemide, but nephrotoxicity may be worse.

Uses

Acute oliguric renal failure

May convert acute oliguric to non-oliguric renal failure: other measures must be taken to ensure adequate circulating blood volume and renal perfusion pressure

Pulmonary oedema secondary to acute left ventricular failure

Oedema associated with congestive cardiac failure, hepatic failure and renal disease

Contraindications

Oliguria secondary to hypovolaemia

Administration

- IV bolus: 1–2 mg 1–2 minutes, repeat in 2–3 hours if needed
- IV infusion: 2–5 mg in 100 ml glucose 5% or sodium chloride 0.9% saline, given over 30–60 minutes

Adverse effects

Hyponatraemia, hypokalaemia, hypomagnesaemia

Hyperuricaemia, hyperglycaemia

Hypovolaemia

Ototoxicity

Nephrotoxicity

Pancreatitis

Cautions

Amphotericin (increased risk of hypokalaemia)

Aminoglycosides (increased nephrotoxicity and ototoxicity)

Digoxin toxicity (due to hypokalaemia)

Organ failure

Renal: may need to increase dose for effect

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Buprenorphine Patches

Buprenorphine is an opioid analgesic with a long duration of action. It has both opioid agonist and antagonist properties and its effects are only partially reversed by naloxone.

Uses

Its primary use is as a patch for moderate to severe chronic/cancer pain. The evidence base for use is generally weak and the cost is relatively high. Used patches contain considerable residual buprenorphine so should be disposed of carefully. The onset of action is approximately 20 hours.

Administration

There are several buprenorphine branded patches (e.g. Transtec, Butrans) and they differ in terms of licensed indications, strength, duration to replacement (72/96 hour or 7 day) and cost. To avoid confusion prescribe by brand name. A maximum of two buprenorphine patches may be applied at any one time.

Typically buprenorphine 35 μg per hour is initiated in chronic cancer pain. This dose equivalence is listed below.

Buprenorphine patch (μg/h)	Fentanyl patch (μg/h)	24-hour oral morphine (mg)	Breakthrough oral morphine dose (mg)
35	25	61–90	10–15
52.5	37	91–134	15–20
70	50	135–224	30
105	75	225–314	40
140	100	315–404	60

After buprenorphine patch removal, serum concentrations decrease gradually. It takes about 30 hours for concentrations to decrease by 50% once a Transtec patch is removed (range 22–36 hours) and 12 hours (range 10–24 hours) with a Butrans patch. This should be considered when therapy is to be followed by other opioids. Generally a subsequent opioid should not be administered within 24 hours after removal of a buprenorphine patch.

For reversal: Remove patch, give oxygen by mask

Give IV naloxone 2 mg bolus over 90 seconds

Commence naloxone 4 mg/h IV infusion

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Adverse effects

Erythema on patch removal – remove carefully

Fever

Abdominal pain

Agitation

Vasodilation

Paraesthesia

How not to use buprenorphine patches

Not suitable for use in acute settings with changeable analgesic requirements as it takes a long time to reach steady state, preventing rapid titration

Organ failure

Renal: patch dose as in normal renal function

Liver: avoid or reduce dose

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Chapter

C

Carbocisteine (Mucodyne)

Carbocisteine affects the nature and amount of mucus glycoprotein that is secreted by the respiratory tract. It is a well-tolerated treatment with a favourable safety profile that provides symptomatic relief to some patients with sputum production in COPD. It can be used in the ICU to treat mucous plugging as an alternative to saline or acetylcysteine nebulization. In addition to its mucoregulatory activity, carbocisteine exhibits free-radical scavenging and anti-inflammatory properties. There is a theoretical risk of gastric erosion because carbocisteine may disrupt the gastric mucosal barrier. Peak serum concentrations are achieved at 1–1.7 hours and the plasma half-life is 1.3 hours. It achieves good penetration into lung tissue and bronchial secretions. It is excreted in the urine as unchanged drug and metabolites.

Uses

Reduction of sputum viscosity

Contraindications

Active peptic ulceration

Administration

- Orally: 750 mg 8–12 hourly

Adverse effects

Anaphylactic reactions

Skin rashes/allergy

Gastrointestinal bleeding

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Caspofungin

Caspofungin covers a wider range of *Candida* species, causing invasive candidiasis, than fluconazole, and is active against *Aspergillus* species. It has a better side-effect profile than amphotericin. In mild liver failure, AUC is increased by 20% and moderate liver failure by 75%, hence the dose reduction in moderate liver failure. Side effects are typically mild and rarely lead to discontinuation.

Uses

Invasive candidiasis

Invasive aspergillosis

Contraindications

Breastfeeding

Administration

- IV: Load with 70 mg on day 1, followed by 50 mg daily thereafter, typically for at least 9 days; if >80 kg, continue with maintenance dose of 70 mg daily

  Reconstitute with 10 ml WFI; add the reconstituted solution to a 100 ml or 250 ml bag of sodium chloride 0.9% or Hartmann's solution, given over 1 hour

  Available in vials containing 50 mg and 70 mg powder. Store vials in fridge at 2–8 °C

Child 1–17 years

Children metabolise caspofungin more efficiently than adults and hence they need a relatively higher dose, based on surface area rather than weight; the maximum dose is 70 mg

70 mg/m^2 once daily for 1 day, then 50 mg/m^2 once daily

Dose may be increased to 70 mg/m^2 once daily, if 50 mg/m^2 is tolerated but the response is inadequate

How not to use caspofungin

Do not use diluents containing glucose

Adverse effects

Thrombophlebitis

Fever

https://doi.org/10.1017/9781108349550.003

Headache
Tachycardia
Anaemia
Decreased platelet count
Elevated LFT
Hypokalaemia
Hypomagnesaemia

Cautions

Co-administration with the inducers efavirenz, nevirapine, rifampicin, dexamethasone, phenytoin or carbamazepine may result in a decrease in caspofungin AUC, so increase in the daily dose of caspofungin to 70 mg

Ciclosporin increases the AUC of caspofungin by approximately 35%

Caspofungin lowers trough concentrations of tacrolimus by 26%

Initially, rifampicin causes a 170% increase in trough concentration of caspofungin on the first day of co-administration; after 2 weeks trough levels of caspofungin are reduced by 30%

Organ failure

Renal: No dose adjustment necessary

Hepatic: Mild (Child–Pugh score 5–6): no dose adjustment

Moderate (Child–Pugh score 7–9): 70 mg loading followed by 35 mg daily

Severe (Child–Pugh score >9): no data

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Cefotaxime

A third-generation cephalosporin with enhanced activity against Gram-negative species in comparison with second-generation cephalosporins. It is not active against *Pseudomonas aeruginosa*, enterococci or *Bacteroides spp*. Use is increasingly being compromised by the emergence of Gram-negative strains expressing extended-spectrum beta-lactamases (ESBLs) and chromosomal beta-lactamase producers.

Uses

Surgical prophylaxis, although first- and second-generation cephalosporins are usually preferred

Acute epiglottitis due to *Haemophilus influenzae*

Empiric therapy of meningitis

Intra-abdominal infections including peritonitis

Community-acquired and nosocomial pneumonia

Urinary tract infections

Sepsis of unknown origin

Contraindications

Hypersensitivity to cephalosporins

Serious penicillin hypersensitivity (10% cross-sensitivity)

Porphyria

Administration

- IV: 1 g 12 hourly, increased in life-threatening infections (e.g. meningitis) to 3 g 6 hourly

Reconstitute with 10 ml WFI, given over 3–5 minutes

Infection	Dose (g)	Interval (h)
Mild–moderate	1	12
Moderate–serious	2	8
Life-threatening	3	6

https://doi.org/10.1017/9781108349550.003

Adverse effects

Hypersensitivity
Transient ↑ LFTs
Clostridium difficile-associated diarrhoea

Cautions

Concurrent use of nephrotoxic drugs (aminoglycosides, loop diuretics)
Severe renal impairment (halve dose)
False-positive urinary glucose (if tested for reducing substances)
False-positive Coombs' test

Organ failure

Renal: In severe renal impairment (<10 ml/min), 1 g every 8–12 hours

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Ceftazidime

A third-generation cephalosporin whose activity against Gram-postive organisms, most notably *Staphylococcus aureus*, is diminished in comparison with second-generation cephalosporins, while action against Gram-negative organisms, including *Pseudomonas aeruginosa*, is enhanced. Ceftazidime is not active against enterococci, MRSA or *Bacteroides* spp.

Uses

Acute epiglottitis due to *Haemophilus influenzae*
Meningitis due to *P. aeruginosa*
Intra-abdominal infections including peritonitis
Nosocomial pneumonia
Urinary tract infections
Severe sepsis of unknown origin
Febrile neutropenia

Contraindications

Hypersensitivity to cephalosporins
Serious penicillin hypersensitivity (10% cross-sensitivity)
Porphyria

Administration

- IV: 2 g 8 hourly

  Reconstitute with 10 ml WFI, given over 3–5 minutes

Infection	Dose (g)	Interval (h)
Mild–moderate	0.5–1	12
Moderate–serious	1	8
Life-threatening	2	8

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In renal impairment:

CC (ml/min)	Dose (g)	Interval (h)
31–50 or CVVH rate 1.85–3 l/h	1–2	12
16–30 or CVVH rate to 1–1.8 l/h	1–2	24
6–15	0.5–1	24
<5	0.5–1	48

Adverse effects

Hypersensitivity
Transient ↑ LFTs
Clostridium difficile-associated diarrhoea

Cautions

Renal impairment (reduce dose)
Concurrent use of nephrotoxic drugs (aminoglycosides, loop diuretics)
False-positive urinary glucose (if tested for reducing substances)
False-positive Coombs' test

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Ceftolozane with Tazobactam (Zerbaxa)

Uses

This new antibiotic is licensed to treat complicated intra-abdominal or urinary tract infections. Ceftolozane has similar activity to ceftazidime and ceftriaxone against Gram-postive pathogens. Tazobactam extends activity against extended-spectrum beta-lactamase (ESBL) producers and anaerobic organisms. Ceftolozane has enhanced activity against *Pseudomonas aeruginosa* and most streptococci but has little activity against staphylococci or enterococci.

Contraindications

Hypersensitivity to cephalosporins

Severe hypersensitivity to penicillins or carbapemems

Administration

Each vial contains ceftolozane 1 g and tazobactam 0.5 g, containing 10 mmol of sodium

Stored in a fridge

Reconstitute vial with 10 ml of sodium chloride 0.9% or WFI (final volume 11.4 ml); add the dose to 100 ml of sodium chloride 0.9% or glucose 5%

- IV 1.5 g every 8 hours, infused over 60 minutes; this is the usual dose
- Double dose has be used for severe infections (unlicensed), i.e. 3 g every 8 hours (*J Clin Pharmacol* 2016; 56: 56–66)

In renal impairment:

CC (ml/min)	Dose (g)	Interval (h)
<15	No information	
15–29 or CVVH rate 0.9–1.7 l/h	375 mg (to 750 mg*)	8
30–50 or CVVH rate <1.8–3 l/h	750 mg (to 1.5 g*)	8

* Unlicensed 'double-dose' in severe infection.

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How not to use ceftolozane with tazobactam

Avoid in penicillin-allergic patients with full anaphylaxis

0.5–6.5% of penicillin-sensitive patients will also be allergic to the cephalosporins

Adverse effects

Anxiety

Constipation

Hypotension

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Ceftriaxone

A third-generation cephalosporin which is similar in many respects to cefotaxime, with enhanced activity against Gram-negative species in comparison to second-generation cephalosporins. Ceftriaxone is not active against enterococci, MRSA, *Pseudomonas aeruginosa* or *Bacteroides* spp. Ceftriaxone has a prolonged serum half-life allowing for once-daily dosing. However, twice-daily dosing is normally recommended for severe infections, including meningitis.

Uses

Empiric therapy for meningitis

Intra-abdominal infections including peritonitis

Community-acquired or nosocomial pneumonia

Surgical prophylaxis, although first- and second-generation cephalosporins are usually preferred

Clearance of throat carriage in meningococcal disease

Contraindications

Hypersensitivity to cephalosporins

Serious penicillin hypersensitivity (10% cross-sensitivity)

Porphyria

Administration

- IV: 2 g once daily, increased to 2 g 12 hourly in severe infections
- Reconstitute 2 g vial with 40 ml of glucose 5% or sodium chloride 0.9% given over at least 30 minutes

In renal impairment:

CC (ml/min)	Dose (g)	Interval (h)
CVVH	2	Usual interval
<10	2	24

How not to use ceftriaxone

Not to be dissolved in infusion fluids containing calcium (Hartmann's)

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Adverse effects

Hypersensitivity

Transient ↑ liver enzymes

Clostridium difficile-associated diarrhoea

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Cefuroxime

Cefuroxime is a second-generation cephalosporin, widely used in combination with metronidazole in the post-operative period following most abdominal procedures. It has greater activity against *Staphylococcus aureus* (including penicillinase-producing strains) compared with the third-generation cephalosporins, but is not active against MRSA, enterococcus, *Pseudomonas aeruginosa* or *Bacteroides* spp. It also has poor activity against penicillin-resistant strains of *Streptococcus pneumoniae*.

Uses

Surgical prophylaxis
Acute epiglottitis due to *Haemophilus influenzae*
Intra-abdominal infections including peritonitis
Community-acquired and nosocomial pneumonia
Urinary tract infections
Patients admitted from the community with sepsis of unknown origin
Soft-tissue infections

Contraindications

Hypersensitivity to cephalosporins
Serious penicillin hypersensitivity (10% cross-sensitivity)
Meningitis (high relapse rate)
Porphyria

Administration

- IV: 0.75–1.5 g 6–8 hourly
  Reconstitute with 20 ml WFI, given over 3–5 minutes

In renal impairment:

CC (ml/min)	Dose (g)	Interval (h)
20–50 or CVVH rate 1.2–3 l/h	0.75–1.5	8
10–20 or CVVH rate 0.6–1.2 l/h	0.75–1.5	8–12
<10	0.75–1.5	12–24

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Adverse effects

Hypersensitivity
Transient ↑ LFTs
Clostridium difficile-associated diarrhoea

Cautions

Hypersensitivity to penicillins
Renal impairment

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Chlordiazepoxide

Chlordiazepoxide is a benzodiazepine used to attenuate alcohol withdrawal symptoms, but also has a dependence potential. The risk of dependence is minimized by limiting the duration of treatment and reducing the dose gradually over 7–14 days. It is available as 5 mg and 10 mg capsules or tablets.

Uses

Alcohol withdrawal

Restlessness and agitation

Contraindications

Alcohol-dependent patients who continue to drink

Obstructive sleep apnoea

Severe hepatic impairment

Administration

Alcohol withdrawal:

- Orally:

Day	Dose (mg) at:			
	08:00 h	12:00 h	18:00 h	22:00 h
1	30	30	30	30
2	25	25	25	25
3	20	20	20	20
4	10	10	10	10
5	5	5	5	5
6	–	5	5	5
7	–	–	5	5
8	–	–	–	5

Restlessness and agitation:

- Orally: 10–30 mg 3 times daily

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How not to use chlordiazepoxide

Prolonged use (risk of dependence)
Abrupt withdrawal

Adverse effects

Muscle weakness
Confusion
Ataxia
Hypotension

Cautions

Concurrent use of other CNS depressants will produce excessive sedation
Cardiac and respiratory disease – confusion may indicate hypoxia
Hepatic impairment – sedation can mask hepatic coma (avoid if severe)
Renal impairment – increased cerebral sensitivity

Organ failure

Hepatic: reduced clearance with accumulation. Can precipitate coma
Renal: increased cerebral sensitivity

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Ciclosporin

Ciclosporin is a cyclic peptide molecule derived from a soil fungus. It is a potent nephrotoxin, producing interstitial renal fibrosis with tubular atrophy. Monitoring of ciclosporin blood level is essential.

Normal range: 100–300 µg/l

For renal transplants: lower end of range

For heart/lung/liver: upper end of range

For stem cell transplant: 200–600 µg/l – dependent upon donor, conditioning regimen and T-depletion of graft

Uses

Prevention of organ rejection after transplantation

Administration

- IV dose: 1–5 mg/kg/d, to be diluted 1 in 20 to 1 in 100 with sodium chloride 0.9% or glucose 5%

  To be given over 2–6 hours

  Infusion should be completed within 12 h if using PVC lines

  Switch to oral for long-term therapy

- Oral: 1.5 times IV dose given 12 hourly

  Monitor: hepatic function, renal function, ciclosporin blood level (pre-dose sample)

How not to use ciclosporin

Must not be given as IV bolus

Do not infuse at ≥ 12 hours if using PVC lines – leaching of phthalates from the PVC

Adverse effects

Enhanced renal sensitivity to insults

↑ Plasma urea and serum creatinine secondary to glomerulosclerosis

Hypertension – responds to conventional antihypertensives

Hepatocellular damage (↑ transaminases)

Hyperuricaemia

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Gingival hypertrophy
Hirsutism
Tremors or seizures at high serum levels

Cautions

↑ Susceptibility to infections and lymphoma
↑ Nephrotoxic effects with concurrent use of other nephrotoxic drugs

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Ciprofloxacin

Ciprofloxacin is a fluoroquinolone with bactericidal activity against *Escherichia coli, Klebsiella* spp., *Proteus* spp., *Serratia* spp., *Salmonella* spp., *Campylobacter* spp., *Pseudomonas aeruginosa, Haemophilus influenzae, Neisseria* spp. and *Staphylococcus* spp. Many strains of MRSA in the UK are resistant and the use of ciprofloxacin may be associated with increased rates of MRSA and *C. difficile* colonization. Activity against many other Gram-positive organisms is poor.

Uses

Respiratory tract infection – avoid if possibility of pneumococcal infection

Severe urinary tract infection

Intra-abdominal infections

Meningitis prophylaxis (unlicensed)

Severely ill patients with gastroenteritis

Suspected enteric fever

Sepsis of unknown origin

Administration

For infection:

- IV infusion: 400 mg 12 hourly, given over 30–60 minutes; 400 mg 8 hourly dosing may be required for *P. aeruginosa* and other less susceptible Gram-negative organisms
  Available in 100 ml bottle containing 200 mg ciprofloxacin in sodium chloride 0.9% and 200 ml bottle containing 400 mg ciprofloxacin in sodium chloride 0.9%; contains Na^+ 15.4 mmol/100 ml bottle

  Also available in 100 ml bag containing 200 mg ciprofloxacin in glucose 5% and 200 ml bottle containing 400 mg ciprofloxacin in glucose 5%
- Oral: 500–750 mg 12 hourly

In renal impairment:

CC (ml/min	Dose (% of normal dose)
20–50 or CVVH rate >1.2 l/h	100
10–20 or CVVH rate 0.6–1.2 l/h	50–100
<10	50 (100% if necessary for short periods)

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Meningitis prophylaxis

- Oral: 500 mg as a single dose or 12 hourly for 2 days
  Child 5–12 years: 250 mg orally, as a single dose

How not to use ciprofloxacin

Do not put in fridge (crystal formation)

Do not use as sole agent where pneumococcal infection likely

Adverse effects

Transient increases in bilirubin, liver enzymes and creatinine

Tendon damage and rupture, especially in the elderly and those taking corticosteroids (may occur within 48 hours)

Cautions

Concurrent administration with theophylline (increased plasma level of theophylline)

Concurrent administration with ciclosporin (transient increase in serum creatinine)

Epilepsy (increased risk of fits)

Concurrent administration of corticosteroids (risk of tendon damage and rupture)

Organ failure

Renal: reduce dose

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Clarithromycin

Clarithromycin is an erythromycin derivative, with slightly greater activity, a longer half-life and higher tissue penetration than erythromycin. Adverse effects are thought to be less common than with erythromycin. Resistance rates in Gram-positive organisms limit its use for severe soft-tissue infections.

Uses

Community-acquired pneumonia

Infective exacerbations of COPD

Pharyngeal and sinus infections

Soft-tissue infections

Helicobacter pylori eradication as part of combination therapy with a proton pump inhibitor plus amoxicillin or metronidazole

Administration

- Orally: 250–500 mg 12 hourly
- IV: 500 mg 12 hourly, give over 60 minutes
  Reconstitute in 10 ml WFI; then make up to 250 ml with glucose 5% or sodium chloride 0.9% and give over 60 minutes

How not to use clarithromycin

Should not be given as IV bolus or IM injection

Adverse effects

Gastrointestinal intolerance

↑ LFTs (usually reversible)

Organ failure

Renal: no dose reduction necessary in renal failure

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Clindamycin

Clindamycin is a broad-spectrum antibiotic, active against Gram-positive cocci, including streptococci (except *Streptococcus faecalis*), pneumococci and penicillin-resistant staphylococci, and also against many anaerobes, especially *Bacteroides fragilis*. It is well concentrated in bone and excreted in bile and urine.

Uses

In penicillin allergy cases for aspiration pneumonia, abdominal or soft-tissue infections

Administration

- IV infusion: 600 mg to 2.7 g daily in two to four divided doses
  300 mg (2 ml) and 600 mg (4 ml) ampoules containing 150 mg/ml clindamycin phosphate

  Reconstitute with sodium chloride 0.9% or glucose 5%

  Dilute to a concentration not greater than 18 mg/l

Dose (mg)	Volume of diluent (ml)	Minimum infusion time (min)
300	50	10
600	50	20
900	50–100	30
1,200	100	>40

How not to use clindamycin

Not for IV bolus (hypotension and cardiopulmonary arrest)

Adverse effects

Thrombophlebitis

Hypotension and cardiorespiratory arrest (rapid IV infusion)

Clostridium difficile-associated diarrhoea

Deranged LFTs

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Cautions

Acute porphyrias

Organ failure

Hepatic: reduce dose

Renal: reduce dose

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Clonidine

Clonidine is an α_2-adrenoceptor agonist which may have a protective effect on cardiovascular morbidity and mortality in the critically ill patient. The mechanism of the protective effect is likely to be manifold. α_2-Adrenoceptor agonists attenuate haemodynamic instability, inhibit central sympathetic discharge, reduce peripheral norepinephrine release and dilate post-stenotic coronary vessels. The use of clonidine as an antihypertensive agent has since been superseded by other drugs. It has a useful sedative property, which is synergistic with opioids and other sedative agents. It is a useful short-term adjuvant to sedation, especially following extubation where there is a high sympathetic drive and in the agitated patient. Its usage should generally not usually exceed 3 days, as withdrawal can lead to rebound hypertension and agitation.

Uses

Short-term adjunct to sedation (unlicensed)

Contraindications

Hypotension

Porphyria

Administration

- Orally: 50 μg 8 hourly, may be increased gradually to 400 μg 8 hourly
- IV bolus: 50 μg 8 hourly, given slowly over 10–15 minutes, may be increased gradually to 250 μg 8 hourly
- IV infusion: 30–100 μg/h (up to 200 μg/h have been used)
  Available as 150 μg clonidine hydrochloride in 1 ml ampoule (Catapres)
  750 μg (5 ampoules) made up to 50 ml with glucose 5% or sodium chloride 0.9% (15 μg/ml)

How not to use clonidine

Sudden withdrawal if used for longer than 3 days

Adverse effects

Bradycardia

Hypotension

Fluid retention

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Dry mouth
Sedation
Depression
Constipation

Cautions

Avoid prolonged use and sudden withdrawal (rebound hypertension)
Peripheral vascular disease (concomitant use with beta-blockers may worsen condition)
Second-degree heart block (may progress to complete heart block)
Avoid concomitant use with:

- beta-blockers (bradycardia)
- tricyclics (counteract effect)
- NSAIDs (sodium and water retention)
- digoxin (bradycardia)
- haloperidol (prolongation of QT interval)

Organ failure

Renal: no dose reduction necessary in renal failure, though plasma levels are higher in severe renal dysfunction

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Clopidogrel

In addition to standard therapy (aspirin, LMWH, beta-blocker and nitrate), clopidogrel reduces the risk of MI, stroke and cardiovascular death in patients with unstable angina and non-ST-elevation MI (*N Engl J Med* 2001; **345**: 494–502). The UK National Institute for Health and Care Excellence (NICE) and the European Society of Cardiology both endorse the use of clopidogrel in combination with aspirin in non-ST-elevation acute coronary syndrome patients. Clopidogrel is also used with aspirin in ST-elevation MI and after angioplasty for up to 12 months.

Clopidogrel is a prodrug that is metabolized to an active form, primarily via cytochrome P450 2C19. PPIs inhibit this enzyme to varying degrees, and mechanistic studies show that combined use of clopidogrel with omeprazole or lansoprazole leads to a reduction in activity of clopidogrel as measured by platelet aggregation and associated bio-markers. Avoid omeprazole and esomeprazole in combination with clopidogrel. Pantoprazole is the most appropriate PPI to use in combination. Lansoprazole and rabeprazole are alternatives, but pharmacokinetic data are lacking. There are insufficient data to determine the significance of these interactions. The balance of risks and benefits should guide decision-making.

Uses

Acute coronary syndrome

Prevention of atherothrombotic events in peripheral arterial disease or after MI or ischaemic stroke

Prevention of atherothrombotic and thromboembolic events in patients with atrial fibrillation

Contraindications

Warfarin

Severe liver impairment

Active bleeding

Breastfeeding

Administration

- Unstable angina and non-ST-elevation MI: single 300 mg loading dose (or 600 mg is an unlicensed loading dose that may produce a greater and quicker inhibition of platelet aggregation), followed by 75 mg daily (with aspirin 75 mg/d) for up to 12 months
  AF 75 mg daily (with aspirin)

  Prevention of artherothrombotic events 75 mg daily

https://doi.org/10.1017/9781108349550.003

Monitor: FBC, clotting screen

Discontinue 7 days prior to surgery

How not to use clopidogrel

Omit clopidogrel if patient likely to go for CABG within 5 days

Not recommended under 18 years of age

Pregnancy

Adverse effects

Bleeding (can protect with ranitidine)

Abnormal LFTs and raised serum creatinine

Haematological disorders including pancytopenia

Cautions

Avoid for 7 days after ischaemic stroke

Increased risk of bleeding with the concurrent use of:

- aspirin (although recommended for up to 12 months in CURE study)
- NSAIDs
- heparin
- thrombolytics
- glycoprotein IIb/IIIa inhibitors

Avoid concomitant use of PPIs, fluoxetine, fluconazole, ciprofloxacin and carbamazepine (clopidogrel may be less effective)

Organ failure

Hepatic: avoid in severe liver impairment

Co-Amoxiclav

Co-amoxiclav contains amoxicillin and clavulanic acid. The beta-lactamase inhibitory action of clavulinic acid extends the spectrum of antibacterial activity of amoxicillin.

Uses

Respiratory tract infections

Genitourinary tract infections

Intra-abdominal sepsis

Surgical prophylaxis

Contraindications

Penicillin hypersensitivity

Administration

- IV: 1.2 g 8 hourly (6 hourly in severe infections)
- Reconstitute with 20 ml WFI, given IV over 3–5 minutes

In renal impairment:

For oral therapy, dose reduction is not necessary

IV: Initial dose of 1.2 g, then:

CC (ml/min)	Dose (g)	Interval (h)
>30 or CVVH rate > 1.8 l/h	1.2	Usual interval
10–30 or CVVH rate 0.60–1.8 l/h	1.2	12
<10	1.2 (after initial dose can be reduced to 600 mg every 6 hours)	12

How not to use co-amoxiclav

Do not mix with aminoglycoside in same syringe (will inactivate aminoglycoside)

Adverse effects

Hypersensitivity

https://doi.org/10.1017/9781108349550.003

Cholestatic jaundice (usually self-limiting, up to 2–6 weeks after treatment stops)

Bleeding and prothrombin time may be prolonged

Organ failure

Renal: reduce IV dose

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Codeine Phosphate

Codeine has a low affinity for the μ (OP_3) and *k* (OP_2) opioid receptors. It is relatively more effective when given orally than parenterally. It is useful as an antitussive and for the treatment of diarrhoea. Side effects are uncommon and respiratory depression is seldom a problem. This explains its traditional use to provide analgesia for head-injured and neurosurgical patients. Doses >60 mg do not improve analgesic activity but may increase side effects. Ten per cent undergoes demethylation to morphine – this possibly contributing to the analgesic effect.

Uses

Mild to moderate pain

Diarrhoea and excessive ileostomy output

Antitussive

Contraindications

Airway obstruction

Administration

- Orally: 30–60 mg 4–6 hourly
- IM: 30–60 mg 4–6 hourly

How not to use codeine phosphate

Not for IV use

Adverse effects

Drowsiness

Constipation

Nausea and vomiting

Respiratory depression

Cautions

Enhanced sedative and respiratory depression from interaction with:

- benzodiazepines
- antidepressants
- antipsychotics

MAOI (hypertension, hyperpyrexia, convulsions and coma)

https://doi.org/10.1017/9781108349550.003

Head injury and neurosurgical patients (may exacerbate ↑ ICP as a result of ↑ $PaCO_2$)

May cause renal failure

Organ failure

CNS: sedative effects increased

Hepatic: can precipitate coma

Renal: increase cerebral sensitivity

https://doi.org/10.1017/9781108349550.003

Colistimethate Sodium (Colistin)

Colistin, also known as polymyxin B, has re-emerged for use in severe nosocomal Gram-negative bacterial infections in the ICU. It is effective against *Acinetobacter baumannii, Pseudomonas aeruginosa* and *Klebsiella pneumoniae*. Colistin exhibits a concentration-dependent bactericidal activity. However, in ICU infections, higher doses than have traditionally been used are required. It is used by inhalation in *P. aeruginosa* cystic fibrosis. Colistin has been used in combination with rifampicin, for its synergistic activity. Co-administration with other antibacterials should also be considered in order to prevent the emergence of resistance. Colistin is not absorbed by mouth and is also used as part of a combination of tobramycin/amphotericin (or nystatin)/colistin in liquid and paste form for selective decontamination of the digestive tract (*BMJ* 2014; **348**: g2197). This is widely used in Holland and Scandinavia but less so in the UK and the USA. Sourcing of suitable products is problematic.

No clinically useful absorption of colistin occurs in the gastrointestinal tract. For systemic infection, colistin must be given by injection. The main toxicities with IV treatment are nephrotoxicity and neurotoxicity, but this may reflect the very high doses given, which are much higher than the doses currently recommended by any manufacturer and for which no adjustment was made for renal disease. Neuro- and nephrotoxic effects appear to be transient and subside on discontinuation of therapy or reduction in dose. The main toxicity described with nebulized treatment is bronchospasm, which can be treated or prevented with the use of β_2-agonists such as salbutamol.

Uses

IV in severe nosocomal Gram-negative bacterial infections in the ICU

Prophylactically as selective decontamination of the digestive tract, in combination with an antibiotic and a antifungalplasma cleara

Contraindications

Hypersensitivity to colistin or to polymyxin B

Acute porphyria

Administration

Reconstitute vial with 10 ml of WFI or sodium chloride 0.9%; roll vial in hand, do not shake to avoid foam formation

- IV bolus over 5 minutes or IV infusion – dilute to a suitable volume of sodium chloride 0.9% and administer over 30–60 minutes

https://doi.org/10.1017/9781108349550.003

- IV: 9 million units loading dose, then 4.5 million units every 12 hours
- Nebulized solution: 1–2 million units two to three times daily (maximum 6 million units/d)

In renal impairment:

Nebulized: dose adjustment is not necessary

IV: 9 million units loading dose should be given as independent of renal function, then as below

For CVVH rate >3 l/h: use the usual dose

CC (ml/min)	IV dose (million units)
10–30 or CVVH rate 0.6–1.8 l/h	1.2 million units 12 hourly
10–30 or CVVH rate 0.6–1.7 l/h	2.25–2.75 million units 12 hourly
<10	1.45 million units 12 hourly

Adverse effects

Renal toxicity

Acute porphyria

Facial paraesthesia

Visual disturbance

Psychosis/confusion

Cautions

Inhalation: severe haemoptysis – risk of further haemorrhage

May reduce effectiveness of pyridostigmine

Increased nephrotoxicity with other nephrotoxic drugs (e.g. ciclosporin, vancomycin, aminoglycosides)

Increased effects of neuromuscular blockers and suxamethonium

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Co-Trimoxazole

Co-Trimoxazole contains trimethoprim and sulphamethoxazole. They are used in combination because of their synergistic activity. Increasing resistance to sulphonamides and the high incidence of sulphonamide-related side effects have diminished the value of co-trimoxazole. Trimethoprim alone is now preferred for urinary tract infections and exacerbations of chronic bronchitis. However, high-dose co-trimoxazole is the preferred treatment for *Pneumocystis jirovecii* pneumonia (previously known as *Pneumocystis carinii* pneumonia – PCP). It has certain theoretical advantages over pentamidine: pentamidine accumulates slowly in the lung parenchyma and improvement may occur more slowly; co-trimoxazole has a broad spectrum of activity and may treat any bacterial co-pathogens. Pneumonia caused by *P. jirovecii* occurs in immunosuppressed patients; it is a common cause of pneumonia in AIDS. High-dose co-trimoxazole with corticosteroid therapy is the treatment of choice for moderate to severe infections. Co-trimoxazole prophylaxis should be considered for severely immunocompromised patients.

Uses

Pneumocystis jirovecii pneumonia

Contraindications

Pregnancy

Severe renal/hepatic failure

Blood disorders

Acute porphyria

Administration

Can infuse undiluted solution via central line (unlicensed)

Pneumocystis jirovecii pneumonia:

- 60 mg/kg 12 hourly IV for 14 days followed orally for a further 7 days
  Some units reduce the dose from day 3 to 45 mg/kg 12 hourly as this appears to reduce side effects but maintain efficacy
- IV infusion: dilute every 1 ml (96 mg) in 25 ml glucose 5% or sodium chloride 0.9%, given over 1.5–2 hours
  If fluid restriction necessary, dilute in half the amount of glucose 5%

Adjuvant corticosteroid has been shown to improve survival. The steroid should be started at the same time as the co-trimoxazole and should be withdrawn before the antibiotic treatment is complete

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- Oral prednisolone 50–80 mg daily or IV hydrocortisone 100 mg 6 hourly or IV dexamethasone 8 mg 6 hourly or IV methylprednisolone 1 g for 5 days, then dose reduced to complete 21 days of treatment

P. jirovecii pneumonia prophylaxis:

- Oral: 960 mg daily or 960 mg on alternate days (3 times a week) or 480 mg daily to improve tolerance

In renal impairment:

- CVVH rate >1.8 l/h: normal dose
- CC 15–30 ml/min (or CVVH rate 0.9 to 1.8 l/h): reduce dose to 50% after day 3
- For *P. jirovecii* pneumonia treatment CC <15 ml/min: reduce dose to 50%; should only be given with renal replacement therapy

Note: treatment should be stopped if rashes or serious blood disorders develop. A fall in white cell count should be treated with folic/folinic acid and a dose reduction to 75%.

How not to use co-trimoxazole

Concurrent use of co-trimoxazole and pentamidine is not of benefit and may increase the incidence of serious side effects

Adverse effects

Nausea, vomiting and diarrhoea (including pseudomembranous colitis)

Hyperkalaemia

Rashes (including Stevens–Johnson syndrome)

Blood disorders (includes leukopenia, thrombocytopenia, anaemia)

Fluid overload (due to large volumes required)

Cautions

Elderly

Renal impairment (rashes and blood disorders increase, may cause further deterioration in renal function)

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Cyclizine

Cyclizine is a histamine H_1-receptor antagonist (antihistamine) with anticholinergic/antimuscarinic effects.

Uses

Nausea and vomiting

Administration

- IM/IV/PO/NG: 50 mg 8 hourly

Adverse effects

Anticholinergic: drowsiness, dry mouth, blurred vision, tachycardia, urinary retention

Cautions

Sedative effect enhanced by concurrent use of other CNS depressants

Organ failure

CNS: sedative effects enhanced

https://doi.org/10.1017/9781108349550.003

Chapter

D

Dalteparin (Fragmin)

Dalteparin is an LMWH with greater anti-factor Xa activity than anti-IIa (antithrombin) activity, which theoretically makes it more effective at preventing thrombin formation than standard (unfractionated) heparin with an equal anti-factor Xa and anti-IIa ratio.

After SC injection, LMWHs are better absorbed than unfractionated heparin, and bind less to proteins in plasma and in the endothelial wall. As a result they have around 90% bioavailability compared with 10–30% with unfractionated heparin. After SC injection, the plasma half-life of LMWHs is around 4 hours, enabling a single dose to provide effective anticoagulant activity for up to 24 hours in the treatment of venous thromboembolism, peri- and post-operative surgical thomboprophylaxis, and the prevention of clotting in the extracorporeal circulation during haemodialysis or haemofiltration.

The incidence of bleeding is similar between LMWHs and unfractionated heparin. The incidence of immune-mediated thrombocytopenia is about 2–3% of patients treated with unfractionated heparin, typically developing after 5–10 days' treatment. In clinical trials with dalteparin, thrombocytopenia occurred in up to 1% of patients receiving treatment for unstable angina, undergoing abdominal surgery or hip replacement surgery.

LMWHs are preferred over unfractionated heparin because they are as effective, simplify treatment (once-daily dosing, no IV cannulation), have a lower risk of HIT and monitoring is not required.

Uses

Prophylaxis of DVT

Treatment of DVT and PE or both

Unstable angina

Prevention of clotting in extracorporeal circuits

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Contraindications

Generalized bleeding tendencies

Acute gastrointestinal ulcer

Platelets <50 – seek advice

Cerebral haemorrhage

Subacute endocarditis

HIT

Injuries to and operations on the CNS, eyes and ears

Known haemorrhagic diathesis

Hypersensitivity to dalteparin or other LMWHs and/or heparins

Administration

Post-operative surgical prophylaxis:

- Starting 6–8 h post-operation if no bleeding concerns, then 5,000 units SC once daily, >100 kg 5,000 units twice daily SC, >150 kg 7,500 units twice daily SC (unlicensed dose)

Prophylaxis of DVT in medical patients:

5,000 units once daily SC, >100 kg 5,000 units twice daily SC, 150–200 kg consider 7,500 units twice daily SC (unlicensed dose), >200 kg seek advice

Consider dose reduction to 2,500 units SC daily if weight <45 kg, frail elderly or CC <30 ml/min

Lumbar puncture, epidural insertion/removal, etc. avoid prophylactic dose dalteparin 12 hours before and 4 hours post procedure (12 hours if traumatic)

Treatment of DVT and pulmonary embolus or both:

- Start dalteparin with oral warfarin (as soon as possible) until INR in therapeutic range 200 units/kg once daily SC up to maximum daily dose of 18,000 units or 100 units/kg twice daily if increased risk of haemorrhage

Actual body weight (kg)	Dose (unit) standard risk of bleeding (approximately 200 units/kg SC)	Dose (unit) increased risk of bleeding (approximately 100 u/kg 12 hourly SC)
36–46	7,500 once daily	5,000 am/2,500 pm
46–56	10,000 once daily	5,000 am/5,000 pm
57–68	12,500 once daily	7,500 am/5,000 pm

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(cont.)

Actual body weight (kg)	Dose (unit) standard risk of bleeding (approximately 200 units/kg SC)	Dose (unit) increased risk of bleeding (approximately 100 u/kg 12 hourly SC)
69–82	15,000 once daily	7,500 am/7,500 pm
83–99	18,000 once daily	10,000 am/7,500 pm
100–109	10,000 twice daily	
>110	an increased (unlicensed) dose may be warranted (given in two divided doses), with anti-Xa monitoring	

Acute coronary syndrome:

Acute phase: 120 units/kg 12 hourly SC

Maximum dose: 10,000 units twice daily

Concomitant treatment with low-dose aspirin

Recommended treatment period up to 8 days

- Extended phase: men <70 kg, 5,000 units once daily SC, >70 kg 7,500 units once daily SC
- Women <80 kg, 5,000 units once daily SC, >80 kg 7,500 units once daily SC

Treatment should not be given for more than 45 days

Monitor: platelets; APTT monitoring is not usually required

In overdose, 100 units dalteparin is inhibited by 1 mg protamine

Adverse effects

SC haematoma at injection site

Bleeding at high doses, e.g. anti-factor Xa levels greater than 1.5 units/ml; however, at recommended doses bleeding rarely occurs

Transient increase in liver enzymes (alanine aminotransferase – ALT) but no clinical significance has been demonstrated

Rarely thrombocytopenia

Rarely hypoaldosteronism resulting in increased plasma potassium, particularly in chronic renal failure, diabetes mellitus or pre-existing metabolic acidosis

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Organ failure

Renal: reduce treatment doses where CC <30 ml/min

Dalteparin can be given in two divided doses (unlicensed dose):

CC >30 ml/min or CVVH rate >1.9 l/h: normal dose

CC 25–30 ml/min or CVVH rate 1.5–1.8 l/h: approximately three-quarters of treatment dose

CC 20–24 ml/min or CVVH rate 1.2–1.4 l/h: approximately two-thirds of treatment dose

CC <20 ml/min: approximately 50% of treatment dose

There is an increased risk of bleeding in renal failure and anti-Xa level monitoring is often necessary

For thromboprophylactic doses, it appears safe to use dalteparin 2,500 units SC once daily

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Danaparoid (Orgaran)

Danaparoid preferentially acts on anti-factor Xa rather than anti-thrombin and hence therapy is monitored via anti-Xa levels. For full anticoagulation anti-Xa target 0.5–0.8 units/ml; levels >2 units/ml may lead to serious bleeding complications. It is licensed for prophylaxis and treatment of DVT and PE. It is an option in ICU patients with HIT who need anticoagulation and haemofiltration (unlicensed). Cross-reactivity with HIT immunoglobulin G (IgG) antibody may occur in less than 10% of cases and cannot be predicted by *in vitro* testing prior to onset of therapy.

There is no antidote to its effects, although its action may be partially reversed by protamine. The anti-Xa half-life is 25 hours. Steady-state levels occur after 5 days of therapy in constant conditions. Danaparoid is 50% renally excreted so dose reductions may be required in renal failure and renal replacement therapy.

Uses

Anticoagulation for patients with HIT

Contraindications

Haemophilia and other haemorrhagic disorders
Thrombocytopenia (except HIT)
Recent cerebral haemorrhage
Severe hypertension
Active peptic ulcer (unless this is the reason for operation)
Diabetic retinopathy
Acute bacterial endocarditis
Spinal or epidural anaesthesia with treatment doses of danaparoid

Administration

Danaparoid is available in two strengths:

0.6 ml ampoule containing 750 units
1 ml ampoule containing 1,250 units

Prophylaxis of DVT and PE:

- SC: 750 units SC 12 hourly

Treatment of DVT and PE:

- IV: loading dose (weight dependent) followed by continuous IV infusion

IV loading dose (undiluted) over 15–30 seconds:

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Weight (kg)	Loading dose (units)	Volume of danaparoid 750 units/0.6 ml (ml)
<55 kg	1,250 units	1 ml
55–90 kg	2,500 units	2 ml
>90 kg	3,750 units	3 ml

Followed by IV infusion:

Prepare infusion as follows:

1. Draw up 4 ml of the 750 units/0.6 ml danaparoid solution (5,000 units) into a 50 ml syringe
2. Dilute to 50 ml with either sodium chloride 0.9% or glucose 5%

This solution contains 5,000 units in 50 ml (100 units in 1 ml).
Using a standard strength solution of 100 units in 1 ml:

Dose	Infusion rate (ml/h)	Duration
400 units/h	4	2 h
300 units/h	3	2 h
200 units/h	2	5 d

HIT in haemofiltration

IV loading dose (as previously), then 100 units/h continuous IV infusion, increasing to 200 units/h only if the filter clots or if levels are low and full anticoagulation is required

Monitor anti-Xa levels regularly (e.g. daily)

The IV bolus and infusions can be given by peripheral or central vein

Monitoring of danaparoid

Plasma anti-Xa levels are used to monitor the effects of danaparoid. In general, they are not necessary but should be used if the patient has renal impairment, is on CVVH or is greater than 90 kg in weight

Anti-Xa levels have to be sent to specialist units for assay. Contact your haematology laboratory for advice. Two samples must be collected in citrate bottles (green tube). Sample tubes must be full in order to obtain a viable result

https://doi.org/10.1017/9781108349550.004

	Expected levels
5 to 10 minutes after loading dose	0.5–0.7 units/ml
Adjustment phase of infusion	Not greater than 1 unit/ml
Maintenance infusion	0.5–0.8 units/ml
Patients on CVVH maintenance	0.5–1 units/ml

In renal impairment:

GFR (ml/min)

20–50	Dose as in normal renal function
10–20	Use with caution
<10	Use with caution. Reduce second and subsequent doses for thromboembolism prophylaxis

Adverse effects

Pain at injection site

Bruising

Bleeding

Hypersensitivity reactions (including rash)

Organ failure

Renal: reduce dose

Dantrolene

Dantrolene is thought to work in malignant hyperthermia (MH) by interfering with the release of calcium from the sarcoplasmic reticulum to the myoplasm. The average dose required to reverse the manifestations of MH is 2.5 mg/kg. If a relapse or recurrence occurs, dantrolene should be re-administered at the last effective dose. When used for the short-term treatment of MH there are usually no side effects. Dantrolene has been used in the treatment of hyperthermia and rhabdomyolysis caused by theophylline overdose, consumption of 'Ecstasy' and 'Eve', and in neuroleptic malignant syndrome and thyrotoxic storm. Neuroleptic malignant syndrome is characterized by hyperthermia, muscle rigidity, tachycardia, labile BP, sweating, autonomic dysfunction, urinary incontinence and fluctuating level of consciousness. It has been reported with haloperidol, fluphenazine, chlorpromazine, droperidol, thioridazine, metoclopramide, flupenthixol decanoate and tricyclic antidepressants.

Uses

MH (pp. 326–328)

Neuroleptic malignant syndrome (unlicensed)

Thyrotoxic storm (unlicensed)

Hyperthermia and rhabdomyolysis associated with theophylline overdose, consumption of 'Ecstasy' and 'Eve' (unlicensed)

Contraindications

Hepatic impairment (worsens)

Administration

- IV: 1 mg/kg, repeated PRN up to 10 mg/kg (use actual body weight in obese patients)

  Reconstitute each 20 mg vial with 60 ml WFI and shake well

  Each vial contains a mixture of 20 mg dantrolene sodium, 3 g mannitol and sodium hydroxide to yield a pH 9.5 when reconstituted with 60 ml WFI

Adverse effects

Rash

Diarrhoea

Muscle weakness

Hepatotoxicity

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Cautions

Concurrent use of diltiazem (arrhythmias)

Concurrent use of calcium-channel blockers (hypotension, myocardial depression and hyperkalaemia reported with verapamil)

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Daptomycin

Daptomycin is a cyclic lipopeptide antibiotic, effective against Gram-positive infections. It has a particular role in VRE where linezolid is not suitable due to low platelets or MRSA infection if alternatives are unsuitable or ineffective. It is 90% protein-bound and eliminated by the kidney.

Uses

Gram-positive infections such as VRE, MRSA, *Staphylococcus aureus* (SA) endocarditis

Administration

Licensed dose: complicated skin and soft-tissue infections (cSSTI) without SA 4 mg/kg (with SA 6 mg/kg) IV every 24 hours. In practice for significant ICU infections use the 6 mg/kg dose. Use actual body weight, in extremes of body weight to calculate dose. Vials are 350 mg and 500 mg – and need storage in the fridge.

There is experience with unlicensed higher doses 10 mg/kg per 24 hours in difficult to treat infections (*Adv Ther* 2015; **32**: 1192–1205). Indeed use of 12 mg/kg per day have been reported (unlicensed).

For IV infusion, give intermittently in sodium chloride 0.9%; reconstitute with sodium chloride 0.9% (350 mg in 7 ml, 500 mg in 10 ml); gently rotate vial without shaking; allow to stand for at least 10 minutes then rotate gently to dissolve; dilute requisite dose in 50 ml infusion fluid and give over 30 minutes.

For IV injection, give over 2 minutes.

How not to use daptomycin

Avoid use, if routine alternatives are likely to be effective

Discontinue statins during therapy

Adverse effects

Rhabdomyolysis – measure creatine kinase every 2 days and discontinue therapy if very high

Fungal infections, urinary tract infections

Anaemia

Anxiety, insomnia, dizziness

Hyper- or hypotension

Rash

Infusion site reactions

Raised LFTs

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Cautions

May interfere with PT/INR assay – take blood sample immediately before daptomycin dose

Organ failure

Renal: CC < 30 ml/min, use usual dose (e.g. 4–6 mg/kg) every 48 hours

CC > 30 ml/min or CVVH rate > 1.9 l/h: normal dose

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Desmopressin (DDAVP)

Pituitary diabetes insipidus (DI) results from a deficiency of antidiuretic hormone (ADH) secretion. Desmopressin is an analogue of ADH. Treatment may be required for a limited period only in DI following head trauma or pituitary surgery. It is also used in the differential diagnosis of DI. Restoration of the ability to concentrate urine after water deprivation confirms a diagnosis of pituitary DI. Failure to respond occurs in nephrogenic DI.

Uses

Pituitary DI – diagnosis and treatment

Administration

Diagnosis:

- Intranasally: 20 μg SC/IM: 2 μg

Treatment:

- Intranasally: 5–20 μg once or twice daily
- SC/IM/IV: 1–4 μg daily

  Monitor fluid intake

  Patient should be weighed daily
- Orally: 100–200 μg three times per day (range 50 μg twice daily up to 400 μg three times per day)

Adverse effects

Fluid retention

Hyponatraemia

Headache

Nausea and vomiting

Cautions

Renal impairment

Cardiac disease

Hypertension

Cystic fibrosis (risk of hypernatraemia)

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Dexamethasone

Dexamethasone has very high glucocorticoid activity and insignificant mineralocorticoid activity, making it particularly suitable for conditions where water retention would be a disadvantage. Adjuvant corticosteroid has been shown to improve survival in *Pneumocystis jirovecii* pneumonia (previously known as *Pneumocystis carinii* pneumonia – PCP). It is also a useful anti-emetic when others are contraindicated or ineffective. Its effects are additive to 5-HT_3 antagonists.

Uses

Cerebral oedema

Laryngeal oedema

Adjunct in *Pneumocystis jirovecii* pneumonia (see co-trimoxazole and pentamidine)

Bacterial meningitis, particularly where pneumococcal suspected nausea and vomiting

Contraindications

Systemic infection (unless specific antimicrobial therapy given)

Administration

Cerebral oedema:

- IV bolus: 8 mg initially, then 4 mg 6 hourly as required for 2–10 days

Pneumocystis jirovecii pneumonia:

- IV bolus: 8 mg 6 hourly 5 days, then dose reduced to complete 21 days of treatment

  The steroid should be started at the same time as the co-trimoxazole or pentamidine and should be withdrawn before the antibiotic treatment is complete

Nausea and vomiting:

- 4–8 mg PO/IV 12 hourly
  Give the second dose early afternoon to reduce insomnia

How not to use dexamethasone

Do not stop abruptly after prolonged use (adrenocortical insufficiency)

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Adverse effects

Perineal irritation may follow IV administration of the phosphate ester

Prolonged use may also lead to the following problems:

- increased susceptibility to infections
- impaired wound healing
- peptic ulceration
- muscle weakness (proximal myopathy)
- osteoporosis
- hyperglycaemia
- agitation
- insomnia

Cautions

Diabetes mellitus

Concurrent use of NSAIDs (increased risk of gastrointestinal bleeding)

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Dexmedetomidine

This sedative provides a unique type of sedation, which differs from other agents in terms of the ability to rouse during sedation. Its mechanism of action is similar to clonidine, i.e. it is a selective α_2 receptor agonist. The PRODEX and MIDEX trials (*JAMA* 2012; **307**: 1151–1160) compared dexmedetomidine to propofol and midazolam, respectively. It reported a shorter time for mechanical ventilation for dexmedetomidine compared to midazolam but not propofol; length of stay was similar in ICU and hospital. Dexmedetomidine patients experienced increased hypotension and bradycardia compared with midazolam, although patients were more interactive than with midazolam and propofol. Dexmedetomidine patients had a quicker time to extubation.

The key features of dexmedetomidine are a quick onset and offset of action (the half-life is 90 minutes), and it does not accumulate in renal dysfunction as it is liver metabolized and it generally does not cause respiratory depression. There are a subset of patients who get inadequate sedation from this drug.

While most of the trial data focus on general sedation, there may be particular benefits of this drug in certain subgroups such as:

NIV, where sedation is deemed beneficial or necessary to tolerate, but where respiratory depression from standard sedatives is undesirable and may lead to unnecessary intubation.

Weaning off mechanical ventilation: in the terminal phase of weaning off sedation as an alternative to propofol (where haemodynamic compromise is undesirable) and midazolam (with inherent risks of ICU delirium) as a bridge to analgesia only.

In 'difficult to sedate' patients, as an alternative to clonidine if they do not respond well to it, or if there is a concern of haemodynamic compromise.

Others have used dexmedetomidine for insomnia and delirium.

Uses

Sedation of adult ICU patients requiring a sedation level not deeper than rousal in response to verbal stimulation (corresponding to Richmond Agitation–Sedation Scale (RASS) 0 to –3)

Contraindications

Advanced heart block (grade 2 or 3) unless paced

Uncontrolled hypotension

Acute cerebrovascular conditions

Hypersensitivity to dexmedetomidine or excipients

https://doi.org/10.1017/9781108349550.004

Administration

For patients already intubated and sedated, initial infusion rate of 0.7 μg/kg/h, which may then be adjusted stepwise within the dose range 0.2–1.4 μg/kg/h in order to achieve the desired level of sedation, depending on the patient's response. Propofol or midazolam may be administered if needed until clinical effects are established.

Avoid use a loading dose as it is associated with increased adverse reactions.

Administer centrally or via a large peripheral line. Dilute in glucose 5%, sodium chloride 0.9% or Hartmann's to a final volume of 4 μg/ml; e.g. 2 ml of 100 μg/ml concentrate in 48 ml of diluent. However, in fluid restriction, concentrations up to 10.5 μg/ml have been used in trials (unlicensed), and 1,000 μg in 50 ml in practice (unlicensed).

In obesity a recent study suggests that lean body weight can be used for dosing (*BJA* 2018; **120**: 969e977) (unlicensed).

How not to use

Do not use a loading dose as this increases bradycardia and hypotension

Adverse effects

Hypotension incidence 25% (serious 1.7%)

Hypertension 15%

Bradycardia 13% (serious 0.9%)

Myocardial ischaemia or MI, tachycardia

Hyper-/hypoglycaemia

Nausea/vomiting

Dry mouth

Withdrawal syndrome

Hyperthermia

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Diazepam

Available formulated in either propylene glycol or a lipid emulsion (diazemuls), which causes minimal thrombophlebitis. Also available in a rectal solution (Stesolid) which takes up to 10 minutes to work.

Uses

Termination of epileptic fit

Contraindications

Airway obstruction

Administration

- IV: Diazemuls 5–10 mg over 2 minutes, repeated if necessary after 15 minutes, up to total 30 mg
- PR: Stesolid up to 20 mg

How not to use diazepam

IM injection – painful and unpredictable absorption

Adverse effects

Respiratory depression and apnoea

Drowsiness

Hypotension and bradycardia

Cautions

Airway obstruction with further neurological damage

Enhanced and prolonged sedative effect in the elderly

Additive effects with other CNS depressants

Organ failure

CNS: enhanced and prolonged sedative effect

Respiratory: ↑ respiratory depression

Hepatic: enhanced and prolonged sedative effect. Can precipitate coma

Renal: enhanced and prolonged sedative effect

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Diclofenac

Diclofenac is an NSAID with analgesic, anti-inflammatory and antipyretic properties. It has an opioid-sparing effect. In the critically ill, the side effects of NSAIDs are such that they have to be used with extreme caution – especially where there is a risk of stress ulceration, renal impairment and bleeding diatheses are common. Ensure patient is adequately hydrated.

Uses

Pain, especially musculoskeletal

Antipyretic (unlicensed)

Contraindications

Uncontrolled asthma

Hypersensitivity to aspirin and other NSAIDs (cross-sensitivity)

Active peptic ulceration (bleeding)

Haemophilia and other clotting disorders (bleeding)

Renal and hepatic impairment (worsens)

Hypovolaemia

Anticoagulants including low-dose heparin (bleeding) with IV diclofenac

Administration

Pain:

- IV infusion: 75 mg diluted with 100–500 ml Hartmann's solution, sodium chloride 0.9% or glucose 5%
  For Voltarol: dilution with Hartmann's solution does not require a buffer. If sodium chloride 0.9% or glucose 5% is used, then buffer the solution with sodium bicarbonate (0.5 ml 8.4% or 1 ml 4.2%)

  Give over 30–120 minutes

  Once prepared use immediately

  There is now a preparation of diclofenac, called Dyloject, which does not need diluting or buffering, and can be given as an IV bolus over 3–5 minutes

  Maximum daily dose: 150 mg

  PO/NG: 50 mg 8 hourly – no longer used, rather use safer alternatives such as ibuprofen PO/NG

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Antipyretic:
- IV bolus: 10 mg diluted with 20 ml sodium chloride 0.9%, given over 3 minutes

How not to use diclofenac

Do not give suppository in inflammatory bowel disease affecting anus, rectum and sigmoid colon (worsening of disease)

Adverse effects

Epigastric pain

Peptic ulcer

Rashes

Worsening of LFTs

Prolonged bleeding time (platelet dysfunction)

Acute renal failure – in patients with:

- pre-existing renal and hepatic impairment
- hypovolaemia
- renal hypoperfusion
- sepsis

Cautions

Elderly

Hypovolaemia

Renal and hepatic impairment

Previous peptic ulceration

Organ failure

Hepatic: worsens

Renal: worsens

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Digoxin

Digoxin is a cardiac glycoside with both anti-arrhythmic and inotropic properties. It is useful for controlling the ventricular response in AF and atrial flutter.

Heart failure may also be improved. It is principally excreted unchanged by the kidney and will therefore accumulate in renal impairment.

Uses

SVT

Contraindications

Intermittent complete heart block

Second-degree AV block

WPW syndrome

Hypertrophic obstructive cardiomyopathy

Constrictive pericarditis

Administration

Digoxin: conversion factor from oral to IV = 0.67 i.e. 125 μg PO = 80 μg IV

- IV loading dose: 0.5–1.0 mg in 50 ml glucose 5% or sodium chloride 0.9%, given over 2 hours
- Maintenance dose: 62.5–250 μg daily (renal function is the most important determinant of maintenance dosage)

  CC >20 ml/min or CVVH rate >1.2 l/h: usual dose

  CC 10–20 ml/min, i.e. 125–250 μg per day

  CC <10 ml/min, i.e. 62.5 μg on alternate days or 62.5 μg daily

Monitor: ECG, serum digoxin level (p. 309)

How not to use digoxin

IM injections not recommended

Adverse effects

Anorexia, nausea, vomiting

Diarrhoea, abdominal pain

Visual disturbances, headache

Fatigue, drowsiness, confusion, delirium, hallucinations

https://doi.org/10.1017/9781108349550.004

Arrhythmias – all forms

Heart block

Cautions

Absorption from oral administration reduced by sucralfate and ion-exchange resins, colestyramine and colestipol

Hypokalaemia and hypomagnesaemia increase the sensitivity to digoxin, and the following drugs may predispose to toxicity:

- amphotericin
- β_2 sympathomimetics
- corticosteroids
- loop diuretics
- thiazides

Hypercalcaemia is inhibitory to the positive inotropic action of digoxin and potentiates the toxic effects

Plasma concentration of digoxin increased by:

- amiodarone
- diltiazem
- nicardipine
- propafenone
- quinidine
- verapamil

Digoxin toxicity (direct current (DC) shock may cause fatal ventricular arrhythmia) – stop digoxin at least 24 h before cardioversion

Beta-blockers and verapamil increase AV block and bradycardia

Suxamethonium predisposes to arrhythmias

Organ failure

Renal: toxicity – reduce dose, monitor levels

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Dobutamine

Dobutamine has predominant β_1 effects that increase heart rate and force of contraction. It also has mild β_2 and α_1 effects and decreases peripheral and pulmonary vascular resistance. Systolic BP may be increased because of the augmented cardiac output. Dobutamine has no specific effects on renal or splanchnic blood flow, but may increase renal blood flow due to an increase in cardiac output.

Uses

Low cardiac output states

Contraindications

Before adequate intravascular volume replacement

Idiopathic hypertrophic subaortic stenosis

Administration

- IV infusion: 1–25 μg/kg/min via a central vein

  Titrate dose according to HR, BP, cardiac output, presence of ectopic beats and urine output. Usual dilution is 250 mg made up to 50 ml glucose 5% or sodium chloride 0.9% (5,000 μg/ml)

  Concentrations of 500 mg/50 ml can be used centrally. If limited to peripheral access, give through a large vein, dilute to 1 mg/ml.

Dosage chart (ml/h)

Based on concentration of 5,000 μg/ml solution.

Weight (kg)	Dose (μg/kg/min)					
	2.5	5. 0	7.5	10	15	20
50	1.5	3.0	4.5	6.0	9.0	12.0
60	1.8	3.6	5.4	7.2	10.8	14.5
70	2.1	4.2	6.3	8.4	12.75	16.8
80	2.4	4.8	7.2	9.6	14.4	19.2
90	2.7	5.4	8.1	10.8	16.2	21.6
100	3.0	6.0	9.0	12.0	18.0	24.0
110	3.3	6.6	9.9	13.2	19.8	26.4
120	3.6	7.2	10.8	14.4	21.6	28.8

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How not to use dobutamine

In the absence of invasive cardiac monitoring

Inadequate correction of hypovolaemia before starting dobutamine

Do not connect to CVP lumen used for monitoring pressure (surge of drug during flushing of line)

Incompatible with alkaline solutions, e.g. sodium bicarbonate, furosemide, phenytoin and enoximone

Adverse effects

Tachycardia

Ectopic beats

Cautions

Acute myocardial ischaemia or MI

Beta-blockers (may cause dobutamine to be less effective)

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Dopamine

Dopamine is a naturally occurring catecholamine that acts directly on α-, β_1- and dopaminergic receptors and indirectly by releasing noradrenaline.

- At low doses (0.5–2.5 μg/kg/min) it increases renal and mesenteric blood flow by stimulating dopamine receptors. The ↑ renal blood flow results in ↑ GFR and ↑ renal sodium excretion
- Doses between 2.5 and 10 μg/kg/min stimulate β_1-receptors, causing ↑ myocardial contractility, stroke volume and cardiac output
- Doses >10 μg/kg/min stimulate α-receptors, causing ↑ SVR, ↓ renal blood flow and ↑ potential for arrhythmias

The distinction between dopamine's predominant dopaminergic and β-effects at low doses and α-effects at higher doses is not helpful in clinical practice due to marked inter-individual variation.

Uses

Septic shock

Low cardiac output

Contraindications

Attempt to increase urine output in patients inadequately fluid resuscitated

Phaeochromocytoma

Tachyarrhythmias or VF

Administration

- Larger doses: 2.5–10 μg/kg/min to increase cardiac contractility
- Doses >10 μg/kg/min stimulate α-receptors and may cause renal vasoconstriction

200 mg made up to 50 ml glucose 5% or sodium chloride 0.9% (4,000 μg/ml)

https://doi.org/10.1017/9781108349550.004

Dosage chart (ml/h)

Based on concentration of 4,000 μg/ml solution.

Weight (kg)	Dose (μg/kg/min)				
	2.5	5.0	7.5	10	15
50	1.9	3.8	5.6	7.5	11.3
60	2.3	4.5	6.8	9.0	13.5
70	2.6	5.3	7.9	10.5	15.8
80	3.0	6.0	9.0	12.0	18.0
90	3.4	6.8	10.1	13.5	20.3
100	3.8	7.5	11.3	15	22.5
110	4.1	8.3	12.	16.	24.8

Give via a central vein using accurate infusion pump

1.6 mg/ml solutions may be given via a peripheral line or central line

More concentrated solutions, including the 3.2 mg/ml solution, should be given via a central line only

Reduce dosage if urine output decreases or there is increasing tachycardia or development of new arrhythmias

How not to use dopamine

Do not use a peripheral vein (risk of extravasation)

So-called 'renal dose' dopamine for renal protection (0.5–2.5 μg/kg/min) is no longer recommended (*Crit Care Med* 2008; **36**: 296–327)

Do not connect to CVP lumen used for monitoring pressure (surge of drug during flushing of line)

Incompatible with alkaline solutions, e.g. sodium bicarbonate, furosemide, phenytoin and enoximone

Discard solution if cloudy, discoloured, or >24 hours old

Adverse effects

Ectopic beats

Tachycardia

Angina

https://doi.org/10.1017/9781108349550.004

Gut ischaemia

Vasoconstriction

Cautions

MAOI (reduce dose by one-tenth of usual dose)

Peripheral vascular disease (monitor any changes in colour or temperature of the skin of the extremities)

If extravasation of dopamine occurs – phentolamine 10 mg in 15 ml sodium chloride 0.9% should be infiltrated into the ischaemic area with a 23-gauge needle

Organ failure

May accumulate in septic shock because of ↓ hepatic function

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Dopexamine

Dopexamine is the synthetic analogue of dopamine. It has potent β_2 activity with one-third the potency of dopamine on dopamine 1 receptor (D_1). There is no α-activity. Dopexamine increases HR and CO, causes peripheral vasodilatation, increases renal and splanchnic blood flow and decreases PCWP. Current interest in dopexamine is centred on its dopaminergic and anti-inflammatory activity. The anti-inflammatory activity and improved splanchnic blood flow may be due to dopexamine's β_2 rather than D_1 effect. The usual dose for its anti-inflammatory activity and to improve renal, mesenteric, splanchnic and hepatic blood flow is between 0.25 and 0.5 μg/kg/min. In comparison with other inotropes, dopexamine causes less increase in myocardial oxygen consumption.

Uses

To improve renal, mesenteric, splanchnic and hepatic blood flow

Short-term treatment of acute heart failure

Contraindications

Concurrent MAOI administration

Left ventricular outlet obstruction (HOCM, aortic stenosis)

Phaeochromocytoma

Administration

Correction of hypovolaemia before starting dopexamine

- Dose: start at 0.25 μg/kg/min, increasing up to 6 μg/kg/min

Titrate according to patient's response: HR, rhythm, BP, urine output and, whenever possible, cardiac output

50 mg made up to 50 ml glucose 5% or sodium chloride 0.9% (1,000 μg/ml)

Dosage chart (ml/h)

Based on concentration of 1,000 μg/ml solution.

Weight (kg)	Dose (μg/kg/min)				
	0.25	0.5	1	2	3
50	0.8	1.5	3.0	6.0	9.0
60	0.9	1.8	3.6	7.2	10.8
70	1.1	2.1	4.2	8.4	12.6

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(cont.)

Weight (kg)	Dose (µg/kg/min)				
	0.25	0.5	1	2	3
80	1.2	2.4	4.8	9.6	14.4
90	1.4	2.7	5.4	10.8	16.2
100	1.5	3.0	6.0	12.0	18.0
110	1.7	3.3	6.6	13.2	19.8
120	1.8	3.6	7.2	14.4	21.6

How not to use dopexamine

Do not connect to CVP lumen used for monitoring pressure (surge of drug during flushing of line)

Incompatible with alkaline solutions, e.g. sodium bicarbonate, furosemide, phenytoin and enoximone

Adverse effects

Dose-related increases in HR

Hypotension

Angina

Hypokalaemia

Hyperglycaemia

Cautions

Thrombocytopenia (a further decrease may occur)

Ischaemic heart disease (especially following acute MI)

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Chapter

E

Enoxaparin

Enoxaparin is a widely used LMWH, similar to dalteparin but in comparison it has a longer half-life (7 versus 3–4 hours, respectively).

The incidence of bleeding is similar between LMWHs and unfractionated heparin. The incidence of immune-mediated thrombocytopenia is about 2–3% of patients treated with unfractionated heparin. LMWHs are preferred over unfractionated heparin because they are as effective, simplify treatment (usually once-daily dosing, no IV cannulation), have a lower risk of HIT and monitoring is not required.

Uses

Peri- and post-operative surgical thromboprophylaxis
Medically acutely ill thromboprophylaxis
Treatment of DVT, PE or both
Unstable angina
Prevention of clotting in extracorporeal circuits

Contraindications

Generalized bleeding tendencies
Acute gastrointestinal ulcer
Cerebral haemorrhage
Sub-acute endocarditis
Heparin-induced immune thrombocytopenia
Injuries to and operations on the CNS, eyes and ears
Known haemorrhagic diathesis
Hypersensitivity to enoxaparin or other LMWHs and/or heparins

Administration

Peri- and post-operative surgical prophylaxis – moderate risk:

- 20 mg daily SC

  If CC <30 ml/min (or CVVH rate <1.8 l/h), 20 mg daily SC

Peri- and post-operative surgical prophylaxis – high risk:

- 40 mg daily SC

  If CC <30 ml/min (or CVVH rate <1.8 l/h), 20 mg daily SC

Treatment of DVT and pulmonary embolus or both:

Start enoxaparin with oral warfarin (as soon as possible) until INR in therapeutic range

- 1.5 mg/kg once daily SC

  If CC <30 ml/min (or CVVH rate <1.8 L per hour), 1 mg/kg once daily SC

Acute coronary syndrome:

- 1 mg/kg 12 hourly SC, recommended treatment period up to 8 days

  If CC 20–30 ml/min (or CVVH rate <1.8 l/h), 1 mg/kg once daily SC

  If CC <20 ml/min (or CVVH rate <1.2 l/h) seek advice

  Concomitant treatment with low-dose aspirin

  Monitor: platelets; APTT monitoring is not usually required

  In overdose, 1 mg enoxaparin is inhibited by 1 mg protamine

How not to use enoxaparin

Not to be used for patients with HIT

Adverse effects

SC haematoma at injection site

Bleeding at high doses, e.g. anti-factor Xa levels greater than 1.5 units/ml; however, at recommended doses bleeding rarely occurs

Transient increase in liver enzymes (alanine aminotransferase – ALT) but no clinical significance has been demonstrated

Rarely thrombocytopenia

Rarely hypoaldosteronism, resulting in increased plasma potassium, particularly in chronic renal failure and diabetes mellitus

Cautions

Treatment doses of LMWHs can be used cautiously in renal replacement therapy

Anti-Xa monitoring is required to use safely for very high weight patients

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Enoximone

Enoximone is a selective phosphodiesterase III inhibitor, resulting in increased CO, and decreased PCWP and SVR, without significant increase in HR and myocardial oxygen consumption. It has a long half-life and haemodynamic effects can persist for 8–10 hours after the drug is stopped.

Uses

Severe congestive cardiac failure

Low cardiac output states (used with or without dobutamine)

Contraindications

Severe aortic or pulmonary stenosis (exaggerated hypotension)

HOCM (exaggerated hypotension)

Administration

- IV infusion: 0.5–1.0 mg/kg (this dose can be omitted as can cause hypotension), then 5–20 μg/kg/min maintenance

  Requires direct arterial BP monitoring

  Adjustment of the infusion rate should be made according to haemodynamic response

  Total dose in 24 hours should not exceed 24 mg/kg

  Available in 20 ml ampoules containing 100 mg enoximone (5 mg/ml); dilute this 20 ml solution with 20 ml sodium chloride 0.9% giving a solution containing enoximone 2.5 mg/ml

How not to use enoximone

Glucose 5% or contact with glass may result in crystal formation

Do not dilute with very alkaline solution (incompatible with all catecholamines in solution)

Adverse effects

Hypotension

Arrhythmias

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Cautions

In septic shock, enoximone can cause prolonged hypotension

Organ failure

Renal: reduce dose

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Epoetin

Epoetin (recombinant human erythropoietin) is available as epoetin alpha and beta. Both are similar in clinical efficacy and can be used interchangeably.

Uses

Anaemia associated with erythropoietin deficiency in chronic renal failure

Severe anaemia due to blood loss in Jehovah's Witness (unlicensed)

Contraindications

Uncontrolled hypertension

Anaemia due to iron, folic acid or vitamin B_{12} deficiency

Administration

Chronic renal failure:

Aim to increase haemoglobin concentration at rate not >2 g/100 ml per month to stable level of 10–12 g/100 ml

- SC (maximum 1 ml per injection site) or IV given over 3–5 minutes

Initially 50 units/kg three times weekly, increased according to response in steps of 25 units/kg at intervals of 4 weeks

Maintenance dose (when haemoglobin 10–12 g/100 ml) 50–300 units/kg weekly in two to three divided doses

Severe anaemia due to blood loss in Jehovah's Witness:

- 150–300 units/kg daily SC until desired haemoglobin reached

Supplementary iron (e.g. ferrous sulphate 200 mg PO) and oxygen is mandatory

Monitor: BP, haemoglobin, serum ferritin, platelets, electrolytes

How not to use epoetin

Avoid contact of reconstituted injection with glass; use only plastic materials

Adverse effects

Dose-dependent increase in BP and platelet count

Flu-like symptoms (reduced if IV given over 5 minutes)

Shunt thrombosis

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Hyperkalaemia
Increase in plasma urea, creatinine and phosphate
Convulsions
Skin reactions
Palpebral oedema
MI
Anaphylaxis

Cautions

Hypertension (stop if uncontrolled)
Ischaemic vascular disease
Thrombocytosis (monitor platelet count for first 8 weeks)
Epilepsy
Malignant disease
Chronic liver disease

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Epoprostenol

Epoprostenol has a half-life of only 3 minutes. When given intravenously, it is a potent vasodilator and therefore its side effects include flushing, headaches and hypotension. Epoprostenol may be used instead of or in addition to heparin during haemofiltration to inhibit platelet aggregation. The dose is dictated by clinical need and filter life (ideally at least 2–3 days). There are now two brands of epoprostenol – Flolan (with a solvent pH 12) and Veletri. The preparation of the products is different as described below.

Uses

Haemofiltration (unlicensed), as an alternative to unfractionated heparin in HIT or in addition to heparin if filter life is short

ARDS/pulmonary hypertension (unlicensed)

Peripheral insufficiency

Administration

Haemofiltration:

Infusion into extracorporeal circuit 2–10 ng/kg/min, start 1 hour before haemofiltration

For peripheral insufficiency, administer this dose IV

Available in vials containing 500 μg (500,000 ng) epoprostenol

- Flolan: to prepare 50 ml of 2,000 ng/ml, withdraw 10 ml of 'concentrated solution' (10,000 ng/ml) from a reconstituted 500 μg vial into a 20 ml syringe
  Attach the filter provided

  Withdraw 40 ml of sodium chloride 0.9% into a 50 ml syringe

  Filter the 10 ml of 'concentrated solution' into the 50 ml syringe containing sodium chloride 0.9% over approximately 15 seconds; mix well

  The new pH 12 formulation is stable for 24 hours
- Veletri: Reconstitute each 500 μg vial with 5 ml sodium chloride 0.9% to give a concentration of 100 μg/ml (1,000 ng/ml).

  Roll the vial gently until powder is dissolved

  Further dilute the reconstituted solution immediately, stable for 24 hours

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Dosage chart (ml/h)

Based on concentration of 2,000 ng/ml solution (Flolan).

Weight (kg)	Dose (ng/kg/min)								
	2	3	4	5	6	7	8	9	10
50	0.6	0.9	1.2	1.5	1.8	2.1	2.4	2.7	3.0
60	0.7	1.1	1.4	1.8	2.2	2.5	2.9	3.2	3.6
70	0.8	1.3	1.7	2.1	2.5	2.9	3.4	3.8	4.2
80	1.0	1.4	1.9	2.4	2.9	3.4	3.8	4.3	4.8
90	1.1	1.6	2.2	2.7	3.2	3.8	4.3	4.9	5.4
100	1.2	1.8	2.4	3.0	3.6	4.2	4.8	5.4	6.0

ARDS/pulmonary hypertension:

- Nebulized (unlicensed): 1–20 ng/kg/min of the reconstituted powder (500 µg epoprostenol reconstituted with the 50 ml diluent provided) into ventilator circuit via compressed air nebuliser systems

How not to use epoprostenol

To avoid systemic side effects in CVVH, it may be preferable to administer epoprostenol into the extracorporeal circuit and not into the patient

The integrated syringe pump on some haemofiltration machines may not be accurate enough to deliver the correct dose of epoprostenol. If so, use a stand-alone syringe pump

Adverse effects

Flushing

Headaches

Hypotension

Bradycardia

Cautions

Epoprostenol may potentiate heparin effects

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Erythromycin

Erythromycin has an antibacterial spectrum similar but not identical to that of penicillin; it is thus an alternative in penicillin-allergic patients. Resistance rates in Gram-positive organisms limit its use for severe soft-tissue infections. Erythromycin has also been used as a prokinetic in gastric stasis and in aiding the passage of fine-bore feeding tube beyond the pylorus. Erythromycin is an agonist at motilin receptors. Motilin is a peptide secreted in the small intestine, which induces gastrointestinal contractions, so increasing gut motility. Use as a prokinetic may increase patient colonization with resistant bacterial species, including MRSA.

Uses

Alternative to penicillin (in patients with genuine penicillin allergy)

Community-acquired pneumonia, particularly caused by atypical organisms

Infective exacerbations of COPD

Legionnaires' disease

Pharyngeal and sinus infections

As a prokinetic (unlicensed)

Administration

- IV infusion: 0.5–1.0 g 6 hourly

  Reconstitute with 20 ml WFI, shake well, then further dilute in 250 ml sodium chloride 0.9% given over 1 hour

  CC >10 ml/min (or CVVH rate >0.6 l/h): normal dose

  CC <10 ml/min 50–75% of dose, maximum 2 g daily in split doses
- As a prokinetic: 125 mg 6 hourly PO/NG, 125–250 mg 6–12 hourly IV

How not to use erythromycin

IV bolus is not recommended

No other diluent (apart from WFI) should be used for the initial reconstitution

Do not use concurrently with simvastatin (myopathy) or sertindole (ventricular arrhythmias)

https://doi.org/10.1017/9781108349550.005

Adverse effects

Gastrointestinal intolerance

Hypersensitivity reactions

Reversible hearing loss with large doses

Cholestatic jaundice if given >14 days

Prolongation of QT interval

Cautions

↑ plasma levels of alfentanil, carbamazepine, ciclosporin, midazolam, phenytoin, theophylline, valproate, warfarin and zopiclone

Severe renal impairment (ototoxicity)

Hepatic disease

Organ failure

Renal: reduce dose

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Esmolol (Brevibloc)

Esmolol is a relatively cardioselective beta-blocker with a rapid onset and a very short duration of action. Esmolol is metabolized by esterases in the red blood cells and the elimination half-life is about 9 minutes. It is used IV for the short-term treatment of supraventricular arrhythmias, sinus tachycardia or hypertension and is particularly useful in the peri-operative period.

Uses

AF

Atrial flutter

Sinus tachycardia

Hypertension

Contraindications

Unstable asthma

Severe bradycardia

Sick sinus syndrome

Second- or third-degree AV block

Uncontrolled heart failure

Hypotension

Administration

- IV bolus: 80 mg loading bolus over 15–30 seconds, followed by IV infusion
- IV infusion: 50–200 μg/kg/min (210–840 or 21–84 ml/h in a 70 kg individual)
  Available in 10 ml vial containing 100 mg esmolol (10 mg/ml) to be used undiluted and 10 ml ampoule containing 2.5 g esmolol (250 mg/ml) requiring dilution to 10 mg/ml solution

  Dilute 5 g (two ampoules) in 500 ml sodium chloride 0.9% or glucose 5% (10 mg/ml)

How not to use esmolol

Not compatible with sodium bicarbonate

Esmolol 2.5 g ampoules must be diluted before infusion

https://doi.org/10.1017/9781108349550.005

Adverse effects

Bradycardia

Cautions

Asthma

Heart failure

Hypotension

These side effects should resolve within 30 minutes of discontinuing infusion.

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Chapter

F

Fentanyl

Fentanyl is 100 times as potent as morphine. Its onset of action is within 1–2 minutes after IV injection and a peak effect within 4–5 minutes. The duration of action after a single bolus is 20 minutes. The context-sensitive half-life following IV infusion is prolonged because of its large volume of distribution.

Uses

Analgesia

Contraindications

Airway obstruction

Administration

For sedation:

- IV infusion: 1–5 μg/kg/h

During anaesthesia:

- IV bolus:

  1–3 μg/kg with spontaneous ventilation

  5–10 μg/kg with IPPV

  7–10 μg/kg to obtund pressor response of laryngoscopy

  Up to 100 μg/kg for cardiac surgery

How not to use fentanyl

In combination with an opioid partial agonist, e.g. buprenorphine (antagonizes opioid effects)

https://doi.org/10.1017/9781108349550.006

Adverse effects

Respiratory depression and apnoea
Bradycardia and hypotension
Nausea and vomiting
Delayed gastric emptying
Reduce intestinal mobility
Biliary spasm
Constipation
Urinary retention
Chest wall rigidity (may interfere with ventilation)
Muscular rigidity and hypotension, more common after high dosage

Cautions

Enhanced sedation and respiratory depression from interaction with:

- benzodiazepines
- antidepressants
- antipsychotics

Head injury and neurosurgical patients (may exacerbate ↑ ICP as a result of ↑ $PaCO_2$)

Organ failure

Respiratory: ↑ respiratory depression
Hepatic: enhanced and prolonged sedative effect

https://doi.org/10.1017/9781108349550.006

Fidaxomicin

This is a poorly absorbed, macrocyclic antibiotic with bactericidal activity against *Clostridium difficile*. In a comparison trial (*N Engl J Med* 2011; **364**: 422–431), fidaxomicin was not inferior to vancomycin in the primary endpoint of clinical cure (defined as resolution of diarrhoea for the treatment duration). However, there was a significant difference in the secondary endpoint of recurrence; 15.4% for fidaxomicin compared to 25.3% for vancomycin. The very high cost (£1,600 in the UK for a 10-day course) limits its use. Its place in treating *C. difficile* infections is not clear, but may include previous treatment failures with conventional therapy/concomitant antibiotic therapy/severe cases/or toxin-positive cases.

Uses

Treatment of *C. difficile* infections

Administration

- 200 mg PO/NG every 12 hours for 10 days

  The film coated tablets can be crushed and dissolved in water

How not to use fidaxomicin

Avoid in macrolide allergy

Adverse effects

Nausea and vomiting

Dizziness

Taste disturbance

Dry mouth

Headache

Cautions

Avoid use with amiodarone, ciclosporin, macrolides (clarithromycin and erythromycin), verapamil and ketoconazole

Organ failure

No dose adjustment needed

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Flucloxacillin

Flucloxacillin is a derivative of the basic penicillin structure, which has stability to the staphylococcal penicillinase found in most *Staphylococcus aureus* isolates. It is generally less active than benzylpenicillin against other Gram-positive organisms. Strains which express resistance are designated methicillin-resistant and are known as MRSAs.

Uses

Infections due to penicillinase-producing staphylococci (except MRSA):

- cellulitis
- wound infection
- endocarditis
- adjunct in pneumonia
- osteomyelitis
- septic arthritis

Contraindications

Penicillin hypersensitivity

Administration

- IV: 0.25–2 g 6 hourly, depending on the severity of infection

  For endocarditis (in combination with another antibiotic), 2 g 6 hourly, increasing to 2 g 4 hourly if over 85 kg

  Reconstitute with 20 ml WFI, given over 3–5 minutes

Infection	Dose (g)	Interval (h)
Mild–moderate	0.25–0.5	6
Moderate–serious	1–2	6
Life-threatening	2	6

In renal impairment:

CC >10 ml/min (or CVVH rate >0.6 l/h): normal renal function

CC <10 ml/min dose as in normal renal function up to a total daily dose of 4 g

https://doi.org/10.1017/9781108349550.006

How not to use flucloxacillin

Not for intrathecal use (encephalopathy)

Do not mix in the same syringe with an aminoglycoside (efficacy of aminoglycoside reduced)

Adverse effects

Hypersensitivity

Haemolytic anaemia

Transient neutropenia and thrombocytopenia

Cholestatic jaundice and hepatitis:

- ↑ risk with treatment >2 weeks and increasing age
- may occur up to several weeks after stopping treatment

Cautions

Liver failure (worsening of LFTs)

Organ failure

Renal: reduce dose

Hepatic: avoid

https://doi.org/10.1017/9781108349550.006

Fluconazole

Antifungal active against *Candida albicans, Candida tropicalis, Candida parapsilosis* and *Cryptococcus* spp. It exhibits variable activity against *Candida glabrata* and poor activity for *Candida krusei*. It is rapidly and completely absorbed orally. Oral and IV therapy are equally effective; IV is used for patients who are unable to take it orally. It is widely distributed in tissues and fluids, and it is excreted unchanged in the urine.

Uses

Local or systemic candidiasis

Cryptococcal infections – usually follow-on therapy after amphotericin

Administration

Oropharyngeal candidiasis:

- Orally: 50–100 mg daily for 7–14 days

Oesophageal candidiasis or candiduria:

- Orally: 50–100 mg daily for 14–30 days

Systemic candidiasis or cryptococcal infections:

- IV infusion: 400 mg daily, consider higher doses for less susceptible *Candida* isolates
  Infusion rate 10–20 mg/min

  In obesity, a 12 mg/kg loading dose can be used, followed by 6 mg/kg daily (both doses capped at a maximum weight of 100 kg) (unlicensed practice)

  Continued according to response (at least 6–8 weeks for cryptococcal meningitis; often longer)

In renal impairment:

10 ml/min normal dose

< 10 ml/min use 50% of normal dose

In CVVH double the usual dose used, as fluconazole is effectively cleared by filtration

How not to use fluconazole

Avoid concurrent use with astemizole or terfenadine (arrhythmias)

https://doi.org/10.1017/9781108349550.006

Adverse effects

Rash

Pruritis

Nausea, vomiting, diarrhoea

Raised liver enzymes

Hypersensitivity

Cautions

Renal/hepatic impairment

May increase concentrations of ciclosporin, phenytoin, warfarin, midazolam, theophylline and tacrolimus

Possible increased risk of myopathy with simvastatin and atorvastatin

Organ failure

Renal: reduce dose

https://doi.org/10.1017/9781108349550.006

Flumazenil

Flumazenil is a competitive antagonist at the benzodiazepine receptor. It has a short duration of action (20 minutes).

Uses

To facilitate weaning from ventilation in patients sedated with benzodiazepine

In the management of benzodiazepine overdose

As a diagnostic test for the cause of prolonged sedation

Contraindications

Tricyclic antidepressant and mixed-drug overdose (fits)

Patients on long-term benzodiazepine therapy (withdrawal)

Epileptic patients on benzodiazepines (fits)

Patients with raised ICP (further increase in ICP)

Administration

- IV bolus: 200 μg, repeat at 1-minute intervals until desired response, up to a total dose of 2 mg

  If re-sedation occurs, repeat dose every 20 minutes

How not to use flumazenil

Ensure effects of neuromuscular blockade reversed before using flumazenil

Adverse effects

Dizziness

Agitation

Arrhythmias

Hypertension

Epileptic fits

Cautions

Re-sedation – requires prolonged monitoring if long-acting benzodiazepines have been taken

Organ failure

Hepatic: reduced elimination

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Fondaparinux (Arixtra)

Fondaparinux is a synthetic pentasaccharide that binds to anti-thrombin and enhances the inactivation of clotting factor Xa without interaction with factor II or platelets. It is licensed for thromboprophylaxis and full anticoagulation, including acute coronary syndrome. It can be used in patients with HIT. The main critical care use of this drug will be in HIT and in high-risk post-operative patients. There is no antidote to its use. It has an elimination half-life of 17 hours in the young and 21 hours in the healthy elderly after SC injection, allowing once-daily dosing, but this increases to 29 hours with CC 30–50 ml/min and 72 hours for a CC <30 ml/min. Up to 80% is excreted unmetabolized in the urine, dose reduction and caution are required in renal impairment.

Uses

Anticoagulation in HIT

Prevention of thromboembolism (with or without HIT)

Acute coronary syndrome

Contraindications

Haemophilia and other haemorrhagic disorders

Thrombocytopenia (except HIT)

Recent cerebral haemorrhage

Treatment with DOAC

CC <30 ml/min (or CVVH rate <1.8 l/h)

Severe hypertension

Active peptic ulcer (unless this is the reason for operation)

Diabetic retinopathy

Acute bacterial endocarditis

Spinal or epidural anaesthesia with treatment doses of danaparoid

Administration

Thromboprophylaxis after surgery:

- 2.5 mg SC 6 hours after surgery then 2.5 mg once daily

Thromboprophylaxis in medical patients:

- 2.5 mg SC once daily

https://doi.org/10.1017/9781108349550.006

Treatment of DVT/PE:

Weight	Standard risk of bleeding (SC once daily)	Increased risk of bleeding (SC 12 hourly)
≤45 kg	get advice	
46–50 kg	5 mg	2.5 mg (am)/2.5 mg (pm)
51–100 kg	7.5 mg	5 mg (am)/2.5 mg (pm)
>100 kg	10 mg	5 mg (am)/5 mg (pm)

Warfarin can be started at the same time as fondaparinux (fondaparinux should be continued for at least 5 days and until INR ≥2 for at least 24 hours)

Treatment of superficial-vein thrombosis:

- 50 kg, 2.5 mg SC once daily for at least 30 days (maximum 45 days if high risk of thromboembolic complications); treatment should be stopped 24 hours before surgery and restarted at least 6 hours post-op

Acute coronary syndrome:

- 2.5 mg SC once daily for up to 8 days (or until hospital discharge if sooner); treatment should be stopped 24 hours before CABG surgery (where possible) and restarted 48 hours post-op

In renal impairment:

CC (ml/min)	
20–50 (or CVVH rate 1.8–3 l/h)	Prophylactic dose: 1.5 mg SC daily
30–70 (or CVVH rate 1.8–4.2 l/h) and >100 kg	Treatment of DVT/PE: initial dose of 10 mg SC then reduce to 7.5 mg SC daily
30–40 (or CVVH rate <1.8 – 2.4 l/h)	Seek advice
20–30 (or CVVH rate <1.8 l/h)	Treatment dose is contraindicated; for prophylaxis, reduce dose, use with caution
<20 (or CVVH rate <1.2 l/h)	Do not use (alternative is lower dose LMWH)

https://doi.org/10.1017/9781108349550.006

Adverse effects

Bleeding

Hypersensitivity reactions (including rash)

Caution

If weight <50 kg (plasma clearance reduces with weight leading to increased bleeding risk)

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Furosemide

Furosemide is a widely used loop diuretic. Following an IV bolus, the diuretic effect peaks within 30 minutes. It produces relief of dyspnoea (by reduction in pre-load) sooner than would be expected from the diuresis. The diuretic effect is dose-related. In patients with impaired renal function larger doses may be necessary.

Uses

Acute oliguric renal failure – may convert acute oliguric to nonoliguric renal failure; other measures must be taken to ensure adequate circulating blood volume and renal perfusion pressure

Pulmonary oedema – secondary to acute left ventricular failure

Oedema – associated with congestive cardiac failure, hepatic failure and renal disease

Contraindications

Oliguria secondary to hypovolaemia

Administration

- IV bolus: 10–40 mg over 3–5 minutes
- IV infusion: 2–10 mg/h

For high-dose parenteral therapy (up to 1000 mg/d), dilute in 250– 500 ml sodium chloride 0.9% given at a rate not greater than 240 mg/h

How not to use furosemide

Glucose-containing fluid is not recommended as a diluent (infusion pH >5.5, otherwise may precipitate)

Do not give at >240 mg/h (transient deafness)

Adverse effects

Hyponatraemia, hypokalaemia, hypomagnesaemia

Hyperuricaemia, hyperglycaemia

Ototoxicity

Nephrotoxicity

Pancreatitis

https://doi.org/10.1017/9781108349550.006

Cautions

Amphotericin (increased risk of hypokalaemia)

Aminoglycosides (increased nephrotoxicity and ototoxicity)

Digoxin toxicity (due to hypokalaemia)

Organ failure

Renal: may need to increase dose for effect

https://doi.org/10.1017/9781108349550.006

Chapter

G

Ganciclovir (Cymevene)

Ganciclovir is related to aciclovir but is more active against CMV. It is also more toxic. It causes profound myelosuppression when given with zidovudine; the two should not be given together, particularly during initial ganciclovir therapy.

Uses

CMV infections in immunocompromised patients

Prevention of CMV infection during immunosuppression following organ transplantation

Contraindications

Hypersensitivity to ganciclovir and aciclovir

Abnormally low neutrophil counts

Administration

- IV infusion: 5 mg/kg 12 hourly, given over 1 hour through filter provided Though not cytotoxic, this product should preferably be made up aseptically as it is myelosuppressive. Reconstitute 500 mg powder with 10 ml WFI, then dilute with 50–100 ml sodium chloride 0.9% or glucose 5%

  Wear polythene gloves and safety glasses when preparing solution

  Duration of treatment: 7–14 days for prevention and 14–21 days for treatment

  Ensure adequate hydration

  Monitor: FBC, U&E, LFTs

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In renal impairment:

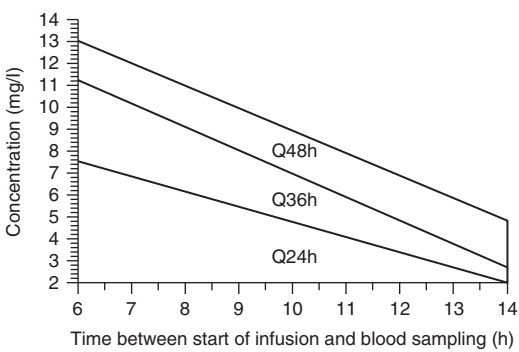
CC (ml/min)	Dose (mg/kg)	Interval (h)
70 or CVVH rate >4.2 l/l	5.0	12
50–69 or CVVH rate 3–4.1 l/h	2.5	12
25–49 or CVVH rate 1.5–2.9 l/h	2.5	24
0–24 or CVVH rate <1.4 l/h	1.25	24

Adverse effects

Leukopenia
Thrombocytopenia
Anaemia
Fever
Rash
Abnormal LFT

Cautions

History of cytopenia, low platelet count
Concurrent use of myelosuppressants
Renal impairment



https://doi.org/10.1017/9781108349550.007

Gentamicin

This is the aminoglycoside most commonly used in the UK. It is effective against Gram-negative organisms such as *Escherichia coli, Klebsiella* spp., *Proteus* spp., *Serratia* spp. and *Pseudomonas aeruginosa*. It is also active against *Staphylococcus aureus*. It is inactive against anaerobes and has poor activity against all streptococci including *Streptococcus pyogenes, Streptococcus pneumoniae* and *Enterococcus* spp. When given in combination with a penicillin, excellent synergy is achieved against most strains of streptococci and enterococci. When used for the 'blind' therapy of undiagnosed serious infections it is usually given with a penicillin and metronidazole, if indicated (e.g. abdominal sepsis).

It is not appreciably absorbed orally and is renally excreted unchanged. In renal impairment the half-life is prolonged. Most side effects are related to sustained high trough concentrations. Efficacy, on the other hand, is related to peak concentrations that are well in excess of the MIC of the infecting organism. Plasma concentration monitoring is essential.

High-dose single daily dosing of aminoglycosides has become more popular. It ensures that target peak concentrations are achieved in all patients and may also be less nephrotoxic. It also makes monitoring of gentamicin levels easier.

Uses

Sepsis of unknown origin (with a penicillin and/or metronidazole)

Intra-abdominal infections (with a penicillin and metronidazole)

Acute pyelonephritis (with ampicillin)

Infective endocarditis (beta-lactam)

Hospital-acquired pneumonia (with a third-generation cephalosporin)

Severe infections due to *P. aeruginosa* (with ceftazidime or piperacillin/tazobactam)

Enterococcal infections (with amoxicillin)

Febrile neutropenia (with ceftazidime or piperacillin/tazobactam)

Contraindications

Pregnancy

Myasthenia gravis

Administration

- Rapid IV bolus: 1–1.5 mg/kg IV 8 hourly

  One hour peak levels should not exceed 10 mg/ml and pre-dose trough should be <2 mg/L

https://doi.org/10.1017/9781108349550.007

In renal impairment, loading dose of 2 mg/kg then:

CC (ml/min)	Dose (mg/kg)	Interval (h)
20–50 or CVVH rate 1.2–3 l/h	1.5	12–24
10–20 or CVVH rate <1.1 l/h	1.0–1.5	12–24
<10	1.0	24–48

Monitor plasma level (p. 309): adjust dose/interval accordingly

- High-dose single daily dosing protocol
  Avoid this regimen in if the CC <20 ml/min (or in CVVH)
- IV infusion: 7 mg/kg in 50 ml glucose 5% or sodium chloride 0.9% given over 1 hour
  For obese patients, corrected body weight should be used (the maximum dose should NOT exceed 640 mg)

  The interval is then decided after referring to the Hartford nomogram (developed and validated by D. P. Nicolau et al., Division of Infectious Diseases, Hartford Hospital, Hartford, Connecticut, USA)

  A blood level is taken after the first dose to determine subsequent dosing interval

  Alternative nomograms have also been developed for 5 mg/kg dosing; do not use this nomogram for any other single dosing protocol

  Monitoring: Take a single blood sample at any time 6–14 hours after the *start* of an IV infusion; it is essential that the *exact* time is recorded accurately (see figure)

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Evaluate the nomogram: if the level lies in the area designated Q24h, Q36h or Q48h, the interval should be every 24, 36 or 48 hourly respectively

Frequency of repeat levels depends on the underlying renal function

If the point is on the line, choose the longer interval

If the dosing interval is greater than 48 hours, an alternative antibiotic should be used

Single daily dosing should not be used for children, pregnant women, burns patients, infective endocarditis and patients with significant pre-existing renal impairment

It should be used with caution in very septic patients with incipient renal failure

How not to use gentamicin

Do not mix in a syringe with penicillins and cephalosporins (aminoglycosides inactivated)

Adverse effects

Nephrotoxicity – ↑ risk with amphotericin, bumetanide, furosemide, vancomycin and lithium

Ototoxicity – ↑ risk with pre-existing renal insufficiency, elderly, bumetanide and furosemide

Prolonged neuromuscular blockade – may be clinically significant in patients being weaned from mechanical ventilation

Cautions

Renal impairment (reduce dose)

Concurrent use of:

- amphotericin – ↑ nephrotoxicity
- bumetanide, furosemide – ↑ ototoxicity
- neuromuscular blockers – prolonged muscle weakness

Organ failure

Renal: increased plasma concentration – ↑ ototoxicity and nephrotoxicity

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Glutamine

Glutamine is primarily synthesized in skeletal muscle and is the most abundant amino acid. It is a major metabolic fuel for the enterocytes in the gut mucosa. Glutamine is also required for lymphocyte and macrophage function, and is a precursor for nucleotide synthesis. Glutathione is a product of glutamine metabolism, and has an important role as an antioxidant. Although not regarded as an essential amino acid, it becomes conditionally essential in catabolic states. Surgery, trauma or sepsis decreases plasma concentrations. Some studies have shown that glutamine-supplemented enteral feeds improve nitrogen balance, reduce infections and length of hospital stay. This may, at least in part, be explained by the reduced bacterial translocation. However, none of these studies has shown improved survival when compared with standard feeds (p. 351).

Uses

Immunonutrition – to maintain gut integrity and prevent bacterial translocation during critical illness

Administration

- Orally: 5 g 6 hourly
  Dissolve the 5 g sachet in 20 ml WFI

Cautions

Phenylketonuria (contains aspartame)

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Glycerol Suppository

Glycerol suppositories act as a rectal stimulant by virtue of the mildly irritant action of glycerol.

Uses

Constipation

Contraindications

Intestinal obstruction

Administration

- PR: 4 g suppository moistened with water before insertion

How not to use glycerol suppository

Not for prolonged use

Adverse effects

Abdominal discomfort

Cautions

Prolonged use (atonic colon and hypokalaemia)

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Glyceryl Trinitrate (GTN)

GTN is a widely used vasodilator that can be administered by continuous IV infusion to enable precise control. Tolerance can occur to its effect. For oral conversion use isosorbide mononitrate or dinitrate.

Uses

Angina

Hypertension

Contraindications

Aortic stenosis

Cardiac tamponade

Constrictive pericarditis

Hypertrophic cardiomyopathy (HOCM)

Hypotension/hypovolaemia

Marked anaemia

Mitral stenosis

Raised ICP due to cerebral haemorrhage or head trauma

Toxic pulmonary oedema

Administration

- IV infusion: up to 12 mg/h
  No dilution required, make up syringe 50 mg 50 ml

  Titrate response according to BP and HR

  Various strengths of GTN patches are available which are occasionally useful, for blood pressure control or in an attempt to increase local perfusion

How not to use GTN

Do not give by IV bolus

Do not connect to CVP lumen used for monitoring pressure (surge of drug during flushing of line)

Adverse effects

Headache

https://doi.org/10.1017/9781108349550.007

Tachycardia
Hypotension

Cautions

Heart failure due to obstruction
Hypothermia
Hypothyroidism

Organ failure

Severe hepatic: no dose adjustment
Severe renal: no dose adjustment

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Chapter

Haloperidol

Haloperidol is a butyrophenone, which is used to treat delirium in the ICU when the oral/NG route is not available (see p. 331). It has anti-emetic and neuroleptic effects, with minimal cardiovascular and respiratory effects. It is a mild alpha-blocker and may cause hypotension in the presence of hypovolaemia.

Uses

Acute agitation and delirium

Contraindications

QT prolongation, torsades de pointe, ventricular arrhythmias, agitation caused by hypoxia, hypokalaemia or a full bladder

Parkinson's disease

Administration

- IV bolus: 2.5–5 mg usually 6 hourly plus when required (unlicensed indication and route)
- IV infusion: 30 mg in 50 ml of glucose 5% at a rate of 0–10 mg/h (unlicensed administration)
- IM: 5–10 mg

  Up to every 4–8 hours

How not to use haloperidol

Hypotension resulting from haloperidol should not be treated with adrenaline as a further decrease in BP may result

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Adverse effects

Extrapyramidal movements
Neuroleptic malignant syndrome (treat with dantrolene)
Prolongation of QT interval (typically by 14 ms)
Concurrent use of other CNS depressants (enhanced sedation)

Organ failure

CNS: sedative effects increased
Hepatic: can precipitate coma
Renal: increased cerebral sensitivity

https://doi.org/10.1017/9781108349550.008

Heparin

Uses

Prophylaxis of DVT and PE
Treatment of DVT and PE
Extracorporeal circuits

Contraindications

Haemophilia and other haemorrhagic disorders
Peptic ulcer
Cerebral haemorrhage
Severe hypertension
Severe liver disease (including oesophageal varices)
Severe renal failure
Thrombocytopenia
Hypersensitivity to heparin

Administration

Prophylaxis of DVT and PE:

- SC: 5,000 units 8–12 hourly until patient is ambulant

Treatment of DVT and PE:

- IV: Loading dose of 5,000 units followed by continuous infusion of 1,000–2,000 units/h 20,000 units heparin in 20 ml undiluted (1000 units/ml)

  Check APTT 6 hours after loading dose and adjust rate to keep APTT between 1.5 and 2.5 times normal (or 2–3 depending on laboratory reference range)

Unfractionated heparin nomogram:

APTT ratio	Infusion rate change (NB: do NOT use this for heparin infusion post-acute MI)
>7	Stop for 1 h, recheck APTT ratio and then reduce by 500 units/h
5.1–7.0	Reduce by 500 units/h
4.1–5.0	Reduce by 300 units/h
3.1–4.0	Reduce by 100 units/h

https://doi.org/10.1017/9781108349550.008

(cont.)

APTT ratio	Infusion rate change (NB: do NOT use this for heparin infusion post-acute MI)
2.6–3.0	Reduce by 50 units/h
1.5–2.5	NO CHANGE
1.2–1.4	Increase by 200 units/h
<1.2	Consider 2,500 units IV bolus, increase by 400 units/h

Start oral warfarin as soon as the patient is stable

Haemofiltration:

1,000 units to run through the system

Then a bolus of 1,500–3,000 units injected into the pre-filter port, followed by 5–10 units/kg/h infused into the pre-filter port

Dose is dictated by clinical need and filter life (ideally at least 2–3 days)

Adverse effects

Haemorrhage

Skin necrosis

Thrombocytopenia

Hypersensitivity

Osteoporosis after prolonged use

Cautions

Hepatic impairment (avoid if severe)

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Hydralazine (Apresoline)

Hydralazine lowers the BP by reducing arterial resistance through a direct relaxation of arteriolar smooth muscle. This effect is limited by reflex tachycardia and so it is best combined with a beta-blocker. Metabolism occurs by hepatic acetylation, the rate of which is genetically determined. Fast acetylators show a reduced therapeutic effect until the enzyme system is saturated.

Uses

All grades of hypertension

Pre-eclampsia

Contraindications

Systemic lupus erythematosus

Dissecting aortic aneurysm

Right ventricular failure due to pulmonary hypertension (cor pulmonale)

Severe tachycardia and heart failure with a high cardiac output state, e.g. thyrotoxicosis

Severe aortic outflow obstruction (aortic stenosis, mitral stenosis, constrictive pericarditis)

Administration

- IV bolus: 10–20 mg over 3–5 minutes
  Reconstitute the ampoule containing 20 mg powder with 1 ml WFI, further dilute with 10 ml sodium chloride 0.9% give over 3–5 minutes

  Expect to see response after 20 minutes

  Repeat after 20–30 minutes as necessary
- IV infusion: 2–15 mg/h

  Reconstitute three ampoules (60 mg) of hydralazine with 1 ml WFI each

  Make up to 60 ml with sodium chloride 0.9% (1 mg/ml)

  Give at a rate between 2 mg/h and 15 mg/h depending on the BP and pulse

  Rapid acetylators may require higher doses
- PO: hypertension 25 mg twice daily (up to 50 mg twice daily)

  Heart failure 25 mg 6–8 hourly, increased every 2 days to 50–75 mg 6 hourly

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How not to use hydralazine

Do not dilute in fluids containing glucose (causes breakdown of hydralazine)

Adverse effects

Headache

Tachycardia

Hypotension

Myocardial ischaemia

Sodium and fluid retention, producing oedema and reduced urinary volume (prevented by concomitant use of a diuretic)

Lupus erythematosus (commoner if slow acetylator status, in women and if treatment >6 months at doses >100 mg daily)

Cautions

Cerebrovascular disease

Cardiac disease (angina, immediately post-MI)

Use with other antihypertensives and nitrate drugs may produce additive hypotensive effects

Organ failure

Hepatic: prolonged effect

Renal: increased hypotensive effect (start with small dose)

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Hydrocortisone

In the critically ill patient, adrenocortical insufficiency should be considered when an inappropriate amount of inotropic support is required. Baseline cortisol levels and a short synacthen test do not predict the response to steroids. In patients who demonstrate a normal short synacthen test, but yet show a dramatic response to steroids, it is possible that the abnormality lies in altered receptor function or glucocorticoid resistance rather than abnormality of the adrenal axis. Baseline cortisol levels and a short synacthen test are worthwhile to assess hypothalamic–pituitary–adrenal axis dysfunction versus steroid unresponsiveness.

Hydrocortisone is available as the sodium succinate or the phosphate ester.

Uses

Adrenal insufficiency (primary or secondary)

Prolonged resistant vasopressor dependent shock

Severe bronchospasm

Hypersensitivity reactions (pp. 321–22)

Fibroproliferative phase of ARDS (unlicensed)

Adjunct in *Pneumocystis jirovecii* pneumonia (see co-trimoxazole and pentamidine)

Contraindications

Systemic infection (unless specific antimicrobial therapy given)

Administration

Adrenal insufficiency:

Major surgery or stress: IV 100–500 mg 6–8 hourly

Minor surgery: IV 50 mg 8–12 hourly

Reduce by 25% per day until normal oral steroids resumed or maintained on 20 mg in the morning and 10 mg in the evening IV

Prolonged resistant vasopressor-dependent shock:

Initial dose 50 mg IV bolus, 6 hourly for 5 days, then 50 mg 12 hourly for 3 days, then 50 mg daily for 3 days, then stop or 50 mg IV bolus followed by infusion of 10 mg/h for up to 48 hours

Fibroproliferative phase of ARDS:

IV infusion: 100–200 mg 6 hourly for up to 3 days, then dose reduced gradually

https://doi.org/10.1017/9781108349550.008

Adjunct in *Pneumocystis jirovecii* pneumonia (see co-trimoxazole and pentamidine):

IV: 100 mg 6 hourly for 5 days, then dose reduced to complete 21 days of treatment

The steroid should be started at the same time as the co-trimoxazole or pentamidine and should be withdrawn before the antibiotic treatment is complete

Reconstitute 100 mg powder with 2 ml WFI; further dilute 200 mg and make up to 40 ml with sodium chloride 0.9% or glucose 5% (5 mg/ml)

How not to use hydrocortisone

Do not stop abruptly (adrenocortical insufficiency)

Adverse effects

Perineal irritation may follow IV administration of the phosphate ester

Prolonged use may also lead to the following problems:

- increased susceptibility to infections
- impaired wound healing
- peptic ulceration
- muscle weakness (proximal myopathy)
- osteoporosis
- hyperglycaemia

Cautions

Diabetes mellitus

Concurrent use of NSAIDs (increased risk of gastrointestinal bleeding)

https://doi.org/10.1017/9781108349550.008

Chapter

Imipenem + Cilastatin (Primaxin)

Imipenem is given in combination with cilastatin, a specific inhibitor of the renal enzyme dehydropeptidase-1 that inactivates imipenem. Imipenem has been widely replaced by meropenem. Imipenem has an extremely wide spectrum of activity, including most aerobic and anaerobic Gram-negative, including those expressing extended-spectrum beta-lactamases (ESBLs), and Gram-positive bacteria (but not MRSA). It has no activity against *Stenotrophomonas maltophilia*, which emerges in some patients treated with imipenem. Acquired resistance is relatively common in *Pseudomonas aeruginosa* and is starting to emerge in some of the Enterobacteriaceae, including *Enterobacter* spp., *Citrobacter* spp. and *Proteus* spp.

Uses

Mixed aerobic/anaerobic infections

Presumptive therapy prior to availability of sensitivities for a wide range of severe infections

Febrile neutropenia

Contraindications

CNS infections (neurotoxicity)

Meningitis (neurotoxicity)

Administration

- IV infusion: 0.5–1 g 6–8 hourly depending on severity of infection

  Dilute with sodium chloride 0.9% or glucose 5% to a concentration of 5 mg/ml

  500 mg: add 100 ml diluent, infuse over 30 minutes

  1 g: add 200 ml diluent, infuse over 60 minutes

  Unstable at room temperature following reconstitution – use immediately

https://doi.org/10.1017/9781108349550.009

In renal impairment:

CC (ml/min)	Dose (g)	Interval (h)
31–70 or CVVH rate 1.8–4.2 l/h	0.5–1	8
21–30 or CVVH rate 1.3–1.7 l/h	0.5–1	12
<20 or CVVH rate <1.3 l/h	0.25*	12

* or 3.5 mg/kg, whichever is lower

How not to use imipenem

Not compatible with diluents containing lactate

Adverse effects

Hypersensitivity reactions
Blood disorders
Positive Coombs' test
↑ LFTs, serum creatinine and blood urea
Myoclonic activity
Convulsions (high doses or renal impairment)

Cautions

Hypersensitivity to penicillins and cephalosporins
Renal impairment
Elderly

Organ failure

Renal: reduce dose

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Immunoglobulin

Human normal immunoglobulin is prepared by cold alcohol fractionation of pooled plasma from over 1,000 donations. Individual donor units of plasma are screened for hepatitis B surface antigen (HBsAg) and for the presence of antibodies to human immunodeficiency virus type 1 (HIV-1), HIV-2 or hepatitis C virus (HCV), which, combined with careful donor selection, minimizes the risk of viral transmission. In addition, the testing for HBsAg, HIV-1, HIV-2 and HCV antibodies is repeated on the plasma pools.

Uses

Guillain–Barré syndrome

Weakness during exacerbations in myasthenia gravis (unlicensed)

Toxic shock syndromes (unlicensed)

Contraindications

Patients with known class-specific antibody to immunoglobulin A (risk of anaphylactoid reactions)

IV immunoglobulin administration and thromboembolic events such as MI, stroke, PE and deep vein thrombosis, which is assumed to be related to a relative increase in blood viscosity

Administration

For Guillain–Barré syndrome and myasthenia gravis:

- IV infusion: 0.4 g/kg IV daily for 5 consecutive days. Repeat at 4-week intervals if necessary

  Patient treated for the first time: give at rate of 30 ml/h, if no adverse effects occur within 15 min, increase rate to maximum of 150 ml/h

  Subsequent infusions: give at rate of 100 ml/h

Toxic shock:

1 g/kg day 1, then 0.5 g/kg for days 2 and 3 (this regimen was used by Darenberg J., et al.; *CID* 2003; **37**: 333–340)

Immunoglobulin distributes poorly into adipose tissue; for patients with BMI ≥30 kg/m ^{2} or if actual weight >20% more than ideal body weight (IBW), consider using adjusted body weight dosing of immunoglobulin, rounded to the nearest 10% of the calculated dose (www.nsd.scot.nhs.uk/Documents/clinimmumoMarch12.pdf)

IBW for males = 50 + [2.3 × (height in inches – 60)]

https://doi.org/10.1017/9781108349550.009

IBW for female = 45.5 + [2.3 × (height in inches – 60)]

Adjusted body weight (kg): = IBW 0.4 [actual body weight (kg) – IBW]

Certain immunoglobulins require refrigeration. These should be allowed to reach room temperature before administration. Once reconstituted, avoid shaking the bottle (risk of foaming). The solution should be used only if it is clear, and given without delay

How not to use immunoglobulins

Should not be mixed with any other drug and should always be given through a separate infusion line

Live virus vaccines (except yellow fever) should be given at least 3 weeks before or 3 months after an injection of normal immunoglobulin. Doses are not necessarily interchangeable between different IV immunoglobulin products, check product literature on www.medicines.org.uk

Adverse effects

Chills

Fever

Transient ↑ serum creatinine ↑ thromboembolic events, e.g. MI, stroke, PE and DVT – assumed to be related to a relative ↑ in blood viscosity

Anaphylaxis (rare)

https://doi.org/10.1017/9781108349550.009

Insulin

Insulin plays a key role in the regulation of carbohydrate, fat and protein metabolism. Hyperglycaemia and insulin resistance are common in critically ill patients, even if they have not previously had diabetes. Two studies by Van den Berghe (*N Engl J Med* 2001; **345**: 1349–1367 and *N Engl J Med* 2006; **354**: 449–461) have shown that tight control of blood glucose levels (between 4.4 and 6.1 mmol/l) reduces mortality among longer-stay (≥3 days) adult intensive care patients. The incidence of complications such as septicaemia, acute renal failure and critical illness polyneuropathy may also be reduced. In practice, however, many centres have found this tight control problematic, with increased risks of hypoglycaemic events. Indeed the NICE-SUGAR study (*N Engl J Med* 2009; **360:** 1283–1297) reported a higher mortality with tight glucose control.

Uses

Hyperglycaemia

Tight glucose control

Emergency treatment of hyperkalaemia (p. 322)

Administration

Hyperglycaemia:

Soluble insulin (e.g. Actrapid) 50 units made up to 50 ml with sodium chloride 0.9%

Adjust rate according to the sliding scale below or guidelines on p. 423

Insulin sliding scale:

Blood sugar (mmol/l)	Rate (ml/h)
<3.5	0
3.6–55	1
5.6–7.0	2
7.1–9.0	3
9.1–11.0	4
11.1–17.0	5
>17.0	6

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The energy and carbohydrate intake must be adequate; this may be in the form of enteral or parenteral feeding, or IV infusion of glucose 10% containing 10–40 mmol/l KCl running at a constant rate appropriate to the patient's fluid requirements (85–125 ml/h)

The blood glucose concentration should be maintained between 4 mmol/l and 10 mmol/l

Monitor: blood glucose 2 hourly until stable, then 4 hourly; serum potassium 12 hourly

How not to use insulin

SC administration not recommended for fine control. Adsorption of insulin occurs with PVC bags (use polypropylene syringes). If an insulin infusion is running with feed and that feed is interrupted, e.g. for the patient to go for a scan, then the insulin rate should be reduced and re-titrated. This is a common cause of hypoglycaemia

Adverse effects

Hypoglycaemia

Cautions

Insulin resistance may occur in patients with high levels of immunoglobulin G antibodies to insulin, obesity, acanthosis nigricans and insulin receptor defects

Co-administration of corticosteroids and inotropes may adversely affect glycaemic control

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Intralipid

Intralipid should be kept in a designated place so that it is readily available in an emergency for the treatment of local anaesthetic toxicity. Its mechanism is unclear, with possibilities including that the lipid binds the local anaesthetic and removes it from the target tissue. It may involve direct cardiac effects, including effects on sodium channels, fatty acid processing and mitochondrial metabolism or permeability. Lipid infusion appears to accelerate redistribution away from the brain and heart, to reservoir organs such as the liver and skeletal muscle.

Uses

This lipid emulsion is used to treat local anaesthetic toxicity (unlicensed). Consult the AAGBI safety guideline (www.aagbi.org/sites/default/files/la_toxicity_2010_0.pdf) on its use. It is licensed for use in the compounding of parenteral nutrition.

Contraindications

Severe disorders of fat metabolism

Administration

Use Intralipid 20% 500 ml bag.

Immediately:

- Bolus IV 20% solution 1.5 ml/kg over 1 minute AND start IV infusion at 15 ml/kg/h

After 5 mins:

If cardiovascular stability is not restored or an adequate circulation deteriorates, give a maximum of two more boluses (same dose), leaving 5 minutes between doses

Continue infusion at the same rate unless cardiovascular stability is not restored or an adequate circulation deteriorates, then double rate to 30 ml/kg/h and continue until stable and adequate circulation restored or until the max cumulative dose of 12 ml/kg/h is given (e.g. a maximum cumulative dose is 840 ml for a 70 kg patient)

Adverse effects

Interference with laboratory testing, may last for several hours

Centrifugation of blood samples substantially reduces interference

https://doi.org/10.1017/9781108349550.009

Rare cases of pancreatitis and DVT

Interference with haemofilter. May cause fat deposition and blood clots in cardiopulmonary bypass and extracorporeal membrane oxygenator circuits

Caution

Allergy to soy protein

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Ipratropium

Ipratropium is an antimuscarinic bronchodilator, traditionally regarded as more effective in relieving bronchoconstriction associated with COPD.

Uses

Reverse bronchospasm, particularly in COPD

Administration

- Nebuliser: 250–500 μg up to 6 hourly, undiluted (if prolonged delivery time desirable then dilute with sodium chloride 0.9% only)

  For patients with chronic bronchitis and hypercapnia, oxygen in high concentration can be dangerous, and nebulisers should be driven by air

How not to use ipratropium

For nebuliser: do not dilute in anything other than sodium chloride 0.9% (hypotonic solution may cause bronchospasm). Ipratropium is not a logical choice for patients with thick secretions as ipratropium may make these worse

Adverse effects

Dry mouth

Tachycardia

Paradoxical bronchospasm (stop giving if suspected)

Acute-angle closure glaucoma (avoid escape from mask to patient's eyes)

Cautions

Prostatic hypertrophy – urinary retention (unless patient's bladder catheterized)

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Isoprenaline

Isoprenaline is a β_1- and β_2-adrenoceptor agonist causing: ↑ HR, ↑ automaticity, contractility, ↓ diastolic BP, ↑ systolic BP, ↑ myocardial oxygen demand and bronchodilation. It has a half-life of <5 minutes.

Uses

Complete heart block, while getting temporary pacing established

Contraindications

Tachyarrhythmias

Heart block caused by digoxin

Administration

- IV infusion: up to 20 μg/min

  4 mg made up to 50 ml glucose 5% (80 μg/ml)

Dose (μg/min)	Infusion rate (ml/h)
1	0.75
2	1.5
4	3
10	7.5
20	15

How not to use isoprenaline

Do not use sodium chloride 0.9% as a diluent

Adverse effects

Tachycardia

Arrhythmias

Angina

Hypotension

Cautions

Risk of arrhythmias with concurrent use of other sympathomimetics and volatile anaesthetics

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Chapter

K

Ketamine (Ketalar)

Ketamine is a non-competitive antagonist of N-methyl-D-aspartate (NMDA) receptors and also binds to *mu* and *kappa* opioid receptors. It is licensed as an anaesthetic agent for diagnostic and surgical procedures and is best suited to shorter procedures. It has a role in the ICU as a co-analgesic, with opioid-sparing properties. It has good analgesic properties in subanaesthetic doses. Use of midazolam or another benzodiazepine as an adjunct to ketamine reduces the incidence of emergence reactions.

Ketamine has also been used for treatment of patients with severe asthma, as it has bronchodilating properties, probably deriving from two different mechanisms – firstly, via a central effect inducing catecholamine release, thereby stimulating beta-2 (β_2)-adrenergic receptors, and secondly, by inhibition of vagal pathways to produce an anticholinergic effect acting directly on bronchial smooth muscle. Ketamine is metabolized in the liver to an active metabolite – norketamine. This has a potency of around one-third that of ketamine. The metabolites are then excreted renally with an elimination half-life of 2–3 hours in adults. Orally administered, ketamine undergoes extensive first-pass metabolism in the liver, resulting in a bioavailability of ~16%.

Ketamine is used recreationally and is illicitly obtained from healthcare sources. Ketamine exerts strong hallucinogenic and euphoric effects, and it is often combined with other club drugs, where it is snorted, injected or ingested. In the UK, ketamine is classified as a 'controlled drug' (CD), and many hospitals require full CD governance (although this is not required by law). Overuse can cause catatonia, inducing a dissociative state, users describe as falling into a 'k--hole'. Ketamine-induced ulcerative cystitis, 'ketamine bladder', can occur with 'ketamine addicts' or 'near-daily' users.

Uses

As a co-analgesic with opioids (unlicensed), for bronchodilation in asthma (unlicensed)

Anaesthetic for short procedures and intubation

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Contraindications

Where elevation of blood pressure would constitute a serious hazard

Eclampsia or pre-eclampsia

Severe coronary or myocardial disease

Cerebrovascular accident or cerebral trauma

Administration

All doses are expressed as the base: 1.15 mg ketamine hydrochloride 1 mg of base.

Analgesia:

- IV infusion: 10–45 mcg/kg/min adjusted according to response; or
- IV loading dose 2–3 mg/kg, can be followed by IV infusion: 0.05–1 mg/kg/h (higher doses have been used); or
- IM: 1.5–2 mg/kg

Anaesthesia:

- IM short procedures: initially 6.5–13 mg/kg (10 mg/kg usually gives 12–25 minutes of surgical anaesthesia); painful diagnostic manoeuvres: initially 4 mg/kg IV
- Intubation: 1–2 mg/kg IV over 2–4 minutes
- Oral ketamine (unlicensed route), e.g. for dressing changes, the IV preparation can be given orally/sublingually: starting dose 10 mg four times daily, up to 200 mg four times daily; this takes 20 minutes to take effect

  Dilute with juice to counter the bitter taste

  This dose causes hypersalivation in 20% of cases

  May be administered with glycopyrollate (to counteract hypersalivation) and midazolam (to counteract hallucination)

Ketamine is available as 200 mg/20 ml, 500 mg/10 ml and 1,000 mg/10 ml vials. The 200 mg/20 ml and 500 mg/10 ml solutions may be used undiluted. The 1,000 mg/10 ml vial should be diluted with an equal volume of sodium chloride 0.9% or glucose 5% to produce a 50 mg/ml solution.

How not to use ketamine

Ketamine should not be mixed in the same syringe/bag as barbiturates or diazepam as a precipitate will form

Adverse effects

Jaundice

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Tachycardia
Hypertension
Delirium
Lowering the seizure threshold
Hallucination
Hypersalivation
Nausea, vomiting
Dizziness and headache

Cautions

Mild-to-moderate hypertension and tachyarrhythmia
Chronic alcoholism and acute alcohol intoxication
Elevated cerebrospinal fluid pressure
Globe injuries and increased intraocular pressure
Neurotic traits or psychiatric illness (e.g. schizophrenia and acute psychosis)
Acute intermittent porphyria
Seizures
Hyperthyroidism or patients receiving thyroid replacement (increased risk of hypertension and tachycardia)
Pulmonary or upper respiratory tract infection (ketamine sensitizes the gag reflex, potentially causing laryngospasm)
Intracranial mass lesions, a presence of head injury, or hydrocephalus
Daily use for a few weeks can cause dependence and tolerance
Ketamine and theophylline reduces the seizure threshold
Ketamine may potentiate the neuromuscular blocking effects of atracurium
Ketamine antagonizes the hypnotic effect of thiopental
With antihypertensives – enhanced hypotensive effect

Organ failure

Renal: no dose adjustment needed
Liver: mild–moderate hepatic cirrhosis, use usual initial dose then halve subsequent doses
Severe hepatic cirrhosis – no information available – manufacturer advises use only if potential benefit outweighs risk

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Chapter

L

Labetalol (Trandate)

Labetalol is a combined α- and β-adrenoceptor antagonist. The proportion of β-blockade to α-blockade when given orally is 3:1, and 7:1 when given IV. It lowers the blood pressure by blocking α-adrenoceptors in arterioles and thereby reduces the peripheral resistance. Concurrent β-blockade protects the heart from reflex sympathetic drive, normally induced by peripheral vasodilatation.

Uses

All grades of hypertension, particularly useful when there is tachycardia

Pre-eclampsia

Contraindications

Asthma (worsens)

Cardiogenic shock (further myocardial depression)

Second- or third-degree heart block

Administration

- Orally: 100–800 mg 12 hourly
- IV bolus: 10–20 mg over 2 minutes, repeat with 40 mg at 10-minute intervals as necessary, up to 300 mg in 24 hours

  Maximum effect usually occurs within 5 minutes and the duration of action is usually 6 hours
- IV infusion: 20–200 mg/h

  Rate: 4–40 ml/h (20–200 mg/h), adjust rate until satisfactory decrease in BP obtained

  Available in 20 ml ampoules containing 100 mg labetalol (5 mg/ml)

  Draw up three ampoules (60 ml) into a 50 ml syringe

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How not to use labetalol

Incompatible with sodium bicarbonate

Adverse effects

Postural hypotension

Bradycardia

Heart failure

Cautions

Rare reports of severe hepatocellular damage (usually reversible)

Presence of labetalol metabolites in urine may result in false-positive test for phaeochromocytoma

Organ failure

Hepatic: reduce dose

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Lactulose

Lactulose is a semi-synthetic disaccharide that is not absorbed from the gastrointestinal tract. It produces an osmotic diarrhoea of low faecal pH, and discourages the proliferation of ammonia-producing organisms.

Uses

Constipation

Hepatic encephalopathy

Contraindications

Intestinal obstruction

Galactosaemia

Administration

Constipation:

- Orally: 15 ml 12 hourly, gradually reduced according to patient's needs

  May take up to 48 h to act

Hepatic encephalopathy:

- Orally: 30–50 ml 8 hourly, subsequently adjusted to produce 2–3 soft stools daily

Adverse effects

Flatulence

Abdominal discomfort

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Levetiracetam (Keppra)

The use of this broad-spectrum anti-epileptic is expanding in the acute setting. It can be given via a number of routes as it is available in IV, tablet and liquid formulations. Monitoring of levels is unnecessary, which simplifies therapy compared with phenytoin and phenobarbital. It is better tolerated than carbamazepine and has few interactions.

Uses

It is licensed for monotherapy and adjunctive treatment of focal seizures with or without secondary generalization, and for adjunctive therapy of myoclonic seizures in patients with juvenile myoclonic epilepsy and primary generalized tonic-clonic seizures; although experience is accumulating in nonconvulsive status epilepticus (if not responding to phenytoin/phenobarbital).

Contraindications

Hypersensitivity to levetiracetam or excipients

Administration

A gradual increase in dose is recommended to minimize cognitive side effects as follows: initially 500 mg twice daily increased after 1–2 weeks by 1 g daily until anti-epileptic control is achieved; maximum 1.5 g twice daily. However, in the ICU, experience suggests that this can be speeded up (unlicensed) in an acute scenario with an initial dose of 1 g twice daily.

When switching between IV and oral routes of administration, the dose is the same, as absorption is nearly 100%.

- IV: add the dose to 100 ml of sodium chloride 0.9% or glucose 5% and administer over 15 minutes. Each 500 mg vial contains 2.5 mmol sodium

CC (ml/min)	Dose (g)	Interval (h)
50–79 or CVVH rate 3–4.7 l/h	250–1,000 mg	12
30–49 or CVVH rate 2.1–2.9 l/h	250–750 mg	12
<30 or < CVVH rate 1.3 l/h	250–500 mg	12

How not to use levetiracetam (Keppra)

Do not withdraw chronic therapy abruptly

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Adverse effects

Hypotension, headache, somnolence

Depression, aggression, anxiety, insomnia, irritability

Leukopenia, neutropenia, pancytopenia, alopecia, toxic epidermal necrolysis, Stevens–Johnson syndrome

Anorexia, cough, asthenia/fatigue

Cautions

Withdraw established therapy slowly, e.g. 500 mg decreases twice daily every 2–4 weeks to avoid precipitating an increase in the frequency of seizures

Organ failure

Renal: see above

Liver: halve dose in severe hepatic impairment if CC <60 ml/min

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Levosimendan

Levosimendan is licensed in several countries for the treatment of acute decompensated congestive heart failure (CHF). Levosimendan acts by sensitizing the myocardium to calcium so that a greater ventricular contraction (cardiac output) can be achieved without increasing oxygen requirements. Levosimendan also causes coronary and systemic vasodilation, mediated by activation of ATP-sensitive sarcolemmal K-channels, and activation of ATP-sensitive mitochondrial K-channels. Levosimendan has also been shown to possess anti-inflammatory properties. As part of the systemic inflammatory response, myocardial dysfunction is commonly associated with severe sepsis. The calcium-sensitising and anti-inflammatory actions of levosimendan provide a strong rationale for its use in sepsis. Studies have shown that levosimendan increases cardiac output and lowers cardiac filling pressures and is associated with a reduction of cardiac symptoms, risk of death and hospitalization. Its action is independent of interactions with beta (β)-adrenergic receptors. Noradrenaline is the initial vasopressor of choice. Vasopressin may be added in resistant hypotension. It is important to use the lowest dose of vasopressor to achieve an acceptable mean arterial pressure to allow tissue perfusion. Additional inotropic agents may be required. Dobutamine, adrenaline and milrinone may be used in the presence of low cardiac output after fluid resuscitation. Levosimendan has a short plasma half-life of approximately 1 hour, is around 95% bound to plasma proteins and is fully metabolized in the liver and intestine into both active and inactive metabolites. Although the infusion is for 24 hours only, the haemodynamic effects persist for up to 7 days, due to the effects of the active metabolite, OR-1896.

Uses

Acute decompensation of severe chronic heart failure despite maximal standard therapy

Low cardiac output syndrome or cardiogenic shock

Septic shock refractory to inotropes (unlicensed)

Contraindications

Right heart failure

High-output failure

Congenital heart disease

Isolated diastolic dysfunction

Hypertrophic cardiomyopathy

Uncorrected stenotic valve disease

Endocarditis

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Administration

- Supplied as 5 ml ampoules containing 12.5 mg levosimendan in 2.5 mg/ml

  Withdraw 5 ml from a 500-ml bag of glucose 5% and replace with 5 ml (12.5 mg) levosimendan

  Final concentration of infusion is 25 μg/ml; administer peripherally or centrally

  No loading dose required; start with continuous infusion of 0.1 μg/kg/min and if tolerated after 2–4 hours increase to 0.2 μg/kg/min for a duration of 24 hours in total

  In the event of excessive hypotension or tachycardia, reduce rate to 0.05 μg/kg/min

Dosage (ml/h)

Based on concentration of 25 μg/ml solution.

Weight (kg)	Infusion rate at 0.1 μg/kg/min (ml/h)	Infusion rate at 0.2 μg/kg/min (ml/h)	Infusion rate at 0.05 μg/kg/min (ml/h)
40	10	19	5
50	12	24	6
60	14	29	7
70	17	34	8
80	19	38	10
90	22	43	11
100	24	48	12
110	26	53	13
120	29	58	14
130	31	62	16

Adverse effects

Headache

Hypotension (<15%)

Arrhythmias (<10%)

Myocardial ischaemia

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Cautions

Hypotension (exacerbation)

Use with milrinone or enoximone as levosimendan may also have phosphodiesterase inhibitory effects

Hepatic failure (reduced clearance)

Organ failure

Renal: unknown, but in practice the dose is not adjusted; active metabolite (ORG 1896) is renally cleared and has a long half-life of ~80 hours

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Lidocaine

This anti-arrhythmic agent suppresses automaticity of conduction and spontaneous depolarization of the ventricles during diastole. Clearance is related to both hepatic blood flow and hepatic function; it will be prolonged in liver disease, cardiac failure and the elderly. The effects after the initial bolus dose last about 20 minutes. An IV infusion is needed to maintain the anti-arrhythmic effect.

The exact mechanism of action by which IV lidocaine demonstrates analgesia and anti-inflammatory properties remains largely unknown

Uses

Prevention of ventricular ectopic beats, VT and VF after MI

Peri- and post-operative pain (unlicensed) (*BJA* Education 2016; **16**: 292–298)

Contraindications

It is no longer the first-line drug in pulseless VT or VF during cardiac arrest

Hypersensitivity to amide-type local anaesthetics (rare)

Heart block (risk of asystole)

Administration

For cardiac indication:

- Loading dose:

  1.5 mg/kg IV over 2 min, repeat after 5 min to a total dose of 3 mg/kg if necessary. Reduce dose in the elderly

- Maintenance dose:

  4 mg/min for first hour

  2 mg/min for second hour

  1 mg/min thereafter

Reduce infusion rates in patients with hepatic impairment, cardiac failure and in the elderly:

Undiluted 40 ml 2% solution (800 mg)

4 mg/min = 12 ml/h

2 mg/min = 6 ml/h

1 mg/min = 3 ml/h

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Continuous ECG and BP monitoring
For pain indication:

- IV lidocaine 1.5mg/kg up to max 100mg (slow IV bolus over 2–4 minutes)

  In patients with co-morbidities or at the discretion of the anaesthetist, the bolus dose can be reduced or omitted

  Administration of bolus dose:

  1.5 mg/kg to be drawn up to the nearest ml and administered

  e.g. 70 kg patient = 1.5 × 70 mg = 105 mg

  Solution is 10 mg/ml therefore 10.5 ml required which should be rounded up to 11 ml

- Infusion:
  Infuse at 1 mg/kg/h; if BMI >30 then use ideal body weight

  Administration of infusion:

  In a 50 ml syringe, draw up 50 ml of 1% lidocaine; solution is still 10 mg/ml

  Set rate on pump according to dose

  e.g. for 70 kg patient at 1 mg/kg/h

  70 × 1 mg = 70 mg/h

  70 mg is 7 ml of solution therefore rate is 7 ml/h

  Intralipid 20% along with the Association of Anaesthetists of Great Britain and Ireland (AAGBI) guideline (www.aagbi.org/sites/default/files/la_toxicity_2010_0.pdf) must be readily available

How not to use lidocaine

Do not give by rapid IV bolus (should not be given at >50 mg/min)

Adverse effects

Observe/monitorfor local anaesthetic toxicity

Signs and symptoms include: light headedness, tinnitus or numbness, tingling around the mouth and lips, metallic taste in the mouth or on the tongue, dizziness/nausea, visual disturbance, muscle twitching, fitting, respiratory depression, cardio-pulmonary arrest, confusion, increased anxiety, irritability

If the patient shows any of the symptoms, stop pump, call cardiac arrest team

Cautions

Elderly (reduced volume of distribution, reduce dose by 50%)

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Hepatic impairment
Cardiac failure
Other class 1 anti-arrhythmics, e.g. phenytoin, may increase risk of toxicity
For pain indication:
Epidural/continuous regional analgesia
Complete heart block, hypovolaemia
Receiving other local anaesthetics
Pregnancy
Electrolyte abnormalities
Recent MI or unstable coronary artery disease
Moderate to severe liver failure
Severe renal impairment
Acidosis
Hypoalbuminaemia
History of seizures, altered lung function and myasthenia gravis,
Interactions including anti-arrhythmics, antipsychotics, antivirals, beta-blockers, diuretics, H_2 antagonists, muscle relaxants

Organ failure

Cardiac: reduce dose
Hepatic: reduce dose

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Linezolid (Zyvox)

Linezolid is the first example of a new class of antibiotics called the oxazolidinones. It is a reversible, non-selective MAOI. It is highly effective against all Gram-positive organisms including MRSA, penicillin-resistant pneumococci and VRE. Emergence of resistance during therapy has been uncommon to date. Linezolid is a useful alternative to the glycopeptides (teicoplanin and vancomycin) in patients with renal impairment as it is not known to be nephrotoxic, and does not require therapeutic dosage monitoring. The oral route (tablets or suspension) has good bioavailability and is therefore given at the same dose as the IV formulation.

Uses

Community-acquired pneumonia

Nosocomial pneumonia (combined with antibiotic active against Gram-negative organisms)

Severe infections due to MRSA

Complicated skin and soft-tissue infections

Infections due to VRE

Contraindications

Concurrent use of MAOIs (types A or B) or within 2 weeks of taking such drugs

Administration

The recommended duration of treatment is 10–14 consecutive days. The safety and effectiveness of linezolid when administered for periods longer than 28 days have not been established.

- Oral: 600 mg 12 hourly

  Also available as suspension (100 mg/5 ml) 30 ml 12 hourly
- IV: 600 mg (300 ml bag containing 2 mg/ml solution) 12 hourly infused over 30–120 minutes

  Monitor FBC weekly (risk of reversible myelosuppression)

How not to use linezolid

Currently licensed for up to 14 days therapy only (risk of myelosuppression may increase with longer duration)

https://doi.org/10.1017/9781108349550.011

Adverse effects

Oral and vaginal candidiasis

Diarrhoea

Nausea

Reversible myelosuppression

Headaches

Cautions

Severe renal failure

Unless close BP monitoring possible, avoid in uncontrolled hypertension, phaeochromocytoma, carcinoid tumour, thyrotoxicosis and patients on SSRIs, tricyclic antidepressants, pethidine, buspirone or sympathomimetics or dopaminergic drugs

Organ failure

Renal: no dose adjustment required

Hepatic: no dose adjustment required

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Liothyronine

Liothyronine has a similar action to levothyroxine but has a more rapid effect and is more rapidly metabolized. Its effects develop after a few hours and disappear within 1–2 days of discontinuing treatment. It is available both as a tablet for oral administration and as a solution for slow IV injection. It is useful in severe hypothyroid states when a rapid response is desired. If adverse effects occur due to excessive dosage, withhold for 1–2 days and restart at a lower dose. The injectable form is useful in patients unable to absorb enterally, but its cost has escalated significantly recently.

Uses

Thyroxine replacement for those unable to absorb enterally

Hypothyroid states, including coma

Contraindications

Thyrotoxicosis

Administration

Hypothyroid coma:

- 5–20 μg (neat or diluted in 5 ml WFI), given by slow IV over 5 minutes, 12 hourly

  Give concurrent hydrocortisone 100 mg IV, 8 hourly, especially if pituitary hypothyroidism suspected

Replacement for those unable to absorb enterally:

- 5–20 μg (neat or diluted in 5 ml WFI), given by slow IV over 5 minutes, 12 hourly, depending on the normal dose of levothyroxine

Equivalent dose:

Oral levothyroxine (μg/d)	IV liothyronine (μg/12 h)
200	20
150	15
100	10
50	5

https://doi.org/10.1017/9781108349550.011

Monitor: ECG before and during treatment; TSH (T3 and T4 may be unreliable in the critically ill); normal range: TSH 0.5–5.7 microunits (mU)/l, T3 1.2–3.0 nmol/l, T4 70–140 nmol/l

How not to use liothyronine

Rapid IV bolus

Adverse effects

Tachycardia

Arrhythmias

Angina

Muscle cramps

Restlessness

Tremors

Cautions

Panhypopituitarism or predisposition to adrenal insufficiency (give hydrocortisone before liothyronine)

Ischaemic heart disease (may worsen ischaemia)

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Loperamide

Loperamide reduces gastrointestinal motility by direct effect on nerve endings and intramural ganglia within the intestinal wall. Very little is absorbed systemically.

Uses

Acute or chronic diarrhoea

Contraindications

Bowel obstruction

Toxic megacolon

Pseudomembranous colitis

Administration

- Orally: 4 mg, then 2 mg after each loose stool to a usual maximum of 16 mg/d

  To reduce high output from stoma, doses of up to 30 mg four times daily have been used (unlicensed dose) – liquid not suitable for this indication, tablets may be preferable

  Available in 2 mg capsules/tablets and 1 mg/5 ml syrup

  Stools should be cultured

Adverse effects

Bloating

Abdominal pain

QT prolongation, torsades de pointes, and cardiac arrest with very high doses; since the duration of action of loperamide is longer than naloxone (1–3 hours), repeated treatment with naloxone might be needed; monitor for at least 48 hours to detect CNS depression

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Lorazepam (Ativan)

Lorazepam may now be the preferred first-line drug for stopping status epilepticus (p. 337). Although it may have a slower onset of action, it carries a lower risk of cardiorespiratory depression (respiratory arrest, hypotension) than diazepam as it is less lipid-soluble. Lorazepam also has a longer duration of anticonvulsant activity compared with diazepam (6–12 hours versus 15–30 minutes after a single bolus).

Uses

Termination of epileptic fit

Contraindications

Airway obstruction

Administration

- IV: 4 mg over 2 minutes, repeated after 10 minutes if no response
- IM: 4 mg, dilute with 1 ml of WFI or sodium chloride 0.9%

Ampoules stored in refrigerator between 0 °C and 4 °C

How not to use lorazepam

IM injection – painful and unpredictable absorption; only use when IV route not possible

Adverse effects

Respiratory depression and apnoea

Drowsiness

Hypotension and bradycardia

Cautions

Airway obstruction with further neurological damage

Enhanced and prolonged sedative effect in the elderly

Additive effects with other CNS depressants

Organ failure

CNS: enhanced and prolonged sedative effect

Respiratory: ↑ respiratory depression

Hepatic: enhanced and prolonged sedative effect; can precipitate coma

Renal: enhanced and prolonged sedative effect

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Chapter

M

Magnesium Sulphate

Like potassium, magnesium is one of the major cations of the body responsible for neurotransmission and neuromuscular excitability. Regulation of magnesium balance is mainly by the kidneys.

Hypomagnesaemia may result from failure to supply adequate intake, from excess NG drainage or suctioning or in acute pancreatitis. It is usually accompanied by a loss of potassium. The patient may become confused and irritable, with muscle twitching.

Hypomagnesaemia should also be suspected in association with other fluid and electrolyte disturbances when the patient develops unexpected neurological features or cardiac arrhythmias.

Magnesium sulphate has long been the mainstay of treatment for pre-eclampsia/eclampsia in America, but the practice in the UK until recently has been to use more specific anticonvulsant and antihypertensive agents. A large international collaborative trial shows a lower risk of recurrent convulsions in eclamptic mothers given magnesium sulphate compared with those given diazepam or phenytoin.

Normal serum magnesium concentration: 0.7–1.0 mmol/l

Therapeutic range for pre-eclampsia/eclampsia: 2.0–3.5 mmol/l

Uses

Hypomagnesaemia

Hypomagnesaemia associated with cardiac arrhythmias

Pre-eclampsia

Anticonvulsant in eclampsia

Acute asthma attack

Cardiac arrest (pp. 316–18)

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Contraindications

Hypocalcaemia (further ↓ Ca^{2+})

Heart block (risk of arrhythmias)

Oliguria

Administration

Magnesium sulphate solution for injection:

Concentration (%)	g/ml	mEq/ml	mmol/ml
10	0.1	0.8	0.4
25	0.25	2	1
50	0.5	4	2

1 g = 8 mEq = 4 mmol

Hypomagnesaemia:

- IV infusion: 10 mmol magnesium sulphate made up to 50 ml with glucose 5%

  Do not give at >30 mmol/h

  Repeat until plasma level is normal

  Concentrations <20% are suitable for peripheral IV administration

Hypomagnesaemia associated with cardiac arrhythmias:

- IV infusion: 20 mmol diluted in 100 ml glucose 5%, given over 1 h

  Do not give at >30 mmol/h

  Repeat until plasma level is normal

  Concentrations <20% are suitable for peripheral IV administration

Pre-eclampsia/eclampsia:

- Loading dose: 4 g (8 ml 50% solution) diluted to 20 ml with sodium chloride 0.9% IV, given over 10 minutes

  Maintenance: 1 g/h IV, as necessary

  Add 10 ml 50% magnesium sulphate to 40 ml sodium chloride 0.9% and infuse at 10 ml/h

  Newborn – monitor for hyporeflexia and respiratory depression

Acute asthma:

- 2 g in 50 ml sodium chloride 0.9% IV, given over 20 minutes

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- Oral therapy: magnesium glycerophosphate (unlicensed product) 1 g tablets contain 4 mmol of Mg^{2+}

  Usual starting adult dose 1–2 tablets 8 hourly

  Monitor: BP, respiratory rate, ECG, tendon reflexes, renal function, serum magnesium level

  Maintain urine output >30 ml/h

How not to use magnesium sulphate

Rapid IV infusion can cause respiratory or cardiac arrest

IM injections (risk of abscess formation)

Adverse effects

Related to serum level:

- 4.0–6.5 mmol/l

  Nausea and vomiting

  Somnolence

  Double vision

  Slurred speech

  Loss of patellar reflex
- 6.5–7.5 mmol/l

  Muscle weakness and paralysis

  Respiratory arrest

  Bradycardia, arrhythmias and hypotension
- >10 mmol/l

  Cardiac arrest

Plasma concentrations >4.0 mmol/l cause toxicity, which may be treated with calcium gluconate 1 g IV (10 ml 10%)

Cautions

Oliguria and renal impairment (↑ risk of toxic levels)

Potentiates both depolarising and non-depolarising muscle relaxants

Organ failure

Renal: reduce dose and slower infusion rate, closer monitoring for signs of toxicity

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Mannitol

Mannitol is an alcohol capable of causing an osmotic diuresis. Available as 10% and 20% solutions. Crystallization may occur at low temperatures. It has a rapid onset of action and duration of action is up to 4 hours. Rapid infusion of mannitol increases the cardiac output and the BP.

Uses

Cerebral oedema

To preserve renal function peri-operatively in jaundiced patients

To initiate diuresis in transplanted kidneys

Rhabdomyolysis

Contraindications

Congestive cardiac failure

Pulmonary oedema (acute expansion of blood volume)

↑ Intravascular volume (further ↑ intravascular volume)

Administration

Cerebral oedema:

- IV infusion: 0.5–1.0 g/kg as a 20% solution, given over 30 minutes

Weight (kg)	Volume of 20% mannitol at 0.5 g/kg (ml)
60	150
70	175
80	200
90	225
100	250

100 ml 20% solution = 20 g

Jaundice:

- Pre-operative:

  Insert urinary catheter

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1,000 ml sodium chloride 0.9% over 1 hour, 2 hours before surgery

250 ml 20% mannitol over 30 minutes, 1 h before surgery

- Peri-operative:

  200–500 ml 20% mannitol if urine output <60 ml/h

  Sodium chloride 0.9% to match urine output

Kidney transplant:

- IV infusion: 0.5–1.0 g/kg over 30 minutes, given with furosemide 40 mg

  IV on reperfusion of transplanted kidney

Rhabdomyolysis:

- IV infusion: 0.5–1.0 g/kg as a 20% solution over 30–60 minutes

How not to use mannitol

Do not give in the same line as blood

Only give mannitol to reduce ICP when the cause is likely to be relieved surgically (rebound increase in ICP)

Adverse effects

Fluid overload

Hyponatraemia and hypokalaemia

Rebound ↑ ICP

Cautions

Extravasation (thrombophlebitis)

Organ failure

Cardiac: worsens

Renal: fluid overload

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Meropenem

Meropenem is a carbapenem, similar to imipenem but is stable to the renal enzyme dehydropeptidase-1, which inactivates imipenem. Meropenem is also less likely to induce seizures than imipenem. Meropenem has an extremely wide spectrum of activity, including most aerobic and anaerobic Gram-negative and -positive bacteria (but not MRSA).

Some units use extended (or even continuous) infusions of meropenem, based on the principle that beta-lactam effectiveness is related to time above the MIC, which is increased by extending the infusion time.

Uses

Meningitis

Mixed aerobic/anaerobic infections

Presumptive therapy of a wide range of severe infections prior to availability of sensitivities

Febrile neutropenia

Contraindications

Hypersensitivity to beta-lactams

Infections caused by MRSA

Administration

Conventional dosing:

- IV: 0.5–1 g 8 hourly, given over 5 minutes

  Reconstitute with 10 ml WFI
- IV infusion: 0.5–1 g (up to 2 g in less sensitive species) 8 hourly, given over 15–30 minutes

  For neutropenic sepsis 1 g 8 hourly

  For meningitis, increase to 2 g 8 hourly

In renal impairment:

CC (ml/min)	Dose*	Interval (h)
26–50 or CVVH rate 1.5–3 l/h	1 unit dose	12
10–25 or CVVH rate 0.6–1.4 l/h	0.5 unit dose	12
<10	0.5 unit dose	24

* Based on unit doses of 0.5, 1 or 2 g (dependent on indication)

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Extended infusions:

Different (unlicensed) regimens are in use

- 0.5 g loading dose, then 0.5 g 6 hourly over a 3-hour infusion

  Add dose to 50 ml bags of sodium chloride 0.9%

CC (ml/min)	Dose	Interval (h)
>10 or CVVH	0.5 g over 3 h	6
<10	0.5 g over 3 h	12

- 1 g loading dose, then 1 g 8 hourly over a 3–4-hour infusion

CC (ml/min)	Dose	Interval (h)
>20 or CVVH	1 g over 3–4 h	8–12
<20	1 g over 3–4 h	12

Monitor: FBC, LFT

Adverse effects

Thrombophlebitis

Hypersensitivity reactions

Positive Coombs' test

Reversible thrombocythaemia, thrombocytopenia, eosinophilia and neutropenia

Abnormal LFT (↑ bilirubin, transaminases and alkaline phosphatase)

Cautions

Hypersensitivity to penicillins and cephalosporins

Hepatic impairment

Renal impairment

Concurrent use of nephrotoxic drugs

Organ failure

Hepatic: worsens

Renal: reduce dose

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Metaraminol (Aramine)

Metaraminol is a sympathomimetic agent with α_1 effect and it releases noradrenaline from its storage sites indirectly. It can be used as a vasopressor to increase the blood pressure in patients with hypotension, resulting from septic shock and SIRS. It is also used in anaesthesia to counteract the hypotensive effect of epidural and spinal anaesthetics. It is a useful vasopressor when central venous access is not available. The effect starts approximately 1 minute after IV bolus. Reflex bradycardia may occur in response to the increase in BP.

Uses

Hypotension (for patients without central venous access), though for septic shock, central access and noradrenaline administration should be expedited

Contraindications

Peripheral or mesenteric vascular thrombosis (may extend infraction area)

Profound hypoxia or hypercapnia (risk of arrhythmias)

Administration

- IV bolus: 0.5–1 mg, given over 3 minutes
  Reconstitute with 10 ml WFI
- IV infusion: 0.5–5 mg/h
  Titrate the infusion rate according to the patient's BP

  Draw up two ampoules of metaraminol (10 mg in 1 ml) in a 60 ml syringe

  Make up to 40 ml with sodium chloride 0.9% or glucose 5%

  The concentration of the final solution is 20 mg in 40 ml (0.5 mg/ml)

Adverse effects

Hypertension

Bradycardia

Arrhythmias

Cautions

Extravasation (phentolamine may be beneficial)

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Methylprednisolone

Methylprednisolone is a potent corticosteroid with anti-inflammatory activity at least five times that of hydrocortisone. It has greater glucocorticoid activity and insignificant mineralocorticoid activity, making it particularly suitable for conditions where sodium and water retention would be a disadvantage. Corticosteroids have been suggested to reduce lung inflammation in ARDS. The fibroproliferative phase occurs between 7 and 14 days from the onset of ARDS. There are no large controlled trials at present to show conclusive benefit from this practice.

Uses

Fibroproliferative phase of ARDS (unlicensed)

Adjunct in *Pneumocystis jirovecii* pneumonia (previously known as *Pneumocystis carinii* pneumonia – PCP); see co-trimoxazole and pentamidine

Contraindications

Systemic infection (unless specific antimicrobial therapy given)

Administration

Fibroproliferative phase of ARDS (unlicensed):

- IV infusion: 2 mg/kg loading dose (rounded to nearest 20 mg) then 0.5 mg/kg (rounded to the nearest 10 mg) 6 hourly for 14 days or until extubation whichever is quicker

  Then convert to prednisolone 1 mg/kg orally each morning for 7 days, then 0.5 mg/kg each morning for 7 days daily, then 0.25 mg/kg for 2 days, then 0.125 mg/kg for 2 days, then stop

Adjunct in *Pneumocystis jirovecii* pneumonia (see co-trimoxazole and pentamidine):

- IV infusion: 1 g once daily for 3 days; if the patient responds well steroids may be stopped, if not continue as follows: days 4 and 5, 500 mg IV once daily; then days 6–16, prednisolone, reducing regimen, i.e. 60 mg, 50 mg, 40 mg, 30 mg, 20 mg 15 mg, 10 mg, 10 mg, 5 mg, 5 mg; then stop

  The steroid should be started at the same time as the co-trimoxazole or pentamidine and should be withdrawn before the antibiotic treatment is complete

  Reconstitute with WFI; make up to 50 ml sodium chloride 0.9% or glucose 5%, give over at least 30 minutes

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How not to use methylprednisolone

Do not give by rapid IV injection (hypotension, arrhythmia, cardiac arrest)

Avoid live virus vaccinations

Adverse effects

Prolonged use may lead to the following problems:

- increased susceptibility to infections
- impaired wound healing
- peptic ulceration
- muscle weakness (proximal myopathy)
- osteoporosis
- hyperglycaemia

Cautions

Diabetes mellitus

Concurrent use of NSAIDs (increased risk of gastrointestinal bleeding)

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Metoclopramide

Metoclopramide acts by promoting gastric emptying, increasing gut motility and has an anti-emetic effect. It raises the threshold of the chemoreceptor trigger zone. In high doses it has 5-HT_3-antagonist action.

Uses

Anti-emetic

Promotes gastric emptying

Increases lower oesophageal sphincter tone

Administration

- IV/IM/PO/NG: 10 mg 8 hourly

How not to use metoclopramide

Orally not appropriate if actively vomiting

Rapid IV bolus (hypotension)

Adverse effects

Extrapyramidal movements

Neuroleptic malignant syndrome

Cautions

Increased risk of extrapyramidal side effects occurs in the following:

- hepatic and renal impairment
- children, young adults (especially girls) and the very old
- concurrent use of antipsychotics
- concurrent use of lithium

Treatment of acute oculogyric crises includes stopping metoclopramide (usually subside within 24 hours) or giving procyclidine 5–10 mg IV (usually effective within 5 minutes)

Organ failure

Hepatic: reduce dose

Renal: reduce dose

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Metoprolol

Metoprolol is a selective beta-1 (β_1)-adrenoreceptor blocking agent; this preferential effect is not absolute, however, and at higher doses it also inhibits β_2-adrenoreceptors. Plasma levels following oral administration are approximately 50% of levels following IV administration, indicating about 50% first-pass metabolism. For dose conversion purposes, equivalent maximal β-blocking effect is achieved with oral and IV doses in the ratio of approximately 2.5:1. Metoprolol is eliminated mainly by biotransformation in the liver, and the plasma half-life ranges from approximately 3 to 7 hours. Hence, no reduction in dosage is usually needed in patients with renal failure.

Uses

Hypertension

Angina pectoris

Control of tachyarrhythmias

MI

Contraindications

Asthma (worsens unless compelling reasons for use)

Second- or third-degree heart block

Decompensated cardiac failure (pulmonary oedema, hypoperfusion or hypotension)

Administration

- Orally: usually 25–50 mg 8–12 hourly
- IV bolus: initially up to 5 mg at a rate of 1–2 mg/min; can be repeated at 5-minute intervals until a satisfactory response. A total dose of 10–15 mg generally proves sufficient
- IV infusion (unlicensed): dilute 20 mg in 50 ml of sodium chloride 0.9% or glucose 5%. Starting dose 0.04 mg/kg/h and titrate to response, usually up to 0.1 mg/kg/h

Adverse effects

Bradycardia

Heart failure

Postural hypotension

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Cautions

Subject to enzyme inducers and inhibitors (p. 307)

Increased negative inotropic and chronotropic effects may occur when metoprolol is given with verapamil and diltiazem

Avoid IV verapamil in patients treated with β-blockers

Organ failure

Hepatic: reduce dose

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Metronidazole

Metronidazole exhibits high activity against anaerobic bacteria and protozoa. It is also effective in the treatment of *Clostridium difficile*-associated disease, preferably given by the oral route. IV metronidazole may be used in patients with impaired gastric emptying and/or ileus.

Uses

Clostridium difficile-associated diarrhoea

Anaerobic infections

Protozoal infections *Trichomonas vaginalis, Giardia intestinalis* and amoebic dysentery)

Bacterial vaginosis

Eradication of *Helicobacter pylori*

Administration

Clostridium difficile-associated diarrhoea:

- Orally: 400 mg 8 hourly
- IV: 500 mg 8 hourly

Anaerobic infections:

- IV: 500 mg 8 hourly
- PR: 1 g 8 hourly

Eradication of *H. pylori*:

- Metronidazole 400 mg PO/NG 12 hourly and PPI standard dose (e.g. lansoprazole 30 mg/omeprazole 20 mg); plus:
- PO/NG 12 hourly and amoxicillin 1 g PO/NG 12 hourly or clarithromycin 500 mg PO/NG 12 hourly; all for 7 days
- IV eradication therapy has less evidence of success than oral; therefore preferably wait until PO/NG route is available

Adverse effects

Nausea and vomiting

Unpleasant taste

Rashes, urticaria and angioedema

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Darkening of urine
Peripheral neuropathy (prolonged treatment)

Cautions

Hepatic impairment
Disulfiram-like reaction with alcohol

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Micafungin (Mycamine)

Micafungin (Mycamine) is an echinocandin, similar to caspofungin and anidulafungin. It covers a wide range of *Candida* species that cause invasive candidiasis, including *C. krusei* and *C. glabrata*. The key distinguishing features compared with caspofungin are simplicity of dosing regimen (no loading dose), storage at room temperature, narrower clinical indication and fewer drug interactions.

Uses

Invasive candidiasis

Oesophageal candidiasis

Prophylaxis of *Candida* infection in neutropenic patients

Contraindications

Hypersensitivity to echinocandin

Administration

Invasive candidiasis:

- IV infusion: 100 mg once daily, given over 1 hour (increase to 200 mg daily if inadequate response) for a minimum of 14 days

  Weight <40 kg, 2 mg/kg once daily, given over 1 hour (increase to 4 mg/kg daily if inadequate response)

Oesophageal candidiasis:

- IV infusion: 150 mg once daily, given over 1 hour for at least 1 week after resolution of infection

  Weight <40 kg, 3 mg/kg once daily, given over 1 hour

Prophylaxis of *Candida* infection in neutropenic patients:

- IV infusion: 50 mg once daily, given over 1 hour for at least 1 week after neutrophil recovery

  Weight <40 kg, 1 mg/kg once daily, given over 1 hour

Reconstitute each vial with 5 ml sodium chloride 0.9% or glucose 5%. Gently rotate vial, without shaking. Add the reconstituted solution to 100 ml sodium chloride 0.9% or glucose 5%. Protect from light. Available in vials containing 50 mg and 100 mg

How not to use micafungin

Galactose intolerance

Severe hepatic failure

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Adverse effects

Headaches
Diarrhoea, nausea and vomiting
Leukopenia, neutropenia, anaemia and thrombocytopenia
Increased creatinine
Hypokalaemia, hypomagnesaemia and hypocalcaemia
Elevated LFTs
Flushing
Rash
Pruritus

Cautions

Hepatic failure (worsening LFTs)
Breastfeeding and pregnancy

Organ failure

Renal: no dose adjustment necessary, as negligible renal clearance
Hepatic: avoid in severe liver failure

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Midazolam

Midazolam is a water-soluble benzodiazepine with a short duration of action (elimination half-life 1–4 hours). However, prolonged coma has been reported in some critically ill patients, usually after prolonged infusions. Midazolam is metabolized to the metabolite alpha-hydroxymidazolam, which is rapidly conjugated. Accumulation of midazolam after prolonged sedation has been observed in critically ill patients. In renal failure the glucuronide may also accumulate, causing narcosis. This and the link between benzodiazepines with delirium have led routine midazolam use to have been largely replaced by propofol.

Uses

Sedation

Anxiolysis

Contraindications

As an analgesic

Airway obstruction

Administration

- IV bolus: 2.5–5 mg PRN
- IV infusion: 0.5–6 mg/h

Administer neat or diluted in glucose 5% or sodium chloride 0.9%

Titrate dose to level of sedation required

Stop or reduce infusion each day until patient awakes, when it is restarted; failure to assess daily will result in delayed awakening when infusion is finally stopped

Time to end effects after infusion: 30 minutes to 2 hours (but see below)

How not to use midazolam

The use of flumazenil after prolonged use may produce confusion, toxic psychosis, convulsions or a condition resembling delirium tremens

Adverse effects

Residual and prolonged sedation

Respiratory depression and apnoea

Hypotension

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Cautions

Enhanced and prolonged sedative effect results from interaction with:

- opioid analgesics
- antidepressants
- antihistamines
- alpha-blockers
- antipsychotics

Enhanced effect in the elderly and in patients with hypovolaemia, vasoconstriction or hypothermia

Midazolam is metabolized by the hepatic microsomal enzyme system (cytochrome P450s). Induction of the P450 enzyme system by another drug can gradually increase the rate of metabolism of midazolam, resulting in lower plasma concentrations and a reduced effect. Conversely inhibition of the metabolism of midazolam results in a higher plasma concentration and an increased effect. Examples of enzyme inducers and inhibitors are listed on p. 307.

Flumazenil is a specific, but short-acting, antagonist (p. 126).

Organ failure

CNS: sedative effects increased

Cardiac: exaggerated hypotension

Respiratory: ↑ respiratory depression

Hepatic: enhanced and prolonged sedative effect. Can precipitate coma

Renal: increased cerebral sensitivity and prolonged sedative effect

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Milrinone

Milrinone is a selective phosphodiesterase III inhibitor resulting in increasing CO, and decreasing PCWP and SVR, without significant increase in HR and myocardial oxygen consumption. It produces slight enhancement in AV node conduction and may increase ventricular rate in uncontrolled AF/atrial flutter.

Uses

Severe congestive cardiac failure

Contraindications

Severe aortic or pulmonary stenosis (exaggerated hypotension)

Hypertrophic obstructive cardiomyopathy (exaggerated hypotension)

Administration

- IV infusion: 50 μg/kg loading dose over 10 minutes, then maintain on 0.375–0.75 μg/kg/min to a maximum haemodynamic effect

  Requires direct arterial BP monitoring

  Adjustment of the infusion rate should be made according to haemodynamic response

  Available in 10 ml ampoules containing 10 mg milrinone (1 mg/ml)

  Dilute this 10 ml solution with 40 ml sodium chloride 0.9% or glucose 5% giving a solution containing milrinone 200 μg/ml

Dose (μg/kg/min)	Infusion rate (ml/kg/h)
0.375	0.11
0.4	0.12
0.5	0.15
0.6	0.18
0.7	0.21
0.75	0.22

Maximum daily dose: 1.13 mg/kg

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In renal impairment:

CC (ml/min)	Dose (μg/kg/min)
20–50 or CVVH rate 1.2–3 l/h	0.28–0.43
10–20 or CVVH rate 0.6–1.2 l/h	0.23–0.28
<10	0.2–0.23

How not to use milrinone

Furosemide and bumetanide should not be given in the same line as milrinone (precipitation)

Adverse effects

Hypotension

Arrhythmias

Cautions

Uncontrolled AF/atrial flutter

Organ failure

Renal: reduce dose

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Morphine

Morphine is the standard opioid with which others are compared and remains a valuable drug for the treatment of acute, severe pain. Peak effect after IV bolus is 15 minutes. Duration of action is between 2 and 3 hours. Both liver and kidney function are responsible for morphine elimination. The liver mainly metabolizes it. One of the principal metabolites, morphine 6-glucuronide, is also a potent opioid agonist and may accumulate in renal failure.

Uses

Relief of severe pain

To facilitate mechanical ventilation

Acute left ventricular failure – by relieving anxiety and producing vasodilatation

Contraindications

Airway obstruction

Pain caused by biliary colic

Administration

- IV bolus: 2.5 mg every 15 minutes PRN
- IV infusion rate: 1–5 mg/h

  Dilute in glucose 5% or sodium chloride 0.9%

  Stop or reduce infusion each day and restart when first signs of discomfort appear

  Failure to assess daily will result in overdosage and difficulty in weaning patient from ventilation
- If the patient is conscious the best method is to give an infusion pump they can control (PCA): 50 mg made up to 50 ml with sodium chloride 0.9%; IV bolus: 1 mg; lockout: 3–10 minutes

How not to use morphine

In combination with an opioid partial agonist, e.g. buprenorphine (antagonizes opioid effects)

Adverse effects

Respiratory depression and apnoea

Hypotension and tachycardia

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Nausea and vomiting
Delayed gastric emptying
Reduced intestinal mobility
Biliary spasm
Constipation
Urinary retention
Histamine release
Tolerance
Pulmonary oedema

Cautions

Enhanced and prolonged effect when used in patients with renal failure, the elderly and in patients with hypovolaemia and hypothermia

Enhanced sedative and respiratory depression from interaction with:

- benzodiazepines
- antidepressants
- antipsychotics

Head injury and neurosurgical patients (may exacerbate ↑ ICP as a result of ↑ $PaCO_2$)

Organ failure

CNS: sedative effects increased

Respiratory: ↑ respiratory depression

Hepatic: can precipitate coma

Renal: increased cerebral sensitivity. Morphine-6-glucuronide accumulates, so doses should be deceased and titrated to effect.

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Chapter

N

Naloxone

Naloxone is a specific opioid antagonist. The elimination half-life is 60–90 minutes, with a duration of action between 30 and 45 minutes.

Uses

Reversal of opioid adverse effects – respiratory depression, sedation, pruritus and urinary retention

As a diagnostic test of opioid overdose in an unconscious patient

Contraindications

Patients physically dependent on opioids

Administration

Reversal of opioid overdose:

- 200 μg IV bolus, repeat every 2–3 minutes until desired response, up to a total of 2 mg
- Infusion may be required in patients with renal impairment or those who had taken long-acting opioids, e.g. morphine sulphate M/R tablets, usual starting dose is 60% of initial IV bolus dose infused over 1 hour, then adjusted according to respiratory rate and level of consciousness, e.g. if the initial bolus is 1 mg, the infusion is started at 0.6 mg/h

  Dilute 10 mg to 50 ml with sodium chloride 0.9% or glucose 5%

Reversal of spinal opioid-induced pruritus:

- dilute 200 μg in 10 ml WFI

  Give 20 μg boluses every 5 minutes until symptoms resolve

  Titrate dose carefully in post-operative patients to avoid sudden return of severe pain

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How not to use naloxone

Large doses should not be given quickly

Adverse effects

Arrhythmias

Hypertension

Cautions

Withdrawal reactions in patients on long-term opioid for medical reasons or in addicts

Post-operative patients – return of pain and severe haemodynamic disturbances (hypertension, VT/VF, pulmonary oedema)

Organ failure

Hepatic: delayed elimination

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Neostigmine

Neostigmine is a cholinesterase inhibitor leading to prolongation of ACh action. This will enhance parasympathetic activity in the gut and increase intestinal motility. When used for acute colonic pseudo-obstruction, organic obstruction of the gut must first be excluded and it should not be used shortly after bowel anastomosis (*N Engl J Med* 1999; **341:** 137–41). Colonic pseudo-obstruction, which is the massive dilation of the colon in the absence of mechanical obstruction, can develop after surgery or severe illness. Most cases respond to conservative treatment. In patients who do not respond, colonic decompression is often performed to prevent ischaemia and perforation of the bowel. Colonoscopy in these patients is not always successful and can be accompanied by complications such as perforation.

Uses

Colonic pseudo-obstruction (unlicensed)

Administration

- IV bolus: 2.5 mg, repeated 3 hours later if no response to initial dose

  Monitor ECG (may need to give atropine or other anticholinergic drugs to counteract symptomatic bradycardia)

Contraindications

Mechanical bowel obstruction

Urinary obstruction

How not to use neostigmine

It should not be used shortly after bowel anastomosis

Adverse effects

Increased sweating

Excess salivation

Nausea and vomiting

Abdominal cramp

Diarrhoea

Bradycardia

Hypotension

These muscarinic side effects are antagonized by atropine.

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Cautions

Asthma

Organ failure

Renal: reduce dose

Nimodipine

Nimodipine is a calcium-channel blocker with a smooth muscle relaxant effect preferentially in the cerebral arteries. Its use is confined to prevention of vascular spasm after subarachnoid haemorrhage. Nimodipine is used in conjunction with the 'triple H' regimen of hypertension, hypervolaemia and haemodilution to a haematocrit of 30–33.

Uses

Subarachnoid haemorrhage

Administration

- IV infusion

  1 mg/h, ↑ to 2 mg/h if BP not severely ↓

  If <70 kg or BP unstable start at 0.5 mg/h

  Ready prepared solution – do not dilute, but administer into a running infusion (40 ml/h) of sodium chloride 0.9% or glucose 5%, via a central line

  Continue for between 5 and 14 days

  Use only polyethylene or polypropylene infusion sets

  Protect from light

  10 mg in 50 ml vial (0.02%)

  0.5 mg/h = 2.5 ml/h

  1 mg/h = 5 ml/h

  2 mg/h = 10 ml/h

- Orally (prophylaxis)

  60 mg every 4 hours for 21 days

How not to use nimodipine

Avoid PVC infusion sets

Do not use peripheral venous access

Do not give nimodipine tablets and IV infusion concurrently

Avoid concurrent use of other calcium-channel blockers, beta-blockers or nephrotoxic drugs

Adverse effects

Hypotension (vasodilation)

Transient ↑ liver enzymes with IV use

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Cautions

Hypotension (may be counterproductive by ↓ cerebral perfusion)

Cerebral oedema or severely ↑ ICP

Renal impairment

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Noradrenaline

The alpha-1 effect predominates over its beta-1 effect, raising the BP by increasing the SVR. It increases the myocardial oxygen requirement without increasing coronary blood flow. Noradrenaline (norepinephrine) reduces renal, hepatic and muscle blood flow, but in septic shock, noradrenaline may increase renal blood flow and enhance urine production by increasing perfusion pressure. Acute renal failure secondary to inadequate renal perfusion is a common form of kidney failure seen in the ICU. Once intravascular volume has been restored, the mean arterial pressure should be restored to a level that optimally preserves renal perfusion pressure, i.e. above 65 mmHg (or higher in previously hypertensive patients).

Uses

Septic shock, with low SVR

Contraindications

Hypovolaemic shock

Acute myocardial ischaemia or MI

Administration

- Usual dose range: 0.01–0.4 (>3 may be needed very occasionally) μg/kg/min IV infusion via a central vein

  Initially start at a higher rate than intended, to increase the BP more rapidly, and then reduce rate

  4 mg made up to 50 ml glucose 5% (80 μg/ml)

Dosage chart (ml/h):

Based on concentration of 80 μg/ml solution.

Weight (kg)	Dose (μg/kg/min)				
	0.02	0.05	0.1	0.15	0.2
50	0.8	1.9	3.8	5.6	7.5
60	0.9	2.3	4.5	6.8	9
70	1.1	2.6	5.3	7.9	10.5
80	1.2	3	6	9	12
90	1.4	3.4	6.8	10.1	13.5

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Weight (kg)	Dose (μg/kg/min)				
	0.02	0.05	0.1	0.15	0.2
100	1.5	3.8	7.5	11.3	15
110	1.7	4.1	8.3	12.4	16.5
120	1.8	4.5	9	13.5	18

How not to use noradrenaline

In the absence of haemodynamic monitoring

Do not use a peripheral vein (risk of extravasation)

Do not connect to CVP lumen used for monitoring pressure (surge of drug during flushing of line)

Adverse effects

Bradycardia

Hypertension

Arrhythmias

Myocardial ischaemia

Cautions

Hypertension

Heart disease

If extravasation of noradrenaline occurs – phentolamine 10 mg in 15 ml sodium chloride 0.9% should be infiltrated into the ischaemic area with a 23-gauge needle

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Nystatin

Nystatin is a polyene antifungal which is not absorbed when given orally and is too toxic for IV use.

Uses

Oral candida infection

Suppression of gut carriage of candida

Topical therapy of genital candida infections

Administration

Oral candidiasis:

- 1 ml (100 000 units) 6 hourly, holding in mouth

How not to use nystatin

IV too toxic

Adverse effects

Rash

Oral irritation

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Chapter

O

Octreotide

Octreotide is an analogue of somatostatin. It is used to provide relief from symptoms associated with carcinoid tumours and acromegaly. It may also be used for the prevention of complications following pancreatic surgery. For patients undergoing pancreatic surgery, the peri- and post-operative administration of octreotide reduces the incidence of typical post-operative complications (e.g. pancreatic fistula, abscess and subsequent sepsis, post-operative acute pancreatitis). Octreotide exerts an inhibiting effect on gallbladder motility, bile acid secretion and bile flow, and there is an acknowledged association with the development of gallstones in prolonged usage.

Uses

Prevention of complications following pancreatic surgery

Pancreatic leak (unlicensed)

Variceal haemorrhage (second line to terlipressin)

Administration

Prevention of complications following pancreatic surgery:

- SC or IV: 100 μg 8 hourly for 7 days, starting on the day of operation at least 1 hour before laparotomy

Pancreatic leak:

- SC or IV: 100–200 μg 8 hourly

  To reduce pain and irritation on injection, allow solution to reach room temperature and rotate injection site

  IV dose should be diluted with 5 ml sodium chloride 0.9%

  Available as 50, 100 and 500 μg/1 ml ampoules; use the 500 μg/1 ml ampoule for SC injection of doses ≥200 μg to reduce pain arising from the injection volume

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Variceal haemorrhage (unlicensed indication):

- Only use if terlipressin is contraindicated (e.g. ischaemic ECG)

  Dose 100 μg IV stat then a continuous infusion of 50 μg/h continued for 24 hours after variceal banding; then reduce dose to 25 μg/h for 12 hours, then stop

  To prepare solution dilute 5 × 100 μg ampoules to 50 ml with sodium chloride 0.9% = 10 μg/ml solution; 50 μg/h = 5 ml/h; 25 μg/h = 2.5 ml/h

  Dilute to a ratio of not less than 1:1 and not more than 1:9 by volume

  Stored in fridge at 2–8 °C

How not to use octreotide

Abrupt withdrawal (biliary colic and pancreatitis)

Dilution with solution containing glucose is not recommended

Adverse effects

Gastrointestinal disturbances (nausea, vomiting, pain, bloating and diarrhoea)

Pain and irritation at injection site (allow solution to reach room temperature and rotate injection sites)

Elevated LFTs

Gallstone formation with prolonged use

Cautions

Growth hormone-secreting pituitary tumour (may increase in size)

Insulinoma (hypoglycaemia)

Requirement for insulin and oral hypoglycaemic drugs may be reduced in diabetes mellitus

Organ failure

Hepatic: reduce dose

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Olanzapine (Zyprexa)

Olanzapine is an atypical antipsychotic agent that is a dopamine D_1, D_2, D_4, 5-HT_2, histamine-1 and muscarinic-receptor antagonist.

Although licensed for conditions such as acute schizophrenia and mania, there is emerging literature (*Intensive Care Med* 2004; **30:** 444–449) of using this agent as an alternative to haloperidol in delirium. It also offers an alternative parenteral (IM) option for management of acute agitation. For NG therapy, there is a dispersible tablet, which will also dissolve on the tongue.

Uses

Management of delirium in ICU patients (unlicensed), especially in prolonged QT interval as an alternative to benzodiazepines

Licensed indications: schizophrenia, mania, either alone or as combination therapy, preventing recurrence in bipolar disorder

The IM preparation is used for control of agitation and disturbed behaviour in schizophrenia or mania

Contraindications

Patients with known risk for narrow-angle glaucoma

Administration

Delirium:

- PO/NG 5 mg daily (elderly 2.5 mg daily); adjusted to usual range of 5–20 mg daily; maximum 20 mg daily

Control of agitation:

- IM initially 5–10 mg (usual dose 10 mg), then 5–10 mg after 2 hours if needed

  Elderly, initially 2.5–5 mg as a single dose followed by 2.5–5 mg after 2 hours if necessary; only use injection daily for 3 days; maximum daily combined oral and parenteral dose 20 mg

  Available as 5 mg, 10 mg, 15 mg and 20 mg tablets and dispersible tablets; IM 10 mg

How not to use IM olanzapine

IM injections are not suitable for thrombocytopenic patients, as risk of bleeding

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Adverse effects

Transient antimuscarinic effects

Drowsiness, speech difficulty, hallucinations, fatigue

Increased temperature, oedema plus eosinophilia

Less commonly, hypotension, bradycardia, QT-interval prolongation, seizures, leukopenia and rash

IM: sinus pause and hypoventilation

Cautions

QT prolongation

Increased risk of hypotension, bradycardia and respiratory depression when IM olanzapine given with IV benzodiazepines

Increased risk of side effects including neutropenia when olanzapine given with valproate

Increased risk of ventricular arrhythmias with anti-arrhythmics that prolong the QT interval

Increase plasma concentration of tricyclics, possibly increased risk of ventricular arrhythmias

Antagonize anticonvulsant effect of anti-epileptics (convulsive threshold lowered)

Organ failure

Renal: consider initial dose 5 mg

Liver: consider initial dose 5 mg

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Omeprazole

Omeprazole is a PPI which inhibits gastric acid production by the gastric parietal cells. Following endoscopic treatment of bleeding peptic ulcers, omeprazole given intravenously for 72 hours has been shown to reduce the risk of rebleeding (*N Engl J Med* 2000; **343**: 310–316). PPIs are often overused in the ICU and there is emerging data linking PPI use with *Clostridium difficile* infection (*CMAJ* 2004; **171**: 33–38).

Uses

Bleeding peptic ulcers, after endoscopic treatment of bleeding (unlicensed)

Continuation of PPI therapy when the PO/NG route is unavailable

Helicobacter pylori eradication

Administration

Bleeding peptic ulcers, after endoscopic treatment of bleeding:

- IV: Initial 80 mg IV loading dose given over 1 hour, followed by 8 mg/h IV infusion for 72 hours

  Reconstitute with either sodium chloride 0.9% or glucose 5%

Continuation of PPI therapy when the PO/NG route is unavailable:

- IV infusion: 40 mg daily

  Reconstitute 40 mg vial in 100 ml bag of sodium chloride 0.9% or glucose 5%

  Administer over 20–30 minutes

Eradication of *Helicobacter pylori*:

See metronidazole, p. 192

Adverse effects

Gastrointestinal disturbances (nausea, vomiting, abdominal pain, diarrhoea and constipation)

Paraesthesia

Agitation

Liver dysfunction

Hyponatraemia

Leukopenia and thrombocytopenia rarely

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Cautions

Severe hepatic disease (risk of encephalopathy)
Pregnancy (toxic in animal studies)
May mask symptoms of gastric cancer
May enhance anticoagulant effect of warfarin
Monitor INR
May increase phenytoin levels
May reduce the effectiveness of clopidogrel

Organ failure

Hepatic: reduce dose

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Ondansetron

Ondansetron is a specific 5-HT_3 antagonist. Its efficacy is enhanced by addition of dexamethasone.

Uses

Severe post-operative nausea and vomiting (PONV)

Highly emetogenic chemotherapy

Administration

PONV:

- IV bolus: 4 mg over 3–5 minutes when required up to 8 hourly. Dose may be doubled

Highly emetogenic chemotherapy:

- IV bolus: 8 mg over 3–5 minutes, followed by two doses of 8 mg 2–4 hourly or continuous IV infusion of 1 mg/h for up to 24 hours

  Dilution: 24 mg ondansetron made up to 48 ml with sodium chloride 0.9% or glucose 5%

  Rate of infusion: 2 ml/h

How not to use ondansetron

Do not give rapidly as IV bolus

Adverse effects

Headaches

Flushing

Constipation

Increases in liver enzymes (transient)

Cautions

Hepatic impairment

Organ failure

Hepatic: reduced clearance (moderate or severe liver disease: not >8 mg daily)

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Oseltamivir

Oseltamivir is a neuraminidase inhibitor antiviral, used to treat complicated influenza with a low risk of resistance, e.g. A (H3N2) or B. The risk of resistance is highest in people who are severely immunosuppressed and have complicated influenza. Oseltamivir is not a first-line treatment if the dominant circulating strain is influenza A (H1N1) as there is a higher risk for developing oseltamivir resistance, in which case use zanamivir inhaled or IV (unlicensed).

Flucloxacillin or vancomycin (in those with penicillin allergy) is usually added to prevent *Staphylococcus aureus* pneumonia.

Uses

Influenza with a low risk of resistance, e.g. A (H3N2) or B

Administration

Treatment:

- 75 mg PO/NG 12 hourly for 5 days (150 mg doses have been used (unlicensed), but absorption is good in critical illness, so should not be routinely necessary)

No dose adjustment is needed in obesity

Available as capsule and liquid

Prophylaxis:

- 75 mg PO/NG daily for 10 days

Adverse effects

Abdominal pain

Headache

Nausea and vomiting

Altered consciousness

Organ failure

Treatment dosing in relation to renal function (adults and those aged 13 years or over):

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CC (ml/min)	Oseltamivir PO treatment for 5 days
>60 or CVVH rate >3.6 l/h	75 mg twice daily
31–60 or CVVH rate 1.9–3.6 l/h	30 mg twice daily
11–30 or CVVH rate 1–1.8 l/h	30 mg once daily
≤10	30 mg ONCE

Prophylaxis dosing in relation to renal function (adults and those aged 13 years or over):

CC (ml/min)	Oseltamivir PO prophylaxis for 10 days
≥60 or CVVH rate >3.6 l/h	75 mg once daily
31–60 or CVVH rate 1.9–3.6 l/h	30 mg once daily
11–30 or CVVH rate 1–1.8 l/h	30 mg every 48 hours
≤10	30 mg ONCE, repeated after 7 days

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Chapter

P

Pabrinex IVHP (Intravenous High Potency)

Wernicke's encephalopathy can be difficult to diagnose, and the consequences of leaving it untreated can be devastating. Pabrinex is a combination of water-soluble vitamins B and C, which is used parenterally to rapidly treat severe depletion or malabsorption, particularly after alcoholism. As thiamine does not exist as a licensed parenteral product, Pabrinex is widely used to treat and prevent Wernicke's encephalopathy. An alternative approach is to use an unlicensed IV thiamine product. Pabrinex IVHP is supplied in two ampoules which contain:

- Ampoule no. 1 (5 ml):
  thiamine hydrochloride (vitamin B_1) 250 mg
  riboflavin (vitamin B_2) 4 mg
  pyridoxine hydrochloride (vitamin B_6) 50 mg
- Ampoule no. 2 (5 ml):
  ascorbic acid (vitamin C) 500 mg
  nicotinamide (vitamin B_3) 160 mg
  anhydrous glucose 1,000 mg

Note: a double-strength ampoule pair exists of 10 ml. All doses mentioned here refer to the 5 ml product.

Uses

Treatment and prevention of Wernicke's encephalopathy; the at-risk groups are:

alcohol misusers
eating disorders
long-term parenteral nutrition
hyperemesis gravidarum
dialysis
lactic acidosis secondary to beriberi

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Administration

To prepare Pabrinex IVHP:

- Draw up contents of both ampoules 1 and 2 into one syringe and mix

  Add this to 50–100 ml of sodium chloride 0.9% and administer over 30 minutes

  Pabrinex should be administered before parenteral glucose is given, as in thiamine deficiency IV glucose may worsen symptoms and increase thiamine requirements

Prevention of Wernicke's encephalopathy:

- One pair of IVHP 5 ml ampoules once or twice daily for 3–5 days

Treatment of Wernicke's encephalopathy or beriberi:

- Two pairs of IVHP 5 ml ampoules 8 hourly for 3 days

  If no response is seen, discontinue therapy; if a response is seen, decrease the dose to one pair of ampoules daily for as long as improvement continues

  When the Pabrinex course is finished, give oral thiamine 50–100 mg 8 hourly and one to two multivitamin tablets daily for the rest of admission

  For severe vitamin B group deficiency, give one to two vitamin B compound strong tablets 8 hourly

  A short course of folic acid may also be beneficial

How not to give Pabrinex

Do not confuse the IV product with the IM preparation, nor the 5 ml and 10 ml product

Adverse effects

Occasional hypotension and mild paraesthesia

Cautions

Anaphylactic shock rarely

https://doi.org/10.1017/9781108349550.015

Pantoprazole

Pantoprazole is a PPI, similar to omeprazole. The injectable formulation can be used as an alternative to omeprazole. PPIs are often overused in the ICU and there are emerging data linking PPI use with *Clostridium difficile* infection (*CMAJ* 2004; **171:** 33–38).

Uses

Bleeding peptic ulcers, after endoscopic treatment of bleeding (unlicensed)

Continuation of PPI therapy when the PO/NG route is unavailable

Helicobacter pylori eradication

Administration

Bleeding peptic ulcers, after endoscopic treatment of bleeding:

- IV: Initial 80 mg IV loading dose given over 1 hour, followed by 8 mg/h IV infusion for 72 hours

  Reconstitute with either sodium chloride 0.9% or glucose 5%

Continuation of PPI therapy when the PO/NG route is unavailable:

- IV: 40 mg daily

  Reconstitute 40 mg vial with the 10 ml sodium chloride 0.9%; administer as a slow bolus

  Alternatively, add to 100 ml bag of sodium chloride 0.9% or glucose 5% and administer over 15 minutes or as a continuous infusion (unlicensed)

Adverse effects

Gastrointestinal disturbances (abdominal pain, diarrhoea, flatulence and constipation)

Headache

Agitation

Liver dysfunction

Leukopenia and thrombocytopenia rarely

Cautions

Severe hepatic disease (risk of encephalopathy)

Pregnancy (toxic in animal studies)

May mask symptoms of gastric cancer

https://doi.org/10.1017/9781108349550.015

May enhance anticoagulant effect of warfarin – monitor INR

May reduce the effectiveness of clopidogrel

Organ failure

Hepatic: reduce 40 mg dose to 20 mg

Renal: no dose adjustment is necessary

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Paracetamol

The efficacy of single-dose IV paracetamol as a post-operative analgesic has been confirmed by many studies. The IV formulation provides a more predictable plasma concentration and has potency slightly less than that of a standard dose of morphine or the NSAIDs. The mechanism of action remains unclear as, unlike opioids and NSAIDs respectively, paracetamol has no known endogenous binding sites and does not inhibit peripheral cyclooxygenase activity significantly. There is increasing evidence of a central antinociceptive effect, and potential mechanisms for this include inhibition of a central nervous system cyclooxygenase-2 (COX-2), inhibition of a putative central cyclooxygenase, 'COX-3', that is selectively susceptible to paracetamol, and modulation of inhibitory descending serotinergic pathways. Paracetamol has also been shown to prevent prostaglandin production at the cellular transcriptional level, independent of cyclooxygenase activity.

The availability of IV paracetamol (Perfalgan) will enhance and extend the use of this drug as a fundamental component of multi-modal analgesia after surgery and in critically ill patients who are not able to absorb enterally. The dose differs between IV and oral paracetamol (oral bioavailability is around 75–95% relative to IV dose). An average adult could safely be given up to 4 g oral paracetamol daily and 4 g IV.

Uses

Mild to moderate pain

Fever

Administration

- Oral or PR: 0.5–1 g every 4–6 hours; maximum of 4 g daily
- IV infusion: 1 g (100 ml) given over 15 minutes, every 4–6 hours; maximum 4 g daily:

  > 50 kg with additional risk factors for hepatotoxicity, maximum 3 g daily,

  < 50 kg, 15 mg/kg up to 6 hourly

How not to use paracetamol

Do not exceed 4 g/d

Do not use the standard IV dose for patients weighing below 50 kg

https://doi.org/10.1017/9781108349550.015

Adverse effects

Hypotension with IV infusion
Liver damage with overdose

Cautions

Hepatic impairment
Renal impairment
Alcohol dependence

Organ failure

Hepatic: avoid large doses (dose-related toxicity)
Renal: increase IV infusion dose interval to every 8 hours if CC <10 ml/min

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Pentamidine

Pentamidine isetionate given by the IV route is an alternative for patients with severe *Pneumocystis jirovecii* pneumonia (previously known as *Pneumocystis carinii* pneumonia – PCP) pneumonia, unable to tolerate co-trimoxazole, or who have not responded to it. Pentamidine isetionate is a toxic drug and personnel handling the drug must be adequately protected. Nebulized pentamidine may be used for mild disease and for prophylaxis. Thin-walled air-containing cysts (pneumatoceles) and pneumathoraces are more common in patients receiving nebulized pentamidine as prophylaxis. Adverse effects, sometimes severe, are more common with pentamidine than co-trimoxazole.

Uses

Alternative treatment for severe *Pneumocystis jirovecii* pneumonia

Administration

- IV infusion: 4 mg/kg every 24 hours for at least 14 days

  Dilute in 250 ml glucose 5%, given over 1–2 hours

In renal impairment:

CC (ml/min)	Dose (mg/kg)	Interval (h)
10–50 or CVVR rate 0.6–3 l/h	4	24
<10	4	24 for 7–10 days then on alternate days to complete a minimum of 14 doses

Adjuvant corticosteroid has been shown to improve survival. The steroid should be started at the same time as the pentamidine and should be withdrawn before the antibiotic treatment is complete. Oral prednisolone 50–80 mg daily or IV hydrocortisone 100 mg 6 hourly or IV dexamethasone 8 mg 6 hourly or IV methylprednisolone 1 g for 5 days, then dose reduced to complete 21 days of treatment

How not to use pentamidine

Nebulized route not recommended in severe *Pneumocystis jirovecii* pneumonia ($\downarrow PaO_2$)

Concurrent use of both co-trimoxazole and pentamidine is not of benefit and may increase the incidence of serious side effects

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Adverse effects

Acute renal failure (usually isolated ↑ serum creatinine)
Leukopenia, thrombocytopenia
Severe hypotension
Hypoglycaemia
Pancreatitis
Arrhythmias

Cautions

Blood disorders
Hypotension
Renal/hepatic impairment

Organ failure

Renal: reduce dose

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Pethidine

Pethidine has one-tenth the analgesic potency of morphine. The duration of action is between 2 h and 4 h. It has atropine-like actions and relaxes smooth muscles. The principal metabolite is norpethidine, which can cause fits. In renal failure and after infusions, this metabolite can accumulate and cause seizures.

Uses

It may be indicated in controlling pain from pancreatitis, secondary to gallstones, and after surgical procedure involving bowel anastomosis, where it is claimed to cause less increase in intraluminal pressure

It produces less release of histamine than morphine, and may be preferable in asthmatics

Contraindications

Airway obstruction

Concomitant use of MAOI

Administration

- IV bolus: 10–50 mg PRN
  Duration of action: 2–3 hours
- PCA: 600 mg in 60 ml sodium chloride 0.9%
  IV bolus: 10 mg, lockout 5–10 minutes

How not to use pethidine

In combination with an opioid partial agonist, e.g. buprenorphine (antagonizes opioid effects)

Adverse effects

Respiratory depression and apnoea

Hypotension and tachycardia

Nausea and vomiting

Delayed gastric emptying

Reduce intestinal mobility

Constipation

Urinary retention

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Histamine release

Tolerance

Pulmonary oedema

Cautions

Enhanced sedative and respiratory depression from interaction with:

- benzodiazepines
- antidepressants
- antipsychotics

Avoid concomitant use of and for 2 weeks after MAOI discontinued (risk of CNS excitation or depression – hypertension, hyperpyrexia, convulsions and coma)

Head injury and neurosurgical patients (may exacerbate ↑ ICP as a result of ↑ $PaCO_2$)

Organ failure

CNS: sedative effects increased

Respiratory: ↑ respiratory depression

Hepatic: enhanced and prolonged sedative effect. Can precipitate coma

Renal: increased cerebral sensitivity. Norpethidine accumulates

https://doi.org/10.1017/9781108349550.015

Phenobarbital Sodium (Phenobarbitone)

The bioavailability of phenobarbital is 90%, so the IV dose can be regarded as the same as the oral dose. With a half-life of 1.4–4.9 days, steady state may take 5–14 days to be reached. Therapeutic serum levels for seizures range from 10 mg/l to 40 mg/l although the optimal plasma concentration for some individuals may vary outside this range. Phenobarbital usually lowers phenytoin levels but they can also be increased. Laboratory levels may be reported in µmol/l or mg/l. To convert mg/l into µmol/l multiply by 4.31.

Uses

Status epilepticus (p. 337)

Contraindications

Porphyria

Administration

- IV: 10 mg/kg (maximum daily dose 1 g)

  Dilute to 10 times its own volume with WFI immediately before use. Give at <100 mg/min

  Phenobarbital can be continued at a rate of 50 mg/min until seizures cease; maximum cumulative dose in the absence of intubation, 20 mg/ kg

  Reduce dose and inject more slowly in the elderly, patients with severe hepatic and renal impairment, and in hypovolaemic and shocked patients
- Maintenance dose: 1 mg/kg IV 12 hourly (average maintenance dose 30–60 mg 12 hourly)

  To discontinue therapy, wean off slowly over several weeks by reducing daily dose by 15–30 mg/d every fortnight. In obese patients, dosage should be based on lean body weight

Adverse effects

Respiratory depression

Hypotension

Bradycardia

CNS depression

https://doi.org/10.1017/9781108349550.015

Organ failure

CNS: ↑ sedative effects

Respiratory: ↑ respiratory depression

Hepatic: can precipitate coma

Renal: reduce dose

https://doi.org/10.1017/9781108349550.015

Phentolamine

Phentolamine is a short-acting α-blocker that produces peripheral vasodilatation by blocking both α_1- and α_2-adrenergic receptors. Pulmonary vascular resistance and pulmonary arterial pressure are decreased.

Uses

Severe hypertension associated with phaeochromocytoma

Contraindications

Hypotension

Administration

Available in 10 mg ampoules

- IV bolus: 2–5 mg, repeat PRN
- IV infusion: 0.1–2 mg/min

Dilute in sodium chloride 0.9% or glucose 5%

Monitor pulse and BP continuously

How not to use phentolamine

Do not use adrenaline, ephedrine, isoprenaline or dobutamine to treat phentolamine-induced hypotension (beta-2 effect of these sympathomimetics will predominate causing a further paradoxical ↓ BP)

Treat phentolamine-induced hypotension with noradrenaline

Adverse effects

Hypotension

Tachycardia and arrhythmias

Dizziness

Nasal congestion

Cautions

Asthma (sulphites in ampoule may lead to hypersensitivity) ischaemic heart disease

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Phenylephrine

Phenylephrine is a selective α_1-adrenergic receptor agonist, acting mainly on large arterioles. It can be used as a vasopressor to increase the blood pressure in patients with hypotension, resulting from septic shock and SIRS. It is also used in anaesthesia to counteract the hypotensive effect of epidural and spinal anaesthetics. Phenylephrine has the potential to produce splanchnic vasoconstriction and reflex bradycardia.

Uses

Hypotension (for patients without central venous access)

Contraindications

Severe hyperthyroidism

Hypertension

Administration

Ampoule containing 10 mg in 10 ml

- IV infusion: Draw up the 10 mg in 10 ml preparation and inject into a 100 ml bag of glucose 5% or sodium chloride 0.9%, to give a concentration of 100 μg/ml solution.

  Start the phenylephrine IV infusion at 25–50 μg/min. Titrate to response, maximum rate 100 μg/min.

How not to use phenylephrine

When an IV infusion is discontinued, slow the infusion rate gradually; do not stop it abruptly

Do not use with non-selective MAOIs (or within 2 weeks of their withdrawal), risk of hyperthermia and paroxysmal hypertension

Adverse effects

Reduced cardiac output (increased afterload)

Chest pain (patient with coronary artery disease)

Increased blood pressure, tachycardia or reflex bradycardia

Paraesthesia in the extremities

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Cautions

Coronary vascular thrombosis

Coronary heart disease

Extravasation at injection site may cause necrosis

Because of its vasoconstrictive effect, phenylephrine can cause severe *necrosis* if it infiltrates the surrounding tissues. Because of this, it should be given through a central line if at all possible. Damage may be prevented or mitigated by infiltrating the tissue with the alpha-blocker phentolamine by SC injection.

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Phenytoin

Phenytoin is approximately 90% protein-bound. Plasma levels are based on total phenytoin (bound plus free) and dosage must be adjusted when serum albumin is reduced (see equation below). Hypoalbuminaemia will lead to an increased fraction of unbound drug. The free fraction is responsible for the pharmacological action of the drug. Phenytoin demonstrates zero-order kinetics and does not demonstrate a proportional relationship between drug levels and dose. Maintenance dosage should not be increased by increments of more than 50–100 mg per day.

Uses

Status epilepticus (p. 337)

Anticonvulsant prophylaxis in post-neurosurgical operations

Anti-arrhythmic – particularly for arrhythmias associated with digoxin toxicity

Contraindications

Do not use IV phenytoin in sino-atrial block, or second- and third-degree AV block

Administration

Status epilepticus:

- IV bolus: 20 mg/kg (maximum 2 g) dilute in 100–250 ml sodium chloride 0.9%, given at a rate ≤50 mg/min
- IV infusion: 100 mg diluted in 50–100 ml sodium chloride 0.9%, given over 30–60 minutes, 8 hourly for maintenance

  Give through a 0.2 μm filter, via large vein or central vein. Available in 5 ml ampoules containing 250 mg phenytoin

Anticonvulsant prophylaxis:

- PO/IV: 200–600 mg/d

Anti-arrhythmic:

- IV: 100 mg every 15 minutes until arrhythmia stops. Maximum 15 mg/kg/d

  Monitor: ECG and BP; serum phenytoin level (p. 309)

  Recommended therapeutic range 40–80 μmol/l or 10–20 mg/l

Hypoalbuminaemia will lead to an increased fraction of unbound active drug. The reported total phenytoin (bound + free) levels are open to misinterpretation because an apparently 'normal' level in a hypoalbuminaemic patient may hide a toxic level of free phenytoin. A conceptual corrected level can be

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determined, which reflects what the total phenytoin level would be if the patient had normal protein levels. To adjust for a low albumin:

Adjusted phenytoin level = reported level ÷ [(0.02 × serum albumin) + 0.1]

However, this equation depends on the accurate measurement of serum albumin. Some albumin assays are not reliable below 15 g/l. If available, free phenytoin levels are preferable if the albumin is low.

If the patient is fitting and levels are low:

- Consider a loading dose:

  Loading dose (mg) = 0.67 × weight (kg) × change in plasma concentration required (in mg/l)
- Increase maintenance dose as follows:

  < 7 mg/l level, increase daily dose by 100 mg daily

  7–12 mg/l level, increase daily dose by 50 mg daily

  12–16 mg/l level, increase daily dose by 25 mg daily

NG administration and IV to oral/NG conversion: theoretically one should take account of the different salts of the IV and liquid preparation but in practice one can use a one-to-one conversion, but give the oral/NG as a single daily dose. Note that enteral feed reduces the absorption of phenytoin liquid so stop feed for 2 hours before and 2 hours after phenytoin administration. In practice, conversion from IV to NG phenytoin at the same total daily dose often results in reduced levels. Administering phenytoin directly into the jejunum is not recommended as the drug will be less effective (shorter time for absorption and irreversible binding to enteral feeding tube) and can cause diarrhoea (hyperosmolar). If jejunal administration cannot be avoided, monitor plasma levels closely and adjust dose.

How not to use phenytoin

Rapid IV bolus not recommended (hypotension, arrhythmias, CNS depression)

Do not dissolve in solutions containing glucose (precipitation)

IM injection not recommended (absorption slow and erratic)

Do not give into an artery (gangrene)

Do not prescribe NG phenytoin three times daily, as feed will be turned off for 9 hours per day

Adverse effects

Nystagmus, ataxia and slurred speech

Drowsiness and confusion

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Hypotension (rapid IV)
Prolonged QT interval and arrhythmias (rapid IV)
Gingival hyperplasia (long-term)
Rashes
Aplastic anaemia
Agranulocytosis
Folate deficiency
Megaloblastic anaemia
Thrombocytopenia

Cautions

Severe liver disease (reduce dose)
Metabolism subject to other enzyme inducers and inhibitors (p. 307)
Additive CNS depression with other CNS depressants

Organ failure

CNS: enhanced sedation
Hepatic: increased serum level

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Phosphates

Hypophosphataemia may lead to muscle weakness and is a cause of difficulty in weaning a patient from mechanical ventilation. Causes of hypophosphataemia in ICU include failure of supplementation (e.g. during TPN), malnutrition, diarrhoea, use of insulin and high-concentration glucose, continuous renal replacement therapy and use of loop diuretics. IV therapy is generally recommended in symptomatic hypophosphataemia and phosphate levels <0.32 mmol/l. Hypophosphataemia may lead to a multitude of symptoms, including cardiac and respiratory failure, and is associated with higher mortality although it is unknown if correction of hypophosphataemia improves mortality (*Critical Care* 2010; **14:** R147).

Normal range: 0.8–1.4 mmol/l.

Uses

Hypophosphataemia

Contraindications

Hypocalcaemia (further ↓ Ca^{2+})

Severe renal failure (risk of hyperphosphataemia)

Administration

10 ml potassium acid phosphate contains 10 mmol phosphate and 10 mmol potassium. Administer one ampoule (10 ml) (10 mmol phosphate) over 6 hours.

Disodium hydrogen phosphate 21.49% is an alternative to potassium phosphate (used in order to avoid potassium). One ampoule (10 ml) contains 6 mmol phosphate and 12 mmol sodium. Administer two ampoules (20 ml) (12 mmol phosphate) over 6 hours.

The recommended dilution depends on whether it is given via the central (recommended) or peripheral route. For central venous route the dilution is to make up to 50 ml with sodium chloride 0.9% or glucose 5%. For the peripheral route, the dilution is to make up to 250 ml with sodium chloride 0.9% or glucose 5%.

Alternatively phosphate polyfuser, 50 mmol/500 ml (also containing sodium 81 mmol and potassium 9.5 mmol) may be used. This is ready diluted for central or peripheral use. For moderate hypophosphataemia, usually 7.5 ml/h for 12 hours (equivalent to 9 mmol over 12 hours). For severe hypophosphataemia, usual maximum dose over 24 hours: 30 mmol up to 48 mmol may be given over 24 hours.

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- IV infusion
- Central IV route: 10–12 mmol phosphate made up to 50 ml with glucose 5% or sodium chloride 0.9%, given over 6 hours
- Peripheral IV route: 10–12 mmol phosphate made up to 250 ml with glucose 5% or sodium chloride 0.9%, given over 6 hours
- Do not give at >12 mmol over 6 hours
- Repeat until plasma level is normal
- Monitor serum calcium, phosphate, potassium and sodium daily

How not to use phosphates

Do not give at a rate >12 mmol over 6 hours

If using phosphate polyfuser, it is common to use only a small proportion of the bottle

Avoid overdosing the patient by ensuring the infusion is stopped when the prescribed volume has been infused.

Adverse effects

Hypocalcaemia, hypomagnesaemia, hyperkalaemia, hypernatraemia

Arrhythmias

Hypotension

Ectopic calcification

Cautions

Renal impairment

Concurrent use of potassium-sparing diuretics or ACE-I with potassium phosphate may result in hyperkalaemia

Concurrent use of corticosteroids with sodium phosphate may result in hypernatraemia

Organ failure

Renal: risk of hyperphosphataemia

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Piperacillin + Tazobactam (Tazocin)

This combination of piperacillin (a broad-spectrum penicillin) and tazobactam (a beta-lactamase inhibitor) has activity against many Gram-positive, -negative and anaerobic bacteria. Piperacillin/tazobactam (PipTaz) may act synergistically with aminoglycosides against Gram-negative organisms including *Pseudomonas aeruginosa*. However, it remains susceptible to chromosomal beta-lactamases expressed by Enterobacteriaceae such as *Enterobacter* spp. and *Citrobacter* spp. and is unreliable for organisms expressing extended-spectrum beta-lactamases (ESBLs). PipTaz appears to have a lower propensity to cause superinfection with *Clostridium difficile* compared with fluoroquinolones and cephalosporins.

Some units use extended (or even continuous) infusions of PipTaz, based on the principle that beta-lactam effectiveness is related to time above the MIC, which is increased by extending the infusion time.

Uses

Intra-abdominal infection

Respiratory tract infection particularly nosocomial pneumonia

Severe upper urinary tract infection

Empirical therapy of a range of severe infections prior to availability of sensitivities

Febrile neutropenia (usually combined with an aminoglycoside)

Contraindications

Penicillin hypersensitivity

Cephalosporin hypersensitivity

Administration

Reconstitute 4.5 g with 20 ml WFI

- IV infusion: 4.5 g 6–8 hourly, dilute the reconstituted solution with 100 ml 5% glucose or sodium chloride 0.9%, give over 30 minutes
- IV bolus: in fluid restriction (unlicensed) give over 3–5 minutes

Unlicensed administration:

- 4.5 g bolus, then 4.5 g every 6–8 hours over a 3–4 hour infusion. This regimen aims to maximise the time above MIC

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In renal impairment:

CC (ml/min)	Dose (g)	Interval (h)
>40 or CVVH rate >2.4 l/h	4.5	Normal
10–40 or CVVH rate 0.6–2.3 l/h	4.5	8
<10	4.5	12

How not to use piperacillin/tazobactam

Not for intrathecal use (encephalopathy)

Do not mix in the same syringe with an aminoglycoside (efficacy of aminoglycoside reduced)

Adverse effects

Diarrhoea

Muscle pain or weakness

Hallucination

Convulsion (high dose or renal failure)

Cautions

Owing to the sodium content (~2 mmol/g), high doses may lead to hypernatraemia

Organ failure

Renal: reduce dose

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Potassium Chloride

Uses

Hypokalaemia

Contraindications

Severe renal failure

Severe tissue trauma

Untreated Addison's disease

Administration

- IV infusion: 20 mmol in 50 ml sodium chloride 0.9% or glucose 5% via central line

  Prefilled bags/syringes should preferably be used where possible

  Potassium chloride 1.5 g (20 mmol K^+) in 10 ml ampoules

  Concentrations greater than 40 mmol in 1 l should be administered centrally, though concentrations up to 80 mmol/l can be administered via a large peripheral vein

  Do not give at >20 mmol/h

  Monitor serum potassium regularly

  Check serum magnesium in refractory hypokalaemia

How not to use potassium chloride

Do not infuse neat potassium chloride into a peripheral vein

Avoid extravasation and do not give IM or SC (severe pain and tissue necrosis)

Do not use neat potassium chloride to reconstitute antibiotics as this has inadvertently caused several deaths

Adverse effects

Muscle weakness

Arrhythmias

ECG changes

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Cautions

Renal impairment

Concurrent use of potassium-sparing diuretics or ACE-I

Hypokalaemia is frequently associated with hypomagnesaemia

Organ failure

Renal: risk of hyperkalaemia

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Prochlorperazine

Prochlorperazine is a phenothiazine that inhibits the medullary chemoreceptor trigger zone.

Uses

Nausea and vomiting

Contraindications

Parkinson's disease

Administration

- IM/IV: 12.5 mg 6 hourly
  The IV route is not licensed
- PO/NG: acute attack – 20 mg then 10 mg after 2 hours; maintenance dose 5–10 mg 8–12 hourly

Adverse effects

Drowsiness

Postural hypotension

Tachycardia

Extrapyramidal movements particularly in children, elderly and debilitated

Cautions

Concurrent use of other CNS depressants (enhanced sedation)

Organ failure

CNS: sedative effects increased

Hepatic: can precipitate coma

Renal: increase cerebral sensitivity

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Propofol

Propofol is an IV anaesthetic induction agent that is widely used as a sedative drug in the critically ill. Its major advantages are that it has a rapid onset of action and a rapid recovery even after prolonged infusion. Propofol 1% (10 mg/ml) and 2% (20 mg/ml) are formulated in intralipid. If the patient is receiving other IV lipid concurrently, a reduction in quantity should be made to account for the amount of lipid infused as propofol: 1 ml propofol 1% contains 0.1 g fat and 1 kcal.

Cremer et al. (*Lancet* 2001; **357:** 117–18) have suggested an association between long-term (>2 days) high-dose (>5 mg/kg/h) propofol infusion used for sedation and cardiac failure in adult patients with head injuries. All the seven patients who died developed metabolic acidosis, hyperkalaemia or rhabdomyolysis. Reports of similar suspected reactions, including hyperlipidaemia and hepatomegaly, were previously reported in children given propofol infusion for sedation in ICUs, some with fatal outcome (MCA/CSM *Current Problems in Pharmacovigilance* 1992; 34).

Uses

Sedation, especially for weaning from other sedative agents (p. 328)

Status epilepticus (p. 337)

Contraindications

As an analgesic

Hypersensitivity to propofol, soybean oil or egg phosphatide (egg yolk)

Sedation of ventilated children aged 16 years or younger receiving intensive care

Administration

- IV bolus: 10–20 mg PRN
- IV infusion: up to 4 mg/kg/h

Titrate to desired level of sedation – assess daily

Measure serum triglycerides regularly

Contains no preservatives – discard after 12 hours

How not to use propofol

Do not give in the same line as blood or blood products

Do not exceed recommended dose range for sedation (up to 4 mg/kg/h)

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Adverse effects

Hypotension

Bradycardia

Apnoea

Pain on injection (minimized by mixing with lidocaine 1 mg for every 10 mg propofol)

Fat overload

Convulsions and myoclonic movements

Cautions

Epilepsy

Lipid disorders (risk of fat overload)

Organ failure

CNS: sedative effects increased

Cardiac: exaggerated hypotension

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Protamine

Available as a 1% (10 mg/ml) solution of protamine sulphate. Although it is used to neutralise the anticoagulant action of heparin and LMWH for the treatment of severe bleeding, if used in excess it has an anticoagulant effect. It should correct a prolonged APTT but it will only partially reverse LMWH.

Uses

Neutralise the anticoagulant action of heparin and LMWH

Contraindications

Hypersensitivity

Administration

1 ml 1% (10 mg) protamine is required to neutralise 1,000 units of heparin given in the previous 15–30 minutes

Maximum 50 mg protamine sulphate in any one dose; maximum rate 5 mg/min

Slow IV injection 5 ml 1% over 10 minutes

APTT can be checked 15 minutes after a protamine sulphate dose

Once the APTT is corrected, recheck at 2 hours and then every 4–6 hours for the next 24 hours because of the possibility of heparin rebound

For heparin boluses:

As more time elapses after the heparin injection, proportionally less protamine is required, i.e. if 30–60 minutes have elapsed since the IV heparin bolus, then give 0.5–0.75 mg protamine sulphate per 100 units of heparin administered

If approximately 2 hours have elapsed, then give 0.25–0.375 mg per 100 units IV heparin

Ideally, the dosage should be guided by serial measurements of APTT/ACT and the rate guided by watching the direct arterial BP

For heparin infusions

As heparin has a short half-life it is usually sufficient to stop the IV infusion

Coagulation is mostly normal 4 hours after cessation

If severe bleeding, then only heparin given during the preceding few hours needs to be taken into account

The initial dose of protamine sulphate is 25–50 mg by slow IV (maximum 5 mg/min)

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Consider using the lower dose if the infusion has been stopped for 1–2 hours and patient is still bleeding

Check APTT 15 minutes after a protamine sulphate dose; once corrected, recheck at 2 hours and then every 4–6 hours for the next 24 hours because of the possibility of heparin rebound

How not to use protamine

Rapid IV bolus

Adverse effects

Hypersensitivity

Rapid IV administration – pulmonary vasoconstriction, ↓ left atrial pressure and hypotension

Cautions

Hypersensitivity (severe hypotension, may respond to fluid loading)

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Pyridostigmine (Mestinon)

Pyridostigmine is a cholinesterase inhibitor leading to prolongation of ACh action. This enhances neuromuscular transmission in voluntary and involuntary muscle in myasthenia gravis.

Uses

Myasthenia gravis

Administration

- Orally: 60–240 mg 4–6 hourly (maximum daily dose: 1.2 g)

  When relatively large doses are taken it may be necessary to give atropine or other anticholinergic drugs to counteract the muscarinic effects

Contraindications

Bowel obstruction

Urinary obstruction

How not to use pyridostigmine

Excessive dosage may impair neuromuscular transmission and precipitates 'cholinergic crises' by causing a depolarising block

It is inadvisable to exceed a daily dose of 720 mg

Adverse effects

Increased sweating

Excess salivation

Nausea and vomiting

Abdominal cramp

Diarrhoea

Bradycardia

Hypotension

These muscarinic side effects are antagonized by atropine.

Cautions

Asthma

Organ failure

Renal: reduce dose

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Chapter

Q

Quetiapine (Seroquel)

This is an atypical antipsychotic agent that antagonizes a range of receptors, namely dopamine D_1, D_2, 5-HT_2, α_1-adrenoceptor and histamine-1. Although licensed for conditions such as acute schizophrenia, mania, depression and bipolar disorder, there is emerging experience of using this agent as an alternative to haloperidol in delirium (see p. 331), particularly in patients who have a prolonged QT interval. A case series (*Critical Care* 2011; **15**: R159) describes experience with a cohort of ICU patients. It has several attractive features: it is administered 12 hourly, has a relatively short half-life of 7 hours (12 hours for its active metabolite norquetiapine), is titratable and, importantly, has a lower incidence of QTc prolongation and fewer extrapyramidal symptoms than haloperidol.

Uses

Management of delirium in ICU patients (unlicensed), especially in prolonged QT interval as an alternative to benzodiazepines or in refractory or mixed delirium

Licensed indications: schizophrenia, mania, either alone or with mood stabilisers, depression in bipolar disorder, adjunctive treatment in major depressive disorder

Contraindications

Concomitant administration of cytochrome P450 3A4 inhibitors such as HIV protease inhibitors, azole-antifungal agents, e.g. fluconazole, erythromycin, clarithromycin and nefazodone

Administration

- PO/NG initially 12.5 mg 12 hourly, titrated to response, typically to 25 mg 12 hourly for delirium and up to 200 mg 12 hourly. Maximum licensed dose 375 mg 12 hourly
- Available as 25 mg, 100 mg, 150 mg, 200 mg and 300 mg tablets

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Adverse effects

Most common: somnolence, dizziness, dry mouth, mild asthenia, constipation, tachycardia, orthostatic hypotension and dyspepsia

Elevated plasma triglyceride and cholesterol concentrations

QT prolongation

Hyperglycaemia

Withdrawal symptoms after long-term use

Seizures

Cautions

Hepatic enzyme inducers such as carbamazepine or phenytoin substantially decrease quetiapine plasma concentrations

Organ failure

Renal: no dose adjustment is required

Liver: titrate dose to response (lower dose may be necessary)

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Chapter

R

Ramipril

Ramipril is an ACE-I; ACE-I have a beneficial role in all grades of heart failure, usually combined with a beta-blocker and diuretics. Potassium-sparing diuretics (e.g. spironolactone) should be discontinued before starting an ACE-I because of the risk of hyperkalaemia. However, low-dose spironolactone may also be beneficial in severe heart failure, and when used together with an ACE-I serum potassium needs to be monitored closely.

Uses

Hypertension

Heart failure

Contraindications

Aortic stenosis

HOCM

Porphyria

Angioedema (idiopathic or hereditary)

Known or suspected renal artery stenosis (co-existing diabetes, peripheral vascular disease, hypertension)

Administration

- Orally: 1.25 mg once daily, increased gradually to a maximum of 10 mg daily (daily doses of 2.5 mg or more may be taken in one to two divided doses)
- Can be given sublingually, if nil by mouth (unlicensed route)
  Monitor: BP, serum potassium and creatinine

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In renal impairment:

CC (ml/min)	Initial dose (mg)	Maximum once daily dose (mg)
0–30 or CVVH rate up to 1.8 l/h	1.25	5

Adverse effects

Hypotension
Tachycardia
Dry cough
Rash
Pancreatitis
Altered LFT
Acidosis
Angioedema

Cautions

Risk of sudden and precipitous fall in BP in the following patients:

- Dehydrated
- Salt-depleted (Na^+ <130 mmol/l)
- High-dose diuretics (>80 mg furosemide daily)
- Concomitant NSAID (↑ risk of renal damage)
- Concomitant potassium-sparing diuretics (hyperkalaemia)
- Peripheral vascular disease or generalized atherosclerosis (risk of clinically silent renovascular disease)

Organ failure

Renal: reduce dose; hyperkalaemia more common

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Ranitidine

Ranitidine is a specific histamine H_2-antagonist that inhibits basal and stimulated secretion of gastric acid, reducing both the volume and the pH of the secretion.

Uses

Peptic ulcer disease

Prophylaxis of stress ulceration

Premedication in patients at risk of acid aspiration

Administration

- IV bolus: 50 mg 8 hourly

  Dilute to 20 ml with sodium chloride 0.9% or glucose 5% and give over 5 minutes
- Oral 150 mg 12 hourly

  For prevention of NSAID-induced gastrointestinal toxicity, double the doses stated above

In renal impairment:

CC (ml/min)	Percentage of normal dose
CVVH	100
<10	50–100

How not to use ranitidine

Do not give rapidly as IV bolus (bradycardia, arrhythmias)

Adverse effects

Hypersensitivity reactions

Bradycardia

Transient and reversible worsening of LFTs

Reversible leukopenia and thrombocytopenia

Organ failure

Renal: reduce dose

Hepatic: reduce dose (increased risk of confusion)

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Remifentanil

Remifentanil is a potent, short-acting, selective μ opioid receptor agonist. In critical care, it is an ideal analgesic in mechanically ventilated adult patients. The concept of analgesia-based sedation represents a move away from traditional analgesic/hypnotic-based sedation, and with appropriate training this may be an easier regimen to manage. Remifentanil is also licensed for use in general anaesthesia. It has an onset of action of approximately 1 minute and quickly achieves steady state. It is metabolized rapidly by non-specific blood and tissue esterases into clinically inactive metabolites. Thus the elimination half-life of 3–10 minutes is independent of infusion duration and renal and hepatic dysfunction. Some units use remifentanil particularly in patients with renal or hepatic dysfunction, to avoid accumulation and prolonged sedation. Other possible indications for remifentanil include overnight ventilation, tracheostomy and ready to wean, difficult weans (e.g. COPD, cardiovascular disease, obesity, problems of withdrawal following long-term sedation), head injuries or patients with low Glasgow coma score (GCS) requiring regular assessment, raised ICP (resistant to medical management) and to assess neurological function in mechanically ventilated patients.

Concerns around use of remifentanil include side effects of hypotension and bradycardia, possible development of tolerance (common to all opioids) and the onset of pain on discontinuation of remifentanil.

Uses

Analgesia and sedation in mechanically ventilated adults. Trials have been conducted for up to 3 days of use.

Contraindications

Epidural and intrathecal use, as formulated with glycine

Hypersensitivity to fentanyl analogues

Administration

- IV: initially 6–9 μg/kg/h; evaluate after 5 minutes, if pain, anxiety or agitation or difficult to wake, then titrate infusion up or down with steps of 1.5 μg/kg/h

  The usual dose range is 0.36–44.4 μg/kg/h; if the dose of 12 μg/kg/h does not produce adequate sedation, then add a sedative such as propofol

  Additional analgesia will be required for ventilated patients undergoing stimulating procedures such as suctioning, wound dressing and physiotherapy

  An infusion of 15–45 μg/kg/h (and up to 45 μg/kg/h), will be needed

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Maintain infusion rate of at least 6 μg/kg/h for at least 5 minutes prior to the intervention

Adjust every 2–5 minutes according to requirements

Reconstitute vial to 100 μg/ml, i.e. 5 mg vial with 50 ml, 2 mg with 20 ml, and 1 mg with 10 ml of diluent; suitable diluents are WFI, glucose 5% or sodium chloride 0.9%

In obesity, use ideal body weight rather than actual weight

In the elderly, reduce initial dose by 50%

Due to the short half-life, a new syringe should be ready for use at the end of each infusion

How not to use remifentanil

Bolus doses are not recommended in the critical care setting. Not to be used as a sole induction agent

Adverse effects

Hypomagnesaemia

Bradycardia

Hypotension

Respiratory depression

Muscle rigidity, including chest wall rigidity

Dependency

Cautions

Upon discontinuation, the IV line should be cleared or removed to prevent subsequent inadvertent administration

Organ failure

Renal: no dose adjustment necessary

Hepatic: no dose adjustment, but in severe disease respiratory depression more common

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Rifampicin

Rifampicin is active against a wide range of Gram-positive and -negative organisms, but resistance readily emerges during therapy due to pre-existing mutants present in most bacterial populations. It must therefore be used with a second antibiotic active against the target pathogen. Its major use is for therapy of tuberculosis.

Uses

In combination with vancomycin for:

- penicillin-resistant pneumococcal infections including meningitis
- serious Gram-positive infections including those caused by MRSA
- prosthetic device-associated infections

Legionnaires' disease (in combination with a macrolide antibiotic)

Prophylaxis of meningococcal meningitis and *Haemophilus influenzae* (type b) infection

Combination therapy for infections due to *Mycobacterium tuberculosis*

Contraindications

Porphyria

Jaundice

Administration

Serious Gram-positive infections (in combination with vancomycin):

- Oral or IV: 600 mg 12 hourly

Legionnaires' disease (in combination with a macrolide antibiotic):

- Oral or IV: 600 mg 12 hourly

Prophylaxis of meningococcal meningitis infection:

- Oral or IV: 600 mg 12 hourly for 2 days

  Child 10 mg/kg (under 1 year, 5 mg/kg) 12 hourly for 2 days

Prophylaxis of *Haemophilus influenzae* (type b) infection:

- Oral or IV: 600 mg once daily for 4 days

  Child 1–3 months 10 mg/kg once daily for 4 days, over 3 months 20 mg/kg once daily for 4 days (maximum 600 mg daily)

  IV formulation is available as Rifadin

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Reconstitute with the solvent provided, then dilute with 500 ml of glucose 5%, sodium chloride 0.9% or Hartmann's solution given over 2–3 hours

Monitor: FBC, U&E, LFTs

Adverse effects

Gastrointestinal symptoms (nausea, vomiting, diarrhoea)

Bodily secretions (urine, saliva) coloured orange-red

Abnormal LFT

Haemolytic anaemia

Thrombocytopenic purpura

Renal failure

Cautions

Discolours soft contact lenses

Women on oral contraceptive pills will need other means of contraception

Organ failure

Hepatic: avoid or do not exceed 8 mg/kg daily (impaired elimination)

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Rotigotine Transdermal Patch (Neupro)

This dopamine agonist patch is particularly useful in Parkinson's disease patients who are usually established on other oral agents but are currently nil by mouth. Consult conversion tables below.

Uses

Parkinson's disease

Restless leg syndrome

Contraindications

The backing layer of the patch contains aluminium; to avoid skin burns, remove the patch if the patient has to undergo MRI or cardioversion

Administration

Available as 2, 4, 6 and 8 mg/24 h patches

For initiation in Parkinson's disease, initially 2 mg/24 h and increase every 7 days to effective dose up to 8 mg/24 h

Consult conversion tables for most appropriate dose if changing from oral therapy

As soon as the patient can absorb again switch back to the normal Parkinson's disease regimen

How not to use rotigotine

Important to remove patch during MRI or cardioversion

Do not cut patch to achieve a dose

Do not exceed the maximum dose of 16 mg/24 h

Adverse effects

Nausea and vomiting

Skin reaction

Hypotension

Hallucinations

Increased confusion (particularly in a dopamine naive patient)

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Caution

Delirium or dementia, start with a low dose and slowly titrate

No dose adjustment needed in renal or liver impairment

Levodopa-based conversion:

Current levodopa regimen	Rotigotine patch equivalent
Madopar (co-beneldopa) or Sinemet (co-careldopa) 62.5 mg twice daily	2 mg/24 h
Madopar or Sinemet 62.5 mg three times daily	4 mg/24 h
Madopar or Sinemet 62.5 mg four times daily	6 mg/24 h
Madopar or Sinemet 125 mg three times daily	8 mg/24 h
Madopar or Sinemet 125 mg four times daily	10 mg/24 h
Madopar or Sinemet 187.5 mg three times daily	12 mg/24 h
Madopar or Sinemet 187.5 mg four times daily	16 mg/24 h
Madopar or Sinemet 250 mg three or four times daily	16 mg/24 h
Stalevo 50/12.5/200 three times daily	6 mg/24 h
Stalevo 100/25/200 three times daily	10 mg/24 h
Stalevo 100/25/200 four times daily	14 mg/24 h
Stalevo 150/37.5/200 three times daily or Stalevo 200/50/200 three times daily	16 mg/24 h

100 mg of levodopa MR (modified release) is approximately equivalent to 2 mg/24 h rotigotine, therefore if patient is on an additional levodopa MR preparation, increase rotigotone dose by 2 mg/24 h (maximum 16 mg/24 h)

If patient takes levodopa and a dopamine agonist then add the two rotigotine doses together but maximum dose is still 16 mg/24 h

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Dopamine agonist conversion:

Pramipexole (salt content)*	Ropinirole immediate release	Ropinirole modified release	Rotigotine patch equivalent
0.125 mg three times daily	Starter pack	N/A	2 mg/24 h
0.25 mg three times daily	1 mg three times daily	4 mg/d	4 mg/24 h
0.5 mg three times daily	2 mg three times daily	6 mg/d	6 mg/24 h
0.75 mg three times daily	3 mg three times daily	8 mg/d	8 mg/24 h
1 mg three times daily	4 mg three times daily	12 mg/d	10–12 mg/24 h
1.25 mg three times daily	6 mg three times daily	16 mg/d	14 mg/24 h
1.5 mg three times daily	8 mg three times daily	24 mg/d	16 mg/24 h

* Doses and strengths are stated in terms of pramipexole dihydrochloride monohydrate (salt); equivalent strengths in terms of pramipexole (base) are as follows:

0.26 mg base ≡ 0.375 mg salt
0.52 mg base ≡ 0.75 mg salt
1.05 mg base ≡ 1.5 mg salt
1.57 mg base ≡ 2.25 mg salt
2.1 mg base ≡ 3 mg salt
2.62 mg base ≡ 3.75 mg salt
3.15 mg base ≡ 4.5 mg salt

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Chapter

S

Salbutamol

Salbutamol is a short-acting, selective β_2-adrenergic receptor agonist used in the treatment of bronchospasm caused by asthma and COPD. Salbutamol has been used to treat acute hyperkalaemia, as it stimulates potassium uptake into cells, thereby lowering the potassium in the blood.

Uses

Reverses bronchospasm

Administration

- Nebuliser: 2.5–5 mg 6 hourly, undiluted (if prolonged delivery time desirable then dilute with sodium chloride 0.9% only)

  For patients with chronic bronchitis and hypercapnia, oxygen in high concentration can be dangerous, and nebulizers should be driven by air
- IV: 5 mg made up to 50 ml with glucose 5% (100 μg/ml)

  Rate: 200–1,200 μg/h (2–12 ml/h)

How not to use salbutamol

For nebuliser: do not dilute in anything other than sodium chloride 0.9% (hypotonic solution may cause bronchospasm)

Adverse effects

Tremor

Tachycardia

Paradoxical bronchospasm (stop giving if suspected)

Potentially serious hypokalaemia (potentiated by concomitant treatment with aminophylline, steroids, diuretics and hypoxia)

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Cautions

Thyrotoxicosis

In patients already receiving large doses of other sympathomimetic drugs

Sildenafil

Sildenafil (Viagra, Revatio), epoprostenol (Flolan), bosentan (Tracleer) and sitaxentan (Thelin) are licensed for the treatment of pulmonary hypertension. Epoprostenol and sildenafil are both available for IV use. Sildenafil is a potent and selective inhibitor of cyclic guanosine monophosphate (cGMP) specific phosphodiesterase type 5 (PDE5), the enzyme that is responsible for degradation of cGMP. Apart from the presence of this enzyme in the corpus cavernosum of the penis, PDE5 is also present in the pulmonary vasculature. Sildenafil, therefore, increases cGMP within pulmonary vascular smooth muscle cells, resulting in relaxation. In patients with pulmonary arterial hypertension this can lead to vasodilatation of the pulmonary vascular bed and, to a lesser degree, vasodilatation in the systemic circulation.

Uses

Pulmonary hypertension

Contraindications

Recent stroke or MI

Severe hypotension (systolic BP <90 mmHg)

Severe hepatic impairment (Child–Pugh class C)

Avoid concomitant use of nitrates, ketoconazole, itraconazole and ritonavir

Administration

- Orally: 20 mg 8 hourly, start with 20 mg 12 hourly

  Renal impairment: 20 mg 12 hourly

  Hepatic impairment (Child-Pugh class A and B): 20 mg 12 hourly
- IV bolus: 10 mg 8 hourly; ready diluted; vial contains 10 mg (as citrate) in 12.5 ml (0.8 mg/ml)

  10 mg IV has equivalent effect to 20 mg orally

Adverse effects

Gastrointestinal disturbances

Dry mouth

Flushing

Headaches

Back and limb pain

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Visual disturbances
Hearing loss
Pyrexia

Cautions

Hypotension (avoid if systolic BP <90 mmHg)
Dehydration
Left ventricular outflow obstruction
Ischaemic heart disease
Predisposition to priapism
Bleeding disorders
Active peptic ulceration
Hepatic impairment (avoid if severe)
Renal impairment (reduce dose)

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Sodium Valproate (Epilim)

Sodium valproate is used to treat epilepsy. The IV route is chosen only when the oral/NG route is unavailable. The therapeutic range for trough plasma valproic acid levels is 40–100 mg/l (278–694 μmol/l), though there is a less reliable correlation between the level and efficacy. The oral form is available as a liquid (200 mg/5 ml), which is useful for NG administration, and tablets, crushable tablets and in modified release formulations. Sodium valproate should not be confused with valproic acid (as semi-sodium valproate), which is licensed for acute mania. Valproate overdose can cause hyperammonaemia encephalopathy, which can be treated with carnitine (IV 500 mg/m^2 twice daily) (see *Critical Care* 2005; **9**: 431–40)

Uses

All forms of epilepsy, including emergency management

Alternative to valproic acid for NG feeding (unlicensed)

Administration

For conversion of oral to IV doses, the same daily dose is used in divided doses administered over 3–5 minutes

- Initiating IV valproate: 400–800 mg (up to 10 mg/kg), then IV infusion of up to 2.5 g maximum

  To prepare, reconstitute 400 mg vial with 4 ml diluent provided and further dilute to a convenient volume with sodium chloride 0.9% or glucose 5%

  It may be administered as a bolus over 3–5 minutes or as a continuous infusion
- Oral: usually 20–30 mg/kg per day in two divided doses

  Valproic acid cannot be administered NG

  Sodium valproate liquid is a viable alternative, dose conversion: valproic acid 500 mg ~ sodium valproate 600 mg (unlicensed).

How not to use sodium valproate

Do not give to women or girls of childbearing potential unless a Pregnancy Prevention Programme is in place or there are compelling reasons to indicate that there is no risk of pregnancy

Adverse effects

Transient raised LFTs

Severe liver dysfunction, which can be fatal

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Hyperammonaemia and hyponatraemia

Rarely exanthematous rash

Cautions

Pancreatitis

Liver toxicity

Sodium valproate is eliminated mainly through the kidneys, partly in the form of ketone bodies; this may give false positives in urine testing. Sodium valproate concentrations are reduced by carbamazepine and phenytoin. Valproate increases or sometimes decreases phenytoin levels, and increases levels of lamotrigine.

Organ failure

Renal: no dose adjustment required

Hepatic: avoid if possible; hepatotoxicity and hepatic failure may occasionally occur

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Spironolactone

Spironolactone is a potassium-sparing diuretic, which acts by antagonising aldosterone. Low doses of spironolactone have been shown to benefit patients with severe congestive heart failure who are already receiving an ACE-I and a diuretic. It is also of value in the treatment of oedema and ascites in cirrhosis of the liver.

Uses

Congestive heart failure

Oedema and ascites in liver cirrhosis

Contraindications

Hyperkalaemia

Hyponatraemia

Severe renal failure

Addison's disease

Administration

Congestive heart failure:

- Orally: 25–50 mg once daily

Oedema and ascites in liver cirrhosis:

- Orally: 100–400 mg once daily

  If IV route is needed, use potassium canrenoate (unlicensed drug)

  Conversion: potassium canrenoate 140 mg is equivalent to spironolactone 100 mg

  Administer by IV bolus via a large vein at a maximum rate of 100 mg/min, otherwise administer via IV infusion in 250 ml of glucose 5% over 90 minutes

  Monitor: serum sodium, potassium and creatinine

Adverse effects

Confusion

Hyperkalaemia (unlikely to occur with congestive heart failure dose)

Hyponatraemia

Abnormal LFT

Gynaecomastia (usually reversible)

Rashes

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Cautions

Porphyria

Renal impairment (risk of hyperkalaemia)

Concurrent use of:

- ACE-I (risk of hyperkalaemia)
- angiotensin-II antagonist (risk of hyperkalaemia)
- digoxin (↑ plasma concentration of digoxin)
- ciclosporin (risk of hyperkalaemia)
- lithium (↑ plasma concentration of lithium)

Organ failure

Renal: risk of hyperkalaemia; use with caution in severe renal failure

Hepatic: may precipitate encephalopathy

Sucralfate

A complex of aluminium hydroxide and sulphated sucrose. It acts by protecting the mucosa from acid-pepsin attack.

Uses

Prophylaxis of stress ulceration

Contraindications

Severe renal impairment (CC <10 ml/min)

Administration

- Orally: 1 g suspension 4 hourly

Stop sucralfate when enteral feed commences

How not to use sucralfate

Do not give with enteral feed (risk of bezoar formation)

Do not give ranitidine concurrently (may need acid environment to work)

Adverse effects

Constipation

Diarrhoea

Hypophosphataemia

Cautions

Renal impairment (neurological adverse effects due to aluminium toxicity)

Risk of bezoar formation and potential intestinal obstruction

Interferes with absorption of quinolone antibiotics, phenytoin and digoxin when given orally

Organ failure

Renal: aluminium may accumulate; CC 10–20 ml/min, i.e. half normal dose 2–4 g daily

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Sugammadex (Bridion)

Sugammadex is used for rapid reversal of neuromuscular blockade induced by rocuronium or vecuronium. It forms a tight one-to-one complex with rocuronium/vecuronium, encapsulating the drug in the plasma and hence reducing its concentration at the neuromuscular junction and rapidly terminating block. Unlike acetylcholinesterase inhibitors, e.g. neostigmine, sugammadex can be given for immediate reversal without the need for partial recovery. Having no effect on acetylcholinesterase, concomitant anticholinergic drugs, e.g. glycopyrrolate, are not required with sugammadex. Use of this drug replaces the use of suxamethonium, which can cause anaphylactic/allergic reactions, myalgia, cardiac arrest and induce malignant hyperthermia (MH). However, it is substantially more expensive than alternative agents, which may be prohibitive for routine reversal.

Uses

Emergency reversal of neuromuscular blockade where standard reversal is likely to be too slow, i.e. 'cannot intubate, cannot ventilate' scenarios

Administration

The dose is dependent on the level of neuromuscular blockade to be reversed rather than the anaesthetic regimen

For routine reversal: if recovery has reached at least 1–2 post-tetanic counts (PTC), the dose is 4 mg/kg

If spontaneous recovery has reached at least the appearance of T2, the dose is 2 mg/kg

If re-occurrence of blockade occurs post-operatively, a repeat dose of 4 mg/kg may be given with close monitoring for return of neuromuscular function

Administer as an IV bolus over 10 seconds. It can be injected into an IV line of infusions of sodium chloride 0.9%, glucose 5% or Hartmann's solution. Flush with sodium chloride 0.9% after use

At least a 24-hour interval must be observed before re-administration of vecuronium or rocuronium after sugammadex administration. If further neuromuscular blockade is required, a non-steroid neuromuscular blocking agent must be used

How not to use sugammadex

Do not reuse rocuronium/vecuronium within 24 hours of sugammadex use

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Adverse effects

Hypersensitivity reactions

Bronchospasm

Displacement interactions

These can occur as vecuronium or rocuronium may be displaced from sugammadex, carrying a risk of re-occurrence of blockade. This may occur with patients who have received either toremifine or sodium fusidate injection on the day of operation, which may have delayed recovery of the T4/T1 ratio to 0.9.

Cautions

In those with an increased bleeding risk, the anaesthetist needs to make a risk/benefit assessment before use in relation to history of bleeding episodes and type of surgery. High bleeding risk includes: warfarin with INR>3.4, anti-coagulant use with those receiving a dose of sugammadex 16 mg/kg, pre-existing coagulopathies, hereditary vitamin K-dependent clotting factor deficiencies.

Sugammadex can reduce the effect of hormonal contraceptives, so extra precautions are necessary. One 4 mg/kg dose is similar to missing one oral contraceptive dose.

Organ failure

Renal: mild–moderate impairment – no change; CC <30 ml/min not recommended

Hepatic: no adjustment required, in severe impairment, use with caution as no studies in this group

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Suxamethonium

Suxamethonium is the only depolarising neuromuscular blocker available in the UK. It has a rapid onset of action (45–60 seconds) and a short duration of action (5 minutes). Breakdown is dependent on plasma pseudocholinesterase. It is best to keep the ampoule in the fridge to prevent a gradual loss of activity due to spontaneous hydrolysis.

Uses

Agent of choice for:

- rapid tracheal intubation as part of a rapid sequence induction
- for procedures requiring short periods of tracheal intubation, e.g. cardioversion
- management of severe post-extubation laryngospasm unresponsive to gentle positive pressure ventilation

Contraindications

History of malignant hyperpyrexia (potent trigger)

Hyperkalaemia (expect a further increase in K^+ level by 0.5–1.0 mmol/l)

Patients where exaggerated increases in K^+ (>1.0 mmol/l) are expected:

- severe burns
- extensive muscle damage
- disuse atrophy
- paraplegia and quadriplegia
- peripheral neuropathy, e.g. Guillain–Barré syndrome

Administration

As a rapid sequence induction: 1.0–1.5 mg/kg IV bolus, after 3 minutes pre-oxygenation with 100% oxygen and a sleep dose of induction agent

Apply cricoid pressure until tracheal intubation confirmed; intubation possible within 1 minute, effect normally lasting <5 minutes

Repeat dose of 0.25–0.5 mg/kg may be given

Atropine or glycopyrollate should be given at the same time to avoid bradycardia/asystole

How not to use suxamethonium

In the conscious patient

By persons not trained to intubate the trachea

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Adverse effects

Malignant hyperpyrexia
Hyperkalaemia
Transient increase in IOP and ICP
Muscle pain
Myotonia
Bradycardia, especially after repeated dose

Cautions

Digoxin (may cause arrhythmias)
Myasthenia gravis (resistant to usual dose)
Penetrating eye injury (IOP may cause loss of globe contents)

Prolonged block in:

- patients taking aminoglycoside antibiotics, magnesium
- myasthenic syndrome
- pseudocholinesterase deficiency (inherited or acquired)

Organ failure

Hepatic: prolonged apnoea (reduced synthesis of pseudocholinesterase)

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Chapter

T

Teicoplanin

This glycopeptide antibiotic, like vancomycin, has bactericidal activity against both aerobic and anaerobic Gram-positive bacteria: *Staphylococcus aureus*, including MRSA, *Streptococcus* spp., *Listeria* spp. and *Clostridium* spp. It is only bacteriostatic for most *Enterococcus* spp. It does not cause 'red man' syndrome through histamine release and is less nephrotoxic than vancomycin. However, due to the variation between patients, effective therapeutic levels for severe infections may not be reached for a number of days using the most commonly recommended dosage schedules. Serum monitoring of pre-dose levels can be undertaken, particularly for severe infections.

In the UK resistance is well recognized in enterococci and coagulase-negative staphylococci and, more worryingly, is now emerging in *S. aureus*.

Uses

Serious Gram-positive infections:

- prophylaxis and treatment of infective endocarditis (usually combined with gentamicin)
- dialysis-associated peritonitis
- infection caused by MRSA
- prosthetic device infections due to coagulase-negative staphylococci
- alternative to penicillins and cephalosporins where patients are allergic

Contraindications

Hypersensitivity

Administration

IV bolus:

- Bacterial endocarditis
- Teicoplanin 10 mg/kg (max 1 g per dose) IV 12 hourly for three doses, then 10 mg/kg (max 1 g per dose) IV daily

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- Bone and joint infections
- Teicoplanin 12 mg/kg (maximum 1 g per dose) IV 12 hourly for three doses, then 12 mg/kg (max 1g per dose) IV daily
- All other infections

  Teicoplanin 400 mg (6 mg/kg if >70 kg, rounded to the nearest 100 mg) IV 12 hourly (maximum 1 g per dose) for three doses, then 400 mg (6 mg/kg if >70 kg) IV daily (max 1 g per dose)

  Base all doses on actual body weight

  Reconstitute with WFI supplied; gently roll the vial between the hands until powder is completely dissolved

  Shaking the solution will cause the formation of foam; if the solution becomes foamy allow to stand for 15 minutes

  Monitor: FBC, U&E, LFT, serum pre-dose teicoplanin level

Levels are not essential for treatment, but if available:

Pre-dose (trough) serum concentration should not be <10 mg/l

For severe infections, trough serum concentration >20 mg/l is recommended

In renal impairment: dose reduction not necessary until day 4, then reduce dose as below:

CC (ml/min)	Dose	Interval
> 20 (or CVVH rate >1.2 l/h)	Usual dose	Every day
10–20 (or CVVH rate 0.6–1.2 l/h)	Usual dose	Every 24–48 h
<10	Usual dose	Every 48 h

How not to use teicoplanin

Do not mix teicoplanin and aminoglycosides in the same syringe

Adverse effects

Raised LFTs

Hypersensitivity

Blood disorders

Ototoxic

Nephrotoxic

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Cautions

Vancomycin sensitivity

Renal/hepatic impairment

Concurrent use of ototoxic and nephrotoxic drugs

Organ failure

Renal: reduce dose

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Terlipressin

Oesophageal varices are enlarged blood vessels that form in the stomach or oesophagus as a complication of liver disease. When administered in bleeding oesophageal varices, terlipressin (Glypressin and Variquel) is broken down to release lysine vasopressin, which causes vasoconstriction of these vessels thereby reducing the bleeding. In addition, terlipressin may have a role in the treatment of hepatorenal syndrome, by increasing renal perfusion. Terlipressin can also be used as an alternative to vasopressin in resistant septic shock, in addition to noradrenaline.

Uses

Bleeding oesophageal varices

Resistant high-output septic shock

Hepatorenal syndrome

Contraindications

Pregnancy

Administration

Varices:

- IV bolus: 2 mg, then 1–2 mg every 4–6 hourly, for up to 3 days

Resistant high-output septic shock (unlicensed indication) – see p. 422:

- IV 0.25 mg bolus, repeated up to four times with 20-minute intervals between doses or IV infusion (unlicensed) 0.1 mg/h (can increase to 0.3 mg/h)

  Will take 20 minutes for first effect. The infusion can be made up with 1 mg in 5 ml with the diluent provided or the ready diluted solution

Hepatorenal syndrome (unlicensed indication):

- IV bolus: 0.5–1 mg 6 hourly

Terlipressin is available in two brands and three presentations: Glypressin 1 mg/8.5 ml solution (stored in fridge), Glypressin and Variquel, both 1 mg with 5 ml diluent (stored at room temperature)

Monitor: BP, serum sodium and potassium, fluid balance

Adverse effects

Abdominal cramps

Headache

Raised blood pressure

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Cautions

Hypertension

Arrhythmias

Ischaemic heart disease

Organ failure

Renal: no dose reduction needed

Thiopentone

Thiopentone is a barbiturate that is used widely as an IV anaesthetic agent. It also has cerebroprotective and anticonvulsant activities. Awakening from a bolus dose is rapid due to redistribution, but hepatic metabolism is slow and sedative effects may persist for 24 hours. Repeated doses or infusion have a cumulative effect. Available in 500 mg ampoules or 2.5 g vial, which is dissolved in 20 ml or 100 ml WFI, respectively, to make a 2.5% solution.

Uses

Induction of anaesthesia

Status epilepticus (p. 337)

Contraindications

Airway obstruction

Previous hypersensitivity

Status asthmaticus

Porphyria

Administration

Induction of anaesthesia:

- IV bolus: 2.5–4 mg/kg
  After injecting a test dose of 2 ml, if no pain, give the rest over 20–30 seconds until loss of eyelash reflex

  Give further 50–100 mg if necessary

  Reduce dose and inject more slowly in the elderly, patients with severe hepatic and renal impairment, and in hypovolaemic and shocked patients

  In obese patients, dosage should be based on lean body weight

Use in convulsive states:

- IV bolus: 75–125 mg (3–5 ml of a 2.5% solution) should be given as soon as possible after the convulsion begins
- IV infusion: up to 2 mg/kg/h to induce coma to suppress fits for up to 5 days

  Keep bispectral index (BIS) below 15

Use in neurological patients with raised ICP:

- IV bolus: 1.5–3 mg/kg of body weight may be given to reduce elevations of ICP if controlled ventilation is provided

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How not to use thiopentone

Do not inject into an artery (pain and ischaemic damage)
Do not inject solution >2.5% (thrombophlebitis)

Adverse effects

Hypersensitivity reactions (1:14,000–35,000)
Coughing, laryngospasm
Bronchospasm (histamine release)
Respiratory depression and apnoea
Hypotension, myocardial depression
Tachycardia, arrhythmias
Tissue necrosis from extravasation

Cautions

Hypovolaemia
Septic shock
Elderly (reduce dose)
Asthma

Organ failure

CNS: sedative effects increased
Cardiac: exaggerated hypotension and ↓ cardiac output
Respiratory: ↑ respiratory depression
Hepatic: enhanced and prolonged sedative effect; can precipitate coma
Renal: increased cerebral sensitivity

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Ticarcillin + Clavulanic Acid (Timentin)

Timentin is a broad-spectrum antibiotic with bactericidal activity against a wide range of Gram-positive and -negative aerobic and anaerobic bacteria. It contains ticarcillin and clavulanic acid. The presence of clavulanic acid extends the spectrum of activity of ticarcillin to include many beta-lactamase-producing bacteria normally resistant to ticarcillin and other beta-lactam antibiotics. Timentin acts synergistically with aminoglycosides against a number of organisms, including *Pseudomonas* spp.

Timentin is not active against MRSA.

Uses

Intra-abdominal infections, including peritonitis

Pneumonia

Urinary tract infections

Skin and soft-tissue infections

Contraindications

Hypersensitivity to beta-lactam antibiotics (penicillins and cephalosporins)

Administration

- IV infusion: 3.2 g 6–8 hourly (maximum 3.2 g 4 hourly)

  Reconstitute 3.2 g vial with 100 ml WFI or glucose 5%, given over 30 minutes

In renal impairment:

CC (ml/min)	Dose (g)	Interval (h)
>30 or CVVH rate >1.8 l/h	3.2	8
10–30 or CVVH rate 0.6–1.7 l/h	1.6	8
<10	1.6	12

How not use Timentin

Do not give IV infusion over longer than 40 minutes, as this may result in subtherapeutic concentrations

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Adverse effects

Hypersensitivity

Hypokalaemia

False-positive Coombs' test

Thrombocytopenia

Prolonged prothrombin time

Cautions

Renal impairment (reduce dose)

Each 3.2 g vial of Timentin contains 15.9 mmol of Na^+; a typical daily dose regimen may contain over 60 mmol Na^+

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Tigecycline (Tygacil)

Tigecycline is a glycylcycline antibiotic (structurally similar to tetracyclines) with a broad-spectrum bactericidal activity against a wide range of Gram-positive and -negative aerobic and anaerobic bacteria. It acts by inhibiting protein translocation in bacteria. Tigecycline is not active against *Pseudomonas aeruginosa*. The primary route of elimination is biliary excretion of unchanged tigecycline.

Uses

Intra-abdominal infections including peritonitis

Skin and soft-tissue infections

Contraindications

Hypersensitivity to tetracycline

Pregnancy and lactating women (permanent tooth discoloration in foetuses)

Children and adolescents under the age of 18 years (permanent tooth discoloration)

Administration

- IV infusion: initial dose of 100 mg, followed by 50 mg 12 hourly, given over 30–60 minutes, for 5–14 days

  There are data of efficacy and safety in multi-drug resistant severe infections with double dose (that is initial dose 200 mg, then 100 mg 12 hourly) tigecycline (*Critical Care* 2014; **18**: R90), though this is unlicensed

  Reconstitute the 50 mg vial with either 5 ml sodium chloride 0.9% or 5 ml glucose 5%

  For a 100 mg dose, reconstitute using two vials

  Then add the reconstituted solution to 100 ml sodium chloride 0.9% or 100 ml glucose 5% and give over 30–60 minutes

  In severe hepatic impairment (Child–Pugh class C): initial dose of 100 mg, followed by 25 mg 12 hourly

Adverse effects

Hypersensitivity

Acute pancreatitis

Elevated LFTs

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Hyperphosphataemia
Prolonged APTT and PT
Clostridium difficile-associated diarrhoea

Cautions

Severe hepatic impairment (reduce dose)
Concurrent use of warfarin (increased INR)

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Tranexamic Acid

Tranexamic acid is an antifibrinolytic employed in blood conservation. It acts by inhibiting plasminogen activation.

Uses

Uncontrolled haemorrhage following prostatectomy or dental extraction in haemophiliacs

Haemorrhage due to thrombolytic therapy

Haemorrhage associated with DIC with predominant activation of the fibrinolytic system

Contraindications

Thromboembolic disease

DIC with predominant activation of coagulation system

Administration

Uncontrolled haemorrhage following prostatectomy or dental extraction in haemophiliacs:

- Slow IV: 500–1,000 mg 8 hourly, given over 5–10 minutes (100 mg/min)

Haemorrhage due to thrombolytic therapy:

- Slow IV: 10 mg/kg, given at 100 mg/min

Haemorrhage associated with DIC with predominant activation of the fibrinolytic system (prolonged PT, ↓ fibrinogen, ↑ fibrinogen degradation products):

- Slow IV: 1,000 mg over 10 minutes, single dose usually sufficient

Heparin should be instigated to prevent fibrin deposition

In renal impairment:

CC (ml/min)	Dose (mg/kg)	Interval
20–50 or CVVH rate 1.2–3 l/h	10	12 hourly
10–20 or CVVH rate 0.6–1.1 l/h	10	Every 12–24 h
<10	5	Every 12–24 h

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How not to use tranexamic acid

Rapid IV bolus

Adverse effects

Dizziness on rapid IV injection

Hypotension on rapid IV injection

Cautions

Renal impairment (reduce dose)

Organ failure

Renal: reduce dose

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Chapter

V

Vancomycin (Vancocin)

This glycopeptide antibiotic has bactericidal activity against aerobic and anaerobic Gram-positive bacteria, including MRSA. It is only bacteriostatic for most enterococci. It is used for therapy of *Clostridium difficile*-associated diarrhoea unresponsive to metronidazole, for which it has to be given by mouth. It is not significantly absorbed from the gut.

Serum level monitoring is required to ensure therapeutic levels are achieved and to limit toxicity. Successful treatment of MRSA infections requires levels above the traditionally recommended range. Under-dosing and problems associated with the sampling and the timing of serum-level monitoring are problems that may result in decreased efficacy of vancomycin in the treatment of infection. The efficacy of vancomycin depends on the time for which the serum level exceeds the MIC for the micro-organism rather than the attainment of high peak levels. Administration of vancomycin as a continuous IV infusion is therefore an ideal method of administration for optimum efficacy. Once the infusion reaches a steady state, the timing for serum-level monitoring is not crucial, and samples can be taken at any time.

Vancomycin-resistant strains of enterococcus (VRE) are well recognized in the UK. Resistance also occurs less commonly in coagulase-negative staphylococci and is starting to emerge in rare isolates of *Staphylococcus aureus*.

Uses

C. difficile-associated diarrhoea, via the oral route

Serious Gram-positive infections:

- prophylaxis and treatment of infective endocarditis (usually combined with gentamicin)
- dialysis-associated peritonitis
- infection caused by MRSA
- prosthetic device infections due to coagulase-negative staphylococci
- alternative to penicillins and cephalosporins where patients are allergic

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Contraindications

Hypersensitivity

Administration

C. difficile-associated diarrhoea:

- Orally: 125 mg 6 hourly for 7–10 days
- For NG administration, the 500 mg reconstituted vial can be used nasogastrically for the four daily doses, otherwise 125 mg capsules can be used

Infective endocarditis and other serious Gram-positive infections, including those caused by MRSA:

Duration of therapy is determined by severity of infection and clinical response

Vancomycin must be initially reconstituted by adding WFI:

- 250 mg vial – add 5 ml WFI
- 500 mg vial – add 10 ml WFI
- 1 g vial – add 20 ml WFI

Loading dose			
Actual body weight	**Loading dose**	**Infusion volume sodium chloride 0.9% or glucose 5%**	**Duration of infusion**
<60 kg	1 g	250 ml	120 min
60–90 kg	1.5 g	500 ml	180 min
>90 kg	2 g	500 ml	210 min

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Maintenance dose and when to take levels					
CC (ml/min)	**Maintenance dose**	**Infusion volume (sodium chloride 0.9% or glucose 5%)**	**Duration of infusion**	**Dose interval (start time after loading dose and future dosing interval)**	**Time of first vancomycin trough level**
>110	1.5 g	500 ml	180 min	12 hourly	Before 4th dose
90–110	1.25 g	250 ml	150 min	12 hourly	Before 4th dose
75–89	1 g	250 ml	120 min	12 hourly	Before 4th dose
55–74	750 mg	250 ml	90 min	12 hourly	Before 4th dose
40–54	500 mg	250 ml	60 min	12 hourly	Before 4th dose
30–39	750 mg	250 ml	90 min	24 hourly	Before 3rd dose
20–29	500 mg	250 ml	60 min	24 hourly	Before 3rd dose
<20	500 mg	250 ml	60 min	48 hourly	Before 2nd dose
CVVH	Dependent on equivalent CC achieved (p. 366)				

Levels
Pre-dose (trough) level
• 10–15 mg/l • 15–20 mg/l used for less-sensitive strains of MRSA and severe or deep-seated infections, i.e. MRSA pneumonia, osteomyelitis, endocarditis, bacteraemia
Post-dose (peak) level
Post (peak) levels are not required to be measured

Adjustment of according to levels	
Pre-dose (trough) level	**Maintenance dose adjustment**
<5 mg/l	Move up to two levels from current dosing schedule
5–10 mg/l	Move up one level from current dosing schedule
10–15 mg/l	Continue at current dose
>15–20 mg/l	Continue at current dose
>20–25 mg/l	Move down one level without omitting any doses
>25 mg/l	Omit next dose and decrease by two levels from current dosing schedule
>30 mg/l	Seek advice

For continuous IV infusion (see Appendix K)

Monitor: renal function, serum vancomycin levels (p. 309)

How not to use vancomycin

Rapid IV infusion (severe hypotension, thrombophlebitis)

Not for IM administration

Adverse effects

Following IV use:

- severe hypotension
- flushing of upper body ('red man' syndrome)
- ototoxic and nephrotoxic
- blood disorders

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- hypersensitivity
- rashes

Cautions

Concurrent use of:

- aminoglycosides – ↑ ototoxicity and nephrotoxicity
- loop diuretics – ↑ ototoxicity

Organ failure

Renal: reduce dose

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Vasopressin

Vasopressin (antidiuretic hormone) controls water excretion in kidneys via V_2 receptors and produces constriction of vascular smooth muscle via V_1 receptors. In normal subjects, vasopressin infusion has no effect on blood pressure but has been shown to significantly increase blood pressure in septic shock. The implication is that in septic shock there is a deficiency in endogenous vasopressin, and this has been confirmed by direct measurement of endogenous vasopressin in patients with septic shock requiring vasopressors. *In vitro* studies show that catecholamines and vasopressin work synergistically.

Anecdotally, use of 3 units per hour is usually very effective and not associated with a reduction in urine output.

As its pseudonym antidiuretic hormone implies, vasopressin infusion might be expected to decrease urine output, but the opposite is the case at doses required in septic shock. This may be due to an increase in blood pressure and therefore perfusion pressure. It is also worth noting that, whereas noradrenaline constricts the afferent renal arteriole, vasopressin does not, so may be beneficial in preserving renal function. It has been shown that doses as high as 0.1 units/min (6 units/h) do reduce renal blood flow, so should be avoided. A dose of 0.04 units/min (2.4 units/h) is often efficacious in septic shock and does not reduce renal blood flow. The VAAST study (*N Engl J Med* 2008; **358:** 877–887) found that low-dose vasopressin (0.01–0.03 units/min) in addition to noradrenaline did not reduce mortality compared with noradrenaline alone. However, benefit was seen in less severe septic shock, where mortality was lower in the vasopressin group. The less severe group were identified as those stabilized on noradrenaline at doses of 5–15 μg/min.

Vasopressin does not cause vasoconstriction in the pulmonary or cerebral vessels, presumably due to an absence of vasopressin receptors. It does cause vasoconstriction in the splanchnic circulation, hence the use of vasopressin in bleeding oesophageal varices. The dose required in septic shock is much lower than that required for variceal bleeding.

Uses

In septic shock: reserve its use in cases where the noradrenaline dose exceeds 0.3 μg/kg/min (unlicensed)

Contraindications

Vascular disease, especially coronary artery disease

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Administration

- IV infusion: 1–4 units/h

  Dilute 20 units (1 ml ampoule of argipressin) in 20 ml glucose 5% (1 unit/ml) and start at 1 unit/h, increasing to a maximum of 4 units/h

  Do not stop the noradrenaline, as it works synergistically with vasopressin

  As the patient's condition improves, the vasopressin should be weaned down and off before the noradrenaline is stopped

  Available as argipressin (Pitressin)

  Stored in fridge between 2 °C and 8 °C

How not to use vasopressin

Doses in excess of 5 units/h

Adverse effects

Abdominal cramps

Myocardial ischaemia

Peripheral ischaemia

Cautions

Heart failure

Hypertension

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Vecuronium

Vecuronium is a non-depolarising neuromuscular blocker with minimal cardiovascular effects. It is metabolized in the liver to inactive products and has a duration of action of 20–30 minutes. The dose may have to be reduced in hepatic/renal failure.

Uses

Muscle paralysis

Contraindications

Airway obstruction

To facilitate tracheal intubation in patients at risk of regurgitation

Administration

- Initial dose: 100 μg/kg IV
- Incremental dose: 20–30 μg/kg according to response

Monitor with peripheral nerve stimulator

How not to use vecuronium

As part of a rapid sequence induction

In the conscious patient

By persons not trained to intubate the trachea

Cautions

Breathing circuit (disconnection)

Prolonged use (disuse muscle atrophy)

Organ failure

Hepatic: prolonged duration of action

Renal: prolonged duration of action

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Verapamil

Verapamil is a calcium-channel blocker that prolongs the refractory period of the AV node.

Uses

SVT

AF

Atrial flutter

Contraindications

Sinus bradycardia

Heart block

Congestive cardiac failure

VT/VF – may produce severe hypotension or cardiac arrest

WPW syndrome

Administration

- IV bolus: 5–10 mg over 2 minutes, may repeat with 5 mg after 10 minutes if required
- IV infusion (unlicensed): SVT bolus dose (as previously) then continuous infusion of 5 mg/h

Continuous ECG and BP monitoring

Decrease dose in liver disease and in the elderly

How not to use verapamil

Do not use in combination with beta-blockers (bradycardia, heart failure, heart block, asystole)

Adverse effects

Bradycardia

Hypotension

Heart block

Asystole

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Cautions

Sick sinus syndrome

Hypertrophic obstructive cardiomyopathy

Increased risk of toxicity from theophylline and digoxin

Organ failure

Hepatic: reduce dose

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Vitamin K (Phytomenadione)

Vitamin K is necessary for the production of prothrombin, factors VII, IX and X. It is found primarily in leafy green vegetables and is additionally synthesized by bacteria that colonise the gut. Because it is fat-soluble, it requires bile salts for absorption from the gut. Patients with biliary obstruction or hepatic disease may become deficient. Vitamin K deficiency is not uncommon in hospitalized patients because of poor diet, parenteral nutrition, recent surgery, antibiotic therapy or uraemia.

Uses

Liver disease

Reversal of warfarin

Contraindications

Hypersensitivity

Reversal of warfarin when need for re-warfarinization likely (use FFP)

Administration

Konakion® (0.5 ml ampoule containing 1 mg phytomenadione):

- IV bolus: 1–10 mg, give over 3–5 minutes

  Contains polyethoxylated castor oil which has been associated with anaphylaxis; should not be diluted

Konakion® MM (1 ml ampoule containing 10 mg phytomenadione in a colloidal formulation):

- IV bolus: 1–10 mg, give over 3–5 minutes
- IV infusion: dilute with 55 ml glucose 5%; give over 60 minutes. Solution should be freshly prepared and protected from light

  Not for IM injection

  Maximum dose: 40 mg in 24 hours

How not to use vitamin K

Do not give by rapid IV bolus

Do not give IM injections in patients with abnormal clotting

Not for the reversal of heparin

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Adverse effects

Hypersensitivity

Cautions

Onset of action slow (use FFP if rapid effect needed)

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Voriconazole (Vfend)

Voriconazole is a broad-spectrum, triazole antifungal agent that is used mainly to treat invasive aspergillosis. In contrast to echinocandins, it has an oral form as well as an IV formulation, which makes it suitable for long-term therapy. However, it can cause hepatoxicity, which requires cessation of therapy. It also interacts significantly with drugs commonly used in the ICU, which can complicate treatment.

Uses

Treatment of invasive aspergillosis

Serious infections caused by *Scedosporium* spp., *Fusarium* spp., or invasive fluconazole-resistant *Candida* spp. (including *C. krusei*)

Contraindications

Acute porphyria

Administration

- IV: 6 mg/kg every 12 hours for two doses, then 4 mg/kg every 12 hours (reduced to 3 mg/kg every 12 hours if not tolerated) for maximum of 6 months

  Reconstitute each vial with 19 ml WFI to make a 200 mg/20 ml solution

  Add dose to sodium chloride 0.9% or glucose 5% bag, the final solution should be 2–5 mg/ml

  Administer over 2 hours
- PO/NG: 40 kg, 400 mg 12 hourly for two doses then 200 mg 12 hourly, increased if necessary to 300 mg 12 hourly

  <40 kg, 200 mg 12 hourly for two doses then 100 mg 12 hourly, increased if necessary to 150 mg 12 hourly

  Available as 200 mg, 50 mg tablets and 250 mg/5 ml oral suspension

  Take oral dose 1 hour before or an hour after meals (or turn NG feed off for 1 hour before and after dosing)

Adverse effects

Jaundice

Oedema, hypotension

Chest pain, respiratory distress syndrome

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Headache, dizziness, asthenia, anxiety, depression

Confusion, agitation, hallucinations, paraesthesia, tremor

Hypoglycaemia, haematuria, blood disorders

Acute renal failure, hypokalaemia, visual disturbances

Cautions

Cardiomyopathy, bradycardia

Symptomatic arrhythmias, history of QT prolongation, concomitant use with other drugs that prolong QT interval

Those at risk of pancreatitis

Key interactions

Voriconazole inhibits the activity of cytochrome P450 and increases levels of the following:

alfenatnil, artemether/lumefantrine, ciclosporin, clopidogrel, warfarin, diazepam, dronedarone (avoid), efavirenz, fentanyl, methadone, midazolam, oxycodone, phenytoin, quetiapine, rifabutin, sirolimus, tacrolimus, tretinoin

Voriconazole is also metabolized by cytochrome P450; the following drugs affect voriconazole levels:

carbamazepine, efavirenz, phenobarbital (avoid), phenytoin, rifabutin, rifampicin (avoid), ritonavir (avoid), telaprevir

Organ failure

Renal: PO/NG no dose adjustment needed

IV: if CC <50 ml/min, the IV vehicle sulfobutylether-beta-cyclodextrin (SBECD) accumulates. If PO/NG not suitable, then continue with IV but assess risk–benefit ratio; SBECD is removed by haemodialysis

Liver: mild–moderate hepatic cirrhosis use usual initial dose then halve subsequent doses

No information available for severe hepatic cirrhosis; manufacturer advises use only if potential benefit outweighs risk

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Chapter

Z

Zinc

Zinc is an essential constituent of many enzymes. Deficiencies in zinc may result in poor wound healing. Zinc deficiency can occur in patients on inadequate diets, in malabsorption, with increased catabolism due to trauma, burns and protein-losing conditions, and during TPN.

Hypoproteinaemia spuriously lowers plasma zinc levels.

Normal range: 12–23 µmol/l.

Uses

Zinc deficiency

As an antioxidant (p. 354)

Administration

- Orally: zinc sulphate effervescent tablet 125 mg dissolved in water, one to three times daily after food
- IV: 1 mmol zinc sulphate diluted in 250 ml glucose 5% or sodium chloride 0.9%, given over 2 hours
- Available as 1 mmol zinc sulphate in 10 ml vial

Adverse effects

Abdominal pains

Dyspepsia

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Short Notes

Prescribing Using Generic or Brand Names

Prescriptions should normally be written using the current British National Formulary (BNF) recommended generic names.

The exceptions when brand name should be used are:

- Drugs with a narrow therapeutic index where the differences in bioavailability exist between the different products (e.g. lithium, theophylline, ciclosporin, tacrolimus, phenytoin, carbamazepine and valproate)
- Where the BNF recommends prescribing drugs by brand name because they are modified release (e.g. nifedipine, diltiazem)
- Combinations of drugs where there is no generic name
- Insulins (including the device name)
- Inhalers

Routes of Administration

Intravenous (IV)

This is the most common route employed in the critically ill. It is reliable, having no problems of absorption, avoids first-pass metabolism and has a rapid onset of action. Its disadvantages include the increased risk of serious side effects and the possibility of phlebitis or tissue necrosis if extravasation occurs.

Intramuscular (IM)

The need for frequent, painful injections, the presence of a coagulopathy (risk the development of a haematoma, which may become infected) and the lack of muscle bulk often seen in the critically ill means that this route is seldom used in the critically ill. Furthermore, variable absorption because of changes in cardiac output and blood flow to muscles, posture and site of injection makes absorption unpredictable.

Subcutaneous (SC)

This route is rarely used, except for LMWH when used for prophylaxis of DVT. Absorption is variable and unreliable.

Oral

In the critically ill this route includes administrations via NG, NJ, PEG, PEJ or surgical jejunostomy feeding tubes. Medications given via these enteral feeding tubes should be liquid or finely crushed, dissolved in water. Rinsing should

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take place before and after feed or medication has been administered, using 20–30 ml WFI. In the seriously ill patient this route is not commonly used to give drugs. Note than some liquid preparations contain sorbitol, which has a laxative effect at daily doses >15 g. An example of this is baclofen, where the Lioresal liquid preparation contains 2.75 g/5 ml of sorbitol, so a dose of 20 mg 6 hourly would deliver 44 g of sorbitol. In these cases it is preferable to crush tablets than to administer liquid preparations. In general, the effect of pain and its treatment with opioids, variations in splanchnic blood flow and changes in intestinal transit times – as well as variability in hepatic function – make the oral route an unpredictable and less reliable way of giving drugs.

Buccal and sublingual

This route avoids the problem of oral absorption and first-pass metabolism, and it has a rapid onset time. It has been used for glyceryl trinitrate (GTN), buprenorphine, midazolam and prochlorperazine (Buccastem).

Rectal

This route avoids the problems of oral absorption. Absorption may be variable and unpredictable. It depends on absorption from the rectum and from the anal canal. Drugs absorbed from the rectum (superior haemorrhoidal vein) are subject to hepatic metabolism; those from the anal canal enter the systemic circulation directly. Levothyroxine tablets can be used rectally (unlicensed) when the oral route is unavailable.

Tracheobronchial

This route is useful for drugs acting directly on the lungs: β_2-agonists, anticholinergics and corticosteroids. It offers the advantage of a rapid onset of action and a low risk of systemic side effects.

Intraosseous

If IV access is difficult or impossible, consider IO route. IO injection of drugs achieve adequate plasma concentrations in a time comparable with IV injection.

Loading Dose

An initial loading dose is given to quickly increase the plasma concentration of a drug to the desired steady-state concentration. This is particularly important for drugs with long half-lives (amiodarone, digoxin). It normally takes five half-lives to reach steady state if the usual doses are given at the recommended

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interval. Thus, steady state may not be reached for many days. There are two points worth noting:

- For IV bolus administration, the plasma concentration of a drug after a loading dose can be considerably higher than that desired, resulting in toxicity, albeit transiently. This is important for drugs with a low therapeutic index (digoxin, theophylline). To prevent excessive drug concentrations, slow IV administration of these drugs is recommended.
- For drugs that are excreted by the kidneys unchanged (gentamicin, digoxin) reduction of the maintenance dose is needed to prevent accumulation. No reduction in the loading dose is needed, even in renal failure.

Drug Metabolism

Most drugs are lipid-soluble and, therefore, cannot be excreted unchanged in the urine or bile. Water-soluble drugs such as the aminoglycosides and digoxin are excreted unchanged by the kidneys. The liver is the major site of drug metabolism. The main purpose of drug metabolism is to make the drug more water-soluble so that it can be excreted. Metabolism can be divided into two types:

- Phase 1 reactions are simple chemical reactions including oxidation, reduction, hydroxylation and acetylation.
- Phase 2 reactions are conjugations with glucuronide, sulphate or glycine. Many of the reactions are catalyzed by groups of enzyme systems.

Enzyme Systems

These enzyme systems are capable of being induced or inhibited. Enzyme induction usually takes place over several days; induction of enzymes by a drug leads not only to an increase in its own metabolic degradation, but also often that of other drugs. This usually leads to a decrease in effect of the drug, unless the metabolite is active or toxic. Conversely, inhibition of the enzyme systems will lead to an increased effect. Inhibition of enzymes is quick, usually needing only one or two doses of the drug. Below are examples of enzyme inducers and inhibitors:

Inducers	Inhibitors
Barbiturates (phenobarbitone, thiopentone)	Amiodarone
Carbamazepine	Cimetidine
Ethanol (chronic)	Ciprofloxacin

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(cont.)

Inducers	Inhibitors
Inhalational anaesthetics	Clarithromycin
Griseofulvin	Ethanol (binge drinking)
Phenytoin	Etomidate
Primidone	Erythromycin
Rifampicin	Fluconazole
	Grapefruit juice
	Isoniazid
	Ketoconazole
	Metronidazole
	Miconazole
	Omeprazole
	Sodium valproate
	Voriconazole

Drug Excretion

Almost all drugs and/or their metabolites (with the exception of the inhalational anaesthetics) are eventually eliminated from the body in urine or in bile. Compounds with a low molecular weight are excreted in the urine. By contrast, compounds with a high molecular weight are eliminated in the bile. This route plays an important part in the elimination of penicillins, pancuronium and vecuronium.

Drug Tolerance

Tolerance to a drug will over time diminish its effectiveness. Tolerance to the effects of opioids is thought to be a result of a change in the receptors. Other receptors will become less sensitive with a reduction in their number over time when stimulated with large amounts of drug or endogenous agonist, for example catecholamines. Tolerance to the organic nitrates may be the result of the reduced metabolism of these drugs to the active molecule, nitric oxide, as a result of a depletion within blood vessels of compounds containing the sulphydryl group.

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Acetylcysteine, a sulphydryl group donor, is occasionally used to prevent nitrate tolerance.

Drug Interactions

Two or more drugs given at the same time may exert their effects independently or may interact. The potential for interaction increases the greater the number of drugs employed. Most patients admitted to an ICU will be on more than one drug.

Drugs interactions can be grouped into three principal subdivisions: pharmacokinetic, pharmacodynamic and pharmaceutical.

- Pharmacokinetic interactions are those that include transport to and from the receptor site and consist of absorption, distribution, metabolism and excretion.
- Pharmacodynamic interactions occur between drugs which have similar or antagonistic pharmacological effects or side effects. This may be due to competition at receptor sites or can occur between drugs acting on the same physiological system. They are usually predictable from a knowledge of the pharmacology of the interacting drugs.
- Pharmaceutical interactions are physical, and chemical incompatibilities may result in loss of potency, increase in toxicity or other adverse effects. The solutions may become opalescent or precipitation may occur, but in many instances there is no visual indication of incompatibility. Precipitation reactions may occur as a result of pH, concentration changes or 'salting-out' effects.

Therapeutic Drug Monitoring

The serum drug concentration should never be interpreted in isolation, and the patient's clinical condition must be considered. The sample must be taken at the correct time in relation to dosage interval.

Phenytoin

Phenytoin has a low therapeutic index and a narrow target range. Although the average daily dose is 300 mg, the dose needed for a concentration in the target range varies from 100 to 700 mg/d. Because phenytoin has non-linear (zero-order) kinetics, small increases in dose can result in greater increases in blood level.

Aminoglycosides

Gentamicin, tobramycin, netilmicin and amikacin are antibiotics with a low therapeutic index. With the exception of gentamicin or tobramycin 7 mg/kg,

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levels should be taken before and after the third to fifth dose after starting treatment, in those with normal renal function, and earlier in those with abnormal renal function. Levels should be repeated, if the dose requires adjustment, after another two doses. If renal function is stable and the dose correct, a further check should be made every 3 days, but more frequently in those patients whose renal function is changing rapidly. It is often necessary to adjust both the dose and the dose interval to ensure that both peak and trough concentrations remain within the target ranges. In spite of careful monitoring, the risk of toxicity increases with the duration of treatment and the concurrent use of loop diuretics.

Vancomycin

This glycopeptide antibiotic is highly ototoxic and nephrotoxic. Monitoring of serum concentrations is essential, especially in the presence of renal impairment.

Theophylline

Individual variation in theophylline metabolism is considerable and the drug has a low therapeutic index. Concurrent treatment with cimetidine, erythromycin and certain 4-quinolones (ciprofloxacin, norfloxacin) can result in toxicity due to enzyme inhibition of theophylline metabolism.

Digoxin

In the management of AF, the drug response (ventricular rate) can be assessed directly. Monitoring may be indicated if renal function should deteriorate and other drugs (amiodarone and verapamil) are used concurrently. The slow absorption and distribution of the drug means that the sample should be taken at least 6 hours after the oral dose is given. For IV administration, sampling time is not critical.

Target Range of Concentration

Drug	Sampling time(s) after dose	Threshold for therapeutic effect	Threshold for toxic effect
Teicoplanin	Trough: pre-dose	Trough: >10 mg/l Severe infections require >20 mg/l	None defined
Gentamicin (not 7 mg/kg), tobramycin, netilmicin	Peak: 1 hour after bolus or at end of infusion Trough: pre-dose	Trough: 2 mg/l	Peak: 10 mg/l

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Drug	Sampling time(s) after dose	Threshold for therapeutic effect	Threshold for toxic effect
Vancomycin	Peak: 2 h after end of infusion Trough: pre-dose	Trough: 5–10 mg/l May need 15–20 mg/l for MRSA	Peak >30–40 mg/l
Amikacin	Peak: 1 h after end of dose Trough: pre-dose	Trough: <10 mg/l	Peak: 20–30 mg/l
Phenytoin	Trough: pre-dose	10 mg/l (40 µmol/l)	20 mg/l (80 µmol/l)
Theophylline	Trough: pre-dose	10 mg/l (55 µmol/l)	20 mg/l (110 µmol/l)
Digoxin	At least 6 h	0.8 µg/l (1 nmol/l)	Typically >3 µg/l (3.8 nmol/l), but may be lower dependent on plasma electrolytes, thyroid function, PaO_2

The target range lies between the lowest effective concentration and the highest safe concentration. Efficacy is best reflected by the peak level, and safety (toxicity) is best reflected by the trough level (except for vancomycin). The dosage may be manipulated by altering the dosage interval or the dose or both. If the pre-dose value is greater than the trough, increasing the dosage interval is appropriate. If the post-dose value is greater than the peak, dose reduction would be appropriate.

Pharmacology in the Critically Ill

In the critically ill patient, changes of function in the liver, kidneys and other organs may result in alterations in drug effect and elimination. These changes may not be constant in the critically ill patient, but may improve or worsen as the patient's condition changes. In addition, these changes will affect not only the drugs themselves but also their metabolites, many of which may be active.

Hepatic disease

Hepatic disease may alter the response to drugs, in several ways:

- Impairment of liver function slows elimination of drugs, resulting in prolongation of action and accumulation of the drug or its metabolites.
- With hypoproteinaemia there is decreased protein binding of some drugs. This increases the amount of free (active) drug.

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- Bilirubin competes with many drugs for the binding sites on serum albumin. This also increases the amount of free drug.
- Reduced hepatic synthesis of clotting factors increases the sensitivity to warfarin.
- Hepatic encephalopathy may be precipitated by all sedative drugs, opioids and diuretics that produce hypokalaemia (thiazides and loop diuretics).
- Fluid overload may be exacerbated by drugs that cause fluid retention, e.g. NSAIDs and corticosteroids.
- Renal function may be depressed. It follows that drugs having a major renal route of elimination may be affected in liver disease, because of the secondary development of functional renal impairment.
- Hepatotoxic drugs should be avoided.

Renal impairment

Impairment of renal function may result in failure to excrete a drug or its metabolites. The degree of renal impairment can be measured using creatinine clearance (CC), which requires 24-hour urine collection. It can be estimated by calculation using serum creatinine (see Appendix A). Most of the published evidence on dosing in renal failure is based on the Cockcroft–Gault equation. Serum creatinine depends on age, sex and muscle mass. The elderly patients and the critically ill may have CC <50 ml/min but, because of reduced muscle mass, increased serum creatinine may appear 'normal'. The estimated GFR (eGFR) is increasingly reported. It should be recognized that it is normalized to a standardized body surface area of 1.73 m^2. The eGFR should not be used to calculate drug doses for those at high or low body mass, nor for drugs with a low therapeutic index, unless it is first corrected to the actual GFR with the following equation:

$$\text{Actual GFR} = \text{eGFR} = \text{Body surface area}/1.73$$

When the CC is >30 ml/min, it is seldom necessary to modify normal doses, except for certain antibiotics and cardiovascular drugs which are excreted unchanged by the kidneys. There is no need to decrease the initial or loading dose. Maintenance doses are adjusted by either lengthening the interval between doses or by reducing the size of individual doses, or a combination of both. Therapeutic drug monitoring, when available, is an invaluable guide to therapy.

Haemofiltration or dialysis does not usually replace the normal excretory function of the kidneys. A reduction in dose may be needed for a drug eliminated by the kidneys.

Nephrotoxic drugs should, if possible, be avoided. These include furosemide, thiazides, sulphonamides, penicillins, aminoglycosides and rifampicin.

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Cardiac failure

Drug absorption may be impaired because of gastrointestinal mucosal congestion. Dosages of drugs that are mainly metabolized by the liver or mainly excreted by the kidneys may need to be modified. This is because of impaired drug delivery to the liver, which delays metabolism, and impaired renal function leading to delayed elimination.

Body Weight

The dosing of drugs are often based on the patient's weight. Whilst total body weight (TBW) on admission to the critical care unit may be appropriate for patients with a normal body mass index (BMI), it may not be appropriate in the obese patient or patients who have received large volumes of fluids prior to admission. In the obese, TBW will be skewed by the relative increase in fat mass in comparison to their lean body weight, resulting in overdosing.

Lean Body Weight (LBW)

Lean body weight (LBW) has nothing to do with your ideal weight, or what your body should be like if you were lean. LBW refers to the sum of the weight of your bones, muscles and organs. Essentially, the sum of everything other than fat in your body. LBW is a potentially useful predictor of the pharmacokinetic behaviour of highly water soluble drugs.

The calculation for lean body weight using the James formula is:

$$\text{LBW (men)} = [1.10 \times \text{Weight (kg)}] - 128 \times [\text{Weight (kg)}^2/(100 \times \text{Height (m)}^2]$$

$$\text{LBW (women)} = [1.07 \times \text{Weight (kg)}] - 148 \times [\text{Weight (kg)}^2/(100 \times \text{Height (m)}^2]$$

These formulas are based on various types of measurements of human body composition and are averages. They predict the LBW average of a group of people with similar height and weight. Inaccuracies using these formulas can occur in individuals with more muscles, larger internal organs or denser bones.

Ideal Body Weight (IBW)

Derived from insurance data, ideal body weight (IBW) is the ideal weight associated with maximum life expectancy for a given height. The use of IBW has two major disadvantages: (i) it indicates that all patients of the same height receive the same dose, and (ii) it does not account for changes in body composition associated with obesity. Specifically, the calculated IBW of a morbidly obese patient is less than their actual LBW. Therefore, in the obese patient, administration of a drug based on IBW may result in under dosing.

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$$\text{IBW (men) kg} = 50 + [0.9 \times (\text{Height (cm)} - 154)]$$
$$\text{IBW (women) kg} = 45.5 + [0.9 \times (\text{Height (cm)} - 154)]$$

Guide To Ideal Tidal Volume: Protective Lung ventilation

During mechanical ventilation, tidal volumes greater than 6 ml/kg have been shown to increase the risk of ventilator-induced lung injury and mortality in patients with ARDS. The ideal tidal volume (ITV) should be no more than 6 ml/kg during mechanical ventilation. The tidal volume should be calculated based upon the predicted body weight (PBW) rather than the actual body weight.

To calculate the ideal tidal volume (ITV):

1. Obtain the patient's height to work out the PBW (Appendix E). If the height is not known, it can be estimated by measuring the ulna length (Appendix F).
2. ITV can be calculated as 6 × PBW or refer to chart (Appendix E)
3. Adjust the pressure control or pressure support on the ventilator so that the tidal volume is no more than the ITV calculated.
4. If the plateau pressure is >30 cmH_20 with the ITV, then the volume will need to be decreased.

A common consequence of this is a rise in $PaCO_2$ due to the reduction in minute ventilation, resulting in respiratory acidosis. This is usually well tolerated by the patient and will do less harm than correcting it by increasing the tidal volume. There are some exceptions to this: If the patient requires tight control of $PaCO_2$ (e.g. brain injury) or the pH falls below 7.25.

If the patient is on pressure control ventilation, the fall in minute ventilation can be compensated for by increasing the respiratory rate.

In some cases, despite minimal pressure support, the tidal volume achieved is greater than 6 ml/kg. If this is the case, accept the increased tidal volume.

Reassess regularly and reduce the pressure control or pressure support, if the tidal volume is greater than the ITV.

Cardiopulmonary Resuscitation

The 2015 Advanced Life Support (ALS) Guidelines have a change in emphasis, aimed at improved care and implementation of these guidelines in order to improve patient outcomes. The key changes since 2010 are:

- Increased emphasis on minimally interrupted high-quality chest compressions throughout any ALS intervention.
- Chest compressions must only be paused briefly to enable specific interventions. This includes minimizing interruptions in chest

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compressions to less than 5 seconds when attempting defibrillation or tracheal intubation.

- There is a new section on monitoring during ALS.
- Waveform capnography must be used to confirm and continually monitor tracheal tube placement, and may be used to monitor the quality of CPR and to provide an early indication of return of spontaneous circulation (ROSC).
- There are a variety of approaches to airway management during CPR and a stepwise approach based on patient factors and the skills of the rescuer is recommended.
- The recommendations for drug therapy during CPR have not changed, but there is equipoise for the role of drugs in improving outcomes from cardiac arrest.
- The routine use of mechanical chest compression devices is not recommended, but they may be useful in situations where sustained high-quality manual chest compressions are impractical or compromise provider safety.
- Peri-arrest ultrasound may be used to identify reversible causes of cardiac arrest.
- Extracorporeal life support techniques may be used as a rescue therapy in selected patients where standard ALS measures are not successful.
- The ALS algorithm has been modified slightly to show these changes.

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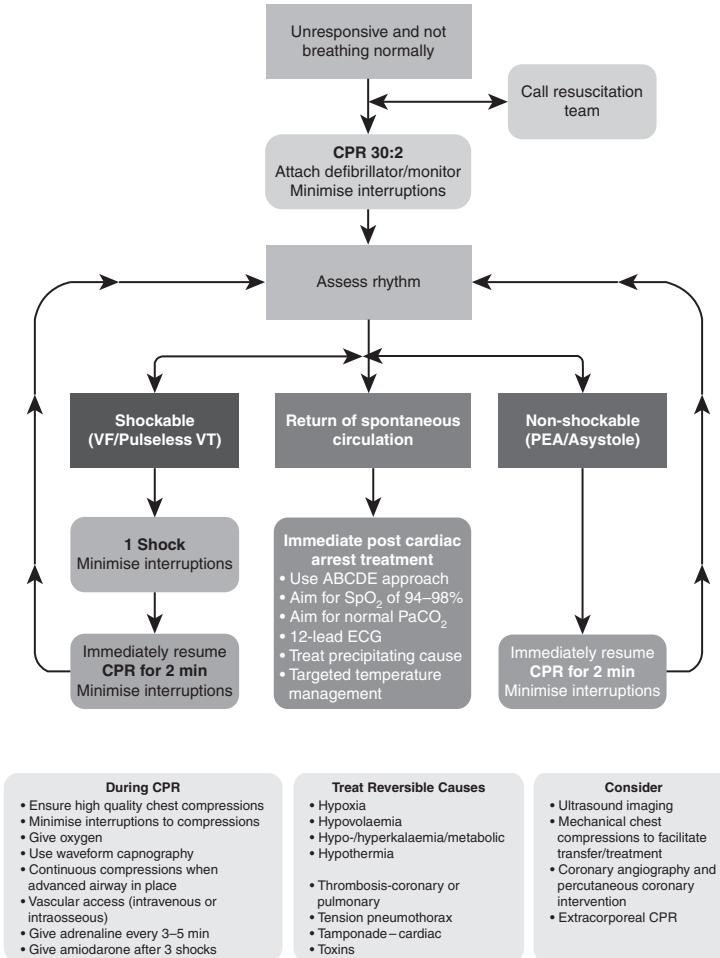

Adult advanced life support (ALS) algorithm. These guidelines are based on the International Liaison Committee on Resuscitation (ILCOR) 2015 Consensus on Science and Treatment Recommendations (CoSTR) for ALS and the European Resuscitation Council 2015 Advanced Life Support Guidelines. Reproduced with the kind permission of The Resuscitation Council (UK).

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ALS Treatment Algorithm

Heart rhythms associated with cardiac arrest are divided into two groups: shockable rhythms (ventricular fibrillation/pulseless ventricular tachycardia (VF/pVT)) and non-shockable rhythms (asystole and PEA). The main difference in the treatment of these two groups is the need for attempted defibrillation in patients with VF/pVT.

Precordial Thump

A single precordial thump has a very low success rate for cardioversion of a shockable rhythm. Its routine use is therefore not recommended. Consider a precordial thump only when it can be used without delay whilst awaiting the arrival of a defibrillator in a monitored VF/pVT arrest. Using the ulnar edge of a tightly clenched fist, deliver a sharp impact to the lower half of the sternum from a height of about 20 cm, then retract the fist immediately to create an impulse-like stimulus.

Treat Reversible Causes

Potential causes or aggravating factors for which specific treatment exists must be considered during all cardiac arrests. For ease of memory, these are divided into two groups of four, based upon their initial letter: either H or T:

- Hypoxia
- Hypovolaemia
- Hyperkalaemia, hypokalaemia, hypoglycaemia, hypocalcaemia, acidaemia and other metabolic disorders
- Hypothermia
- Thrombosis (coronary or pulmonary)
- Tension pneumothorax
- Tamponade – cardiac
- Toxins

The Four 'Hs'

Minimize the risk of **hypoxia** by ensuring that the patient's lungs are ventilated adequately with the maximal possible inspired oxygen during CPR. Make sure there is adequate chest rise and bilateral breath sounds. Using the techniques described below, check carefully that the tracheal tube is not misplaced in a bronchus or the oesophagus.

Pulseless electrical activity caused by **hypovolaemia** is due usually to severe haemorrhage. This may be precipitated by trauma, gastrointestinal bleeding or rupture of an aortic aneurysm. Stop the haemorrhage and restore intravascular volume with fluid and blood products.

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Hyperkalaemia, hypokalaemia, hypocalcaemia, acidaemia and other metabolic disorders are detected by biochemical tests or suggested by the patient's medical history (e.g. renal failure). Give IV calcium chloride in the presence of hyperkalaemia, hypocalcaemia and calcium-channel-blocker overdose.

Hypothermia should be suspected based on the history such as cardiac arrest associated with drowning.

The Four 'Ts'

Coronary **thrombosis** associated with an acute coronary syndrome or ischaemic heart disease is the most common cause of sudden cardiac arrest. An acute coronary syndrome is usually diagnosed and treated after ROSC is achieved. If an acute coronary syndrome is suspected, and ROSC has not been achieved, consider urgent coronary angiography when feasible and, if required, percutaneous coronary intervention. Mechanical chest compression devices and extracorporeal CPR can help facilitate this.

The commonest cause of thromboembolic or mechanical circulatory obstruction is massive PE. If PE is thought to be the cause of cardiac arrest consider giving a fibrinolytic drug immediately. Following fibrinolysis during CPR for acute PE, survival and good neurological outcome have been reported, even in cases requiring in excess of 60 minutes of CPR. If a fibrinolytic drug is given in these circumstances, consider performing CPR for at least 60–90 minutes before termination of resuscitation attempts. In some settings extracorporeal CPR, and/or surgical or mechanical thrombectomy can also be used to treat PE.

A **tension pneumothorax** can be the primary cause of PEA and may be associated with trauma. The diagnosis is made clinically or by ultrasound. Decompress rapidly by thoracostomy or needle thoracocentesis, and then insert a chest drain.

Cardiac **tamponade** is difficult to diagnose because the typical signs of distended neck veins and hypotension are usually obscured by the arrest itself. Cardiac arrest after penetrating chest trauma is highly suggestive of tamponade and is an indication for resuscitative thoracotomy. The use of ultrasound will make the diagnosis of cardiac tamponade much more reliable.

In the absence of a specific history, the accidental or deliberate ingestion of therapeutic or **toxic** substances may be revealed only by laboratory investigations. Where available, the appropriate antidotes should be used, but most often treatment is supportive and standard ALS protocols should be followed.

Drugs in Advanced Life Support

There is currently insufficient evidence to comment on critical outcomes such as survival to discharge and survival to discharge with good neurological outcome with any drug during CPR. There was also insufficient evidence to

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comment on the best time to give drugs to optimize outcome. Although drugs are still included among ALS interventions, they are of secondary importance to high-quality uninterrupted chest compressions and early defibrillation.

Adrenaline (Epinephrine) 1 mg (10 ml 1 in 10,000/1 ml 1 in 1,000)

Despite the continued widespread use of adrenaline during resuscitation, there is no placebo-controlled study that shows that the routine use of adrenaline during human cardiac arrest increases survival to hospital discharge, although improved short-term survival has been documented.

The current recommendation is to continue the use of adrenaline during CPR as for Guidelines 2010. The Resuscitation Council (UK) has decided not to recommend a change to current practice until there are high-quality data on long-term outcomes.

Adrenaline has both alpha and beta effects. The alpha effect increases perfusion pressure and thus myocardial and cerebral blood flow. The beta-1 effect helps to maintain cardiac output after spontaneous heart action has been restored.

Regardless of the arrest rhythm, after the initial adrenaline dose has been given, give further doses of adrenaline 1 mg every 3–5 minutes until ROSC is achieved; in practice, this will be about once every two cycles of the algorithm.

In VF/pVT arrest, the administration of drugs should not delay DC shocks. Defibrillation is still the only intervention capable of restoring a spontaneous circulation.

In PEA, the search for specific and correctable causes (4 Hs and 4 Ts) is of prime importance. Give adrenaline 1 mg IV as soon as IV access is achieved and repeat every 3–5 minutes.

Amiodarone 300 mg IV

No anti-arrhythmic drug given during human cardiac arrest has been shown to increase survival to hospital discharge, although amiodarone has been shown to increase survival to hospital admission. Despite the lack of human long-term outcome data, the balance of evidence is in favour of the use of anti-arrhythmic drugs for the management of arrhythmias in cardiac arrest.

If VF/VT persists after the third shock, give amiodarone 300 mg as an IV bolus. A further 150 mg may be given for recurrent or refractory VF/VT, followed by an IV infusion of 900 mg over 24 hours.

Magnesium 8 mmol IV (4 ml 50% solution)

Give magnesium 8 mmol for refractory VF if there is any suspicion of hypomagnesaemia (e.g. patients on potassium-losing diuretics). Other indications are:

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- ventricular tachyarrhythmias in the presence of hypomagnesaemia
- torsade de pointes
- digoxin toxicity

Calcium chloride 1 g IV (10 ml 10% solution)

Adequate levels of ionized calcium are necessary for effective cardiovascular function. Ionized calcium concentrations decrease during prolonged (>7.5 minute) cardiac arrest. The chloride salt is preferred to the gluconate salt, as it does not require hepatic metabolism to release the calcium ion. 10 ml 10% calcium chloride provides 6.8 mmol Ca^{2+} (10 ml 10% calcium gluconate provides only 2.25 mmol Ca^{2+}).

Caution: calcium overload is thought to play an important role in ischaemic and reperfusion cell injury. It may also be implicated in coronary artery spasm. Excessive doses should not be used.

Calcium chloride is indicated in:

- hypocalcaemia
- hyperkalaemia
- calcium-channel antagonist overdose
- magnesium overdose

Sodium bicarbonate 50 mmol (50 ml 8.4% solution)

Routine use of sodium bicarbonate during cardiac arrest is not recommended.

Give 50 mmol of sodium bicarbonate if cardiac arrest is associated with hyperkalaemia or tricyclic antidepressant overdose. Repeat the dose according to the results of repeated blood gas analysis. Several problems are associated with its use:

(i) CO_2 released passes across the cell membrane and increases intracellular pH.

(ii) The development of an iatrogenic extracellular alkalosis may be even less favourable than acidosis.

(iii) It may induce hyperosmolarity, causing a decrease in aortic diastolic pressure and therefore a decrease in coronary perfusion pressure.

Do not let sodium bicarbonate come into contact with catecholamines (inactivates) or calcium salts (precipitates).

Tracheobronchial route for drugs

Delivery of drugs via a tracheal tube is not recommended – if IV access cannot be achieved, give drugs by the intraosseous (IO) route.

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Atropine is no longer recommended for routine use in asystole or PEA.

Vascular Access During CPR

The role of drugs during cardiac arrest is uncertain. Some patients will already have IV access before they have a cardiac arrest. If this is not the case ensure CPR had started and defibrillation, if appropriate, attempted before considering vascular access.

Peripheral versus central venous drug delivery

Although peak drug concentrations are higher and circulation times are shorter when drugs are injected into a central venous catheter compared with a peripheral cannula, insertion of a central venous catheter requires interruption of CPR and can be technically challenging and associated with complications. Peripheral venous cannulation is quicker, easier to perform and safer. Drugs injected peripherally must be followed by a flush of at least 20 mL of fluid and elevation of the extremity for 10–20 seconds to facilitate drug delivery to the central circulation.

Intraosseous route

If IV access is difficult or impossible, consider the intraosseous (IO) route. This is now established as an effective route in adults. IO injection of drugs achieves adequate plasma concentrations in a time comparable with injection through a vein. Animal studies suggest that adrenaline reaches a higher concentration and more quickly when it is given intravenously as compared with the IO route, and that the sternal IO route more closely approaches the pharmacokinetics of IV adrenaline. The recent availability of mechanical IO devices has increased the ease of performing this technique. There are several IO devices available as well as a choice of insertion sites including the humerus, proximal or distal tibia, and sternum. The decision concerning choice of device and insertion site should be made locally and staff adequately trained in its use.

Management of Acute Major Anaphylaxis

- Immediate therapy

  Stop giving the suspect drug

  Maintain airway, give 100% oxygen

  Adrenaline 50–100 μg (0.5–1.0 ml 1:10,000) IV

  Further 100 μg bolus PRN for hypotension and bronchospasm

  Crystalloid 500–1000 ml rapidly

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• Secondary management

For adrenaline-resistant bronchospasm:

salbutamol 250 µg IV loading dose

5–20 µg/min maintenance

dilute 5 mg in 500 ml glucose 5% or sodium chloride 0.9% (10 µg/ml)

or

aminophylline 5 mg/kg

in 500 ml sodium chloride 0.9%, IV infusion over 5 hours

To prevent further deterioration:

hydrocortisone 200 mg IV

and

chlorphenamine 20 mg IV

dilute with 10 ml sodium chloride 0.9% or WFI given over 1–2 minutes

• Investigation

Plasma tryptase: contact the biochemistry laboratory first. Take 2 ml blood in an EDTA tube at the following times: as soon as possible (within 1 hour), at 3 hours and at 24 hours (as control). The samples should be sent *immediately* to the lab for the plasma to be separated and frozen at 20 °C.

In the UK, when all the samples have been collected, they will be sent to: Department of Immunology, Northern General Hospital, Herries Road, Sheffield, S5 7AU; Telephone: 0114 2715552.

Assay for urinary methyl histamine is no longer available.

Management of Acute Severe Hyperkalaemia

Criteria for treatment

K^+ >6.5 mmol/l

ECG changes (peaked T, absent P, wide QRS or sine wave)

This process begins with an assessment of the risk of arrhythmias, followed by steps to lower the serum potassium concentration by shifting potassium back into cells and removing it from the body. Treatment effectiveness is assessed by monitoring the serum K^+ and frequent monitoring of the blood glucose. Treatment is not complete until the cause is identified and steps are taken to prevent recurrence.

There are five key steps in the treatment of hyperkalaemia:

Step 1: Protect the heart

Step 2: Shift K^+ into cells

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Step 3: Remove K^+ from body

Step 4: Monitor K^+ and glucose

Step 5: Prevent recurrence

Step 1 – Protect the Heart: IV Calcium Salts

IV calcium chloride or calcium gluconate, at an equivalent dose (6.8 mmol)

10 ml 10% calcium chloride = 6.8 mmol Ca^{2+}

10 ml 10% calcium gluconate = 2.26 mmol Ca^{2+}

IV calcium antagonizes the cardiac membrane excitability thereby protecting the heart against arrhythmias. It is given as an IV bolus, over 3–5 minutes and is effective within 3 minutes as shown by an improvement in ECG appearance (e.g. reduction in T wave amplitude and narrowing of the QRS complex). The duration of action is only 30–60 minutes.

The choice of calcium salt, chloride or gluconate, has largely been guided by practicalities such as availability, local practice and the clinical condition of the patient. There are some important differences between the two available solutions. Both calcium chloride and calcium gluconate are available in the form of 10 ml of 10% solution. Calcium chloride contains approximately three times more calcium (6.8 mmol/10 ml) as compared with calcium gluconate (2.26 mmol/10 ml). There is conflicting evidence on the bioavailability of ionized calcium in the two preparations. It has been suggested that calcium gluconate has limited bioavailability because of chelation and the reliance on hepatic metabolism. Given the uncertainty, the chloride salt has been recommended in the setting of haemodynamic instability, including cardiac arrest. This also raises some doubt about the efficacy of the gluconate salt in patients with acute kidney injury, which can be associated with haemodynamic compromise.

The main adverse effect of IV calcium is tissue necrosis if extravasation occurs. For this reason, many guidelines have recommended the use of calcium gluconate, which is regarded as less toxic on peripheral veins. Other potential adverse effects are peripheral vasodilation, hypotension, bradycardia, syncope and arrhythmias.

Caution with administration of IV calcium has historically been advised in patients with known or suspected digoxin toxicity. As hypercalcaemia may potentiate digoxin toxicity, give IV calcium at a slower rate of administration (over 30 minutes).

The use of IV calcium buys time for other interventions to take effect in lowering the serum K^+. Both preparations can be given safely if venous access is adequate. When 10% calcium gluconate is used, repeated doses of 10 ml solution are often required whereas a single dose of calcium chloride is more

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likely to be effective. Therefore, we recommend an equivalent dosage of calcium chloride or gluconate (6.8 mmol) for initial therapy.

If 10 ml 10% calcium gluconate (2.26 mmol Ca^{2+}) is used, the dose may be repeated every 5 minutes if there is no improvement in ECG, to a maximum of 30 ml 10% calcium gluconate.

This will 'buy you 30 minutes'. If there is no improvement in ECG, proceed to the next step.

Step 2 – Shift K^+ into Cells: Insulin–Glucose Infusion

6 units soluble insulin (Actrapid) in 50 ml 50% glucose by IV infusion

Insulin is the most reliable agent for shifting K^+ into cells in patients with hyperkalaemia. This effect is independent of its hypoglycaemic action. There is a higher risk of hypoglycaemia if the dose of insulin used is greater than 6 units.

Step 2 – Shift K^+ into Cells: Salbutamol

Nebulized salbutamol 10–20 mg is used as adjuvant therapy for severe (K^+ ≥ 6.5 mmol/l) hyperkalaemia.

Salbutamol is a β_2-adrenoceptor agonist and promotes the intracellular shift of K^+ by activation of the Na–K ATPase pump. Salbutamol and other β-agonists are equally effective given intravenously or by nebuliser. The nebulized route is easier to administer and causes fewer side effects (tremor, palpitations and headache). Mild hyperglycaemia (2–3 mmol/l increase) has also been reported and this may partly protect against insulin-induced hypoglycaemia. The effect of salbutamol is dose-dependent and the onset of action is within 30 minutes with its peak effect within 60 minutes. Nebulized salbutamol 10 mg decreases serum K^+ by 0.53–0.88 mmol/l and 20 mg decreases serum K^+ by 0.66–0.98 mmol/l. The effects of salbutamol last for at least 2 hours.

The combination of salbutamol with insulin–glucose is more effective than either treatment alone. The peak K^+ lowering effect with combination therapy at 60 minutes was 1.5 mmol/l with IV β-agonist therapy and 1.2 mmol/l with nebulized β-agonist therapy.

Salbutamol may be ineffective in some patients with hyperkalaemia. Non-selective beta-blockers may prevent the hypokalaemic response to salbutamol. Up to 40% of patients with end stage renal disease (ESRD) do not respond to salbutamol, even in the absence of beta-blocker therapy. The degree of potassium lowering is variable and 20–40% of patients have a decline in serum K^+ <0.5 mmol/l. Given that there is no way to predict which patients will respond to salbutamol or to what extent, and there is a potential risk of an early rise in serum K^+ after administration, salbutamol should not be used as monotherapy.

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Step 2 – Shift K^+ into Cells: Sodium Bicarbonate

Sodium bicarbonate infusion is not effective in lowering K^+ acutely. Prolonged administration of sodium bicarbonate may lower K^+, but at the expense of sodium and fluid overload. There is no evidence to suggest that sodium bicarbonate is more effective than all the others at lowering serum K^+ as the severity of metabolic acidosis increases.

Step 3 – Remove K^+ from Body: Cation-Exchange Resins

Cation-exchange resins are not recommended in the emergency management of severe hyperkalaemia, but may be considered in patients with mild to moderate hyperkalaemia.

Cation-exchange resins are cross-linked polymers with negatively charged structural units which can exchange bound sodium (Kayexalate) or calcium (calcium resonium) for cations, including K^+. Their onset of action is slow which limits their use in emergencies. Several doses may be required over several days.

The most serious adverse effect of resins is intestinal necrosis. Constipation is common; therefore, resins are usually given in combination with a laxative.

Resins play no role in the emergency management of hyperkalaemia. However, they may have a role in mild to moderate hyperkalaemia where control over a longer period of time may be acceptable and in circumstances where dialysis is delayed or inappropriate.

Step 4 – Blood Monitoring: Serum Potassium

Monitor serum K^+ at 1, 2, 4, 6 and 24 hours after identification and initiation of treatment of hyperkalaemia.

Insulin–glucose infusion and nebulized salbutamol are the most effective treatments in reducing serum K^+ values. Insulin–glucose and nebulized salbutamol are effective within 30–60 minutes and last for up to 4–6 hours. The time to maximal effect with insulin–glucose ranges from 45 to 180 minutes and for nebulized salbutamol from 30 to 90 minutes. Therefore, the effect of these drugs can be assessed between 60 and 180 minutes after treatment. The reduction in serum K^+ is approximately 1.0 mmol/l if insulin–glucose or nebulized salbutamol is used alone or 1.2 mmol/l if used in combination.

The aim of treatment is to achieve a serum K^+ <6.0 mmol/l within 2 hours of initiation of treatment. Therefore, measure the serum K^+ at 1, 2, 4 and 6 hours after initial treatment to determine if the K^+ value has decreased sufficiently and to detect any rebound in serum K^+ as the effects this therapy lasts 4–6 hours. Measure the serum K^+ at 24 hours to ensure that control of hyperkalaemia has been maintained.

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Step 4 – Blood Monitoring: Blood Glucose

Monitor blood glucose concentration at 0, 15, 30, 60, 90, 120, 180, 240, 300, 360 minutes for a minimum of 6 hours after administration of insulin–glucose infusion in all patients with hyperkalaemia.

Hypoglycaemia (blood glucose of <4.0 mmol/l), is the most common adverse reaction following insulin–glucose infusion for the treatment of hyperkalaemia and should be anticipated with regular blood glucose monitoring following insulin–glucose infusion. The clinical manifestations of hypoglycaemia tend to be progressive, but the early signs are not always detected. Mild hypoglycaemia often presents with sweating, palpitations, tremor and hunger. Severe hypoglycaemia results in more serious symptoms, including confusion, coma or even death. Hypoglycaemia is a significant patient safety event and is associated with significant morbidity and mortality.

The effect of insulin–glucose on the serum K^+ is apparent within 15 minutes, peaks at 45–180 minutes, and lasts for up to 4–6 hours. This prolonged effect of insulin on controlling serum K^+ has also been shown on blood glucose with hypoglycaemia reported as late as 5–6 hours after infusion. Therefore, monitor the blood glucose at 0, 15, 30, 60, 90, 120, and then hourly for up to 6 hours post-infusion.

Management of Malignant Hyperthermia (MH)

Clinical features

- Jaw spasm immediately after suxamethonium
- Generalized muscle rigidity
- Unexplained tachycardia, tachypnoea, sweating and cyanosis
- Increase in $ETCO_2$
- Rapid increase in body temperature (>4 °C/h)

Management

- Inform surgical team and send for experienced help
- Elective surgery: abandon procedure, monitor and treat
- Emergency surgery: finish as soon as possible, switch to 'safe agents', monitor and treat
- Stop all inhalational anaesthetics
- Change to vapour-free anaesthetic machine and hyperventilate with 100% oxygen at two–three times predicted minute volume
- Give dantrolene 1 mg/kg IV

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Response to dantrolene should begin to occur in minutes (decreased muscle tone, heart rate and temperature); if not, repeat every 5 minutes, up to a total of 10 mg/kg

- Give sodium bicarbonate 100 ml 8.4% IV

  Further doses guided by arterial blood gas
- Correct hyperkalaemia with 50 ml glucose 50% and 10 units insulin over 30 minutes
- Correct cardiac arrhythmias according to their nature (usually respond to correction of acidosis, hypercarbia and hyperkalaemia)
- Start active cooling

  Refrigerated sodium chloride 0.9% IV 1–2 l initially (avoid Hartmann's solution because of its potassium content)

  Surface cooling: ice packs and fans (may be ineffective due to peripheral vasoconstriction)

  Lavage of peritoneal and gastric cavities with refrigerated sodium chloride 0.9%
- Maintain urine output with:

  IV fluids

  Mannitol

  Furosemide

Monitoring and investigations

ECG, BP and capnography (if not already)

Oesophageal or rectal temperature: core temperature

Urinary catheter: send urine for myoglobin and measure urine output

Arterial line: arterial gas analysis, U&E and creatine phosphokinase

Central venous line: CVP and IV fluids

Fluid balance chart: sweating loss to be accounted for

After the crisis

Admit to ICU for at least 24 hours (crisis can recur)

Monitor potassium, creatine phosphokinase, myoglobinuria, temperature, renal failure and clotting status

May need to repeat dantrolene (half-life only 5 hours)

Investigate patient and family for susceptibility

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Triggering agents

Suxamethonium

All potent inhalational anaesthetic agents

Safe drug

All benzodiazepines

Thiopentone, propofol

All non-depolarizing muscle relaxants

All opioids

Nitrous oxide

All local anaesthetic agents

Neostigmine, atropine, glycopyrrolate

Droperidol, metoclopramide

Sedation, Analgesia and Neuromuscular Blockade

The most common indication for the therapeutic use of opioids is to provide analgesia. The prevailing concept is to ensure the patient is pain-free and then to focus on any sedation needs. The level of sedation should be minimal. Opioids also elevate mood and suppress the cough reflex. This antitussive effect is a useful adjunct to their analgesic effects in patients who need to tolerate a tracheal tube.

The ideal level of sedation should leave a patient lightly asleep but easily roused. Opioids, in combination with propofol (or a benzodiazepine) are currently the most frequently used agents for analgo-sedation, although benzodiazepines are associated with delirium and are increasingly avoided.

Propofol has achieved widespread popularity for sedation. It is easily titrated to achieve the desired level of sedation and its effects end rapidly when the infusion is stopped, even after several days of use. Propofol is ideal for short periods of sedation on the ICU, and during weaning when longer-acting agents are being eliminated. Some clinicians recommend propofol for long-term sedation. In cardiovascular instability or risk of propofol infusion syndrome (propofol >3–4 mg/kg/h, metabolic acidosis and cardiac dysfunction +/– raised creatine kinase or renal failure), then midazolam should be considered.

Currently, new sedative and analgesic drugs are designed to be short-acting. This means that they usually have to be given by continuous IV infusion. The increased cost of these drugs may be justifiable if they give better control and more predictable analgesia and sedation, and allow quicker weaning from ventilatory support.

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Addition of **clonidine** or **dexmedetomidine** are used in difficult to sedate patients.

Midazolam, the shortest acting of all the benzodiazepines, is the most widely used of the benzodiazepines. It can be given either by infusion or intermittent bolus doses.

Muscle relaxants are neither analgesic nor sedative agents and, therefore, should not be used without ensuring that the patient is both pain-free and unaware. Their use has declined since the introduction of synchronized modes of ventilation and more sophisticated electronic control mechanisms. Their use is also associated with critical illness polyneuropathy. Suxamethonium, atracurium and rocuronium are presently the most commonly used agents. Their use should be restricted to certain specific indications:

- tracheal intubation
- facilitation of procedures, e.g. tracheostomy
- ARDS, where oxygenation is critical and there is risk of barotrauma
- management of neurosurgical or head-injured patients where coughing or straining on the tracheal tube increases ICP
- to stop the spasm of tetanus

Regular monitoring with a peripheral nerve stimulator is desirable; ablation of more than three twitches of the train-of-four is very rarely necessary.

NSAIDS have an opioid-sparing effect and are of particular benefit for the relief of pain from bones and joints, as well as the general aches and pains associated with prolonged immobilization. However, their use in the critically ill is significantly limited by their side effects, which include reduced platelet aggregation, gastrointestinal haemorrhage and deterioration in renal function.

Antidepressants may be useful in patients recovering from a prolonged period of critical illness. At this time depression and sleep disturbances are common. The use of amitriptyline is well established and relatively safe, but it has a higher incidence of antimuscarinic or cardiac side effects than the newer agents. The beneficial effect may not be apparent until 2–4 weeks after starting the drug, so any benefits may not be seen on the ICU. Cardiovascular effects, in particular arrhythmias, have not proved to be a problem. Whether SSRIs (e.g. citalopram) will have any advantages in the critically ill remains to be proved.

Sleep disturbances

Discontinue sleep-disturbing medications as soon as possible. Sedatives, opioids, antidepressants, anticonvulsants, PPIs and ranitidine, asthma and infections alter normal sleep architecture. They decrease restorative sleep; increase total sleep time but not sleep quality; and induce hallucinations and nightmares. If they cannot be discontinued, they should be administered at the lowest possible dose.

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Individual non-pharmacological interventions include:

Keep patient awake during the day to maintain better sleep–awake rhythms

Control pain

Suggest the patients avoid coffee/tea after 3 pm

Provide warm bed-bath before 10 pm; use relaxation exercises and techniques: massage, therapeutic touch, soft classical music

Make earplugs and eye masks available

Encourage relatives to bring in any sleep medications that patients use at home; try these first

Consider **melatonin.** Administer 2 mg (up to 8 mg) at 9 pm.

If melatonin is not effective after two nights, consider **zopiclone**. (Adult: 7.5 mg; elderly (>65 years): 3.75 mg; 3.75 mg if impaired renal function). Maximum treatment 4 weeks (including the tapering off). Treatment should be 2–5 days for transient insomnia; 2–3 weeks for short-term insomnia. Zopiclone can lead to physical and psychological dependence. If discharged while still taking zopiclone, ensure that a clear discontinuation plan is communicated

Chlordiazepoxide is widely used as an alternative for alcohol withdrawal, see p. 341.

Delirium

Delirium is increasingly recognized as an outward manifestation of brain dysfunction. Delirium in hospital is a strong risk factor for increased mortality in hospital and for 11 months after discharge. It is common in the ICU and occurs as hypoactive, mixed or hyperactive manifestation. The CAM-ICU confusion assessment method is commonly used to monitor for delirium. There are many non-drug potential causes, including noise, lack of glasses, language, poor nutrition, insomnia, dehydration, infection, dementia, depression, pain, hypoxia and use of physical restraints.

Drugs that can contribute to delirium:

	Examples
Analgesics	Opioids, NSAIDs
Hypnotics	Benzodiazepines, chloral hydrate, thiopental
Anticholinergics	Atropine, hyoscine
Antihistamines	Chlorpheniramine, promethazine
Anticonvulsants	Phenytoin, carbamazepine, valproic acid

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(cont.)

	Examples
Anti-Parkinson's agents	Levodopa, amantadine
H_2 blockers	Ranitidine
Antibiotics	Penicillin
Cardiac drugs	Beta-blockers, clonidine, digoxin, methyldopa
Corticosteroids	Dexamethasone, hydrocortisone, prednisolone
Anti-emetics	Metoclopramide, prochlorperazine
Antidepressants	Amitriptyline, paroxetine
Cardiovascular drugs	Digoxin, atenolol, dopamine, lidocaine
Miscellaneous	Furosemide, isoflurane, substance withdrawal

Treatment of ICU delirium

Identification of the potential cause of delirium will determine the treatment. Efforts should be made to promote night-time sleep by altering the environment (reducing noise, light, etc.). For hyperactive delirium only, if non-drug measures fail and patient is unsafe, consider drug therapy. If the oral/NG route is available use an atypical antipsychotic, e.g. olanzapine 10 mg daily adjusted to 5–20 mg once daily (for females, elderly or non-smokers, consider lower doses).

For IV therapy use haloperidol. Although some brands are not licensed for IV use in the UK, IV therapy is standard practice if symptomatic control is needed. The main side effects to monitor for are torsades de pointes, extrapyramidal side effects and risk of developing neuroleptic malignant syndrome. In such cases oral/NG olanzapine, quetiapine or risperidone are alternatives, although these are still a caution in torsades de pointes and are not necessarily safe. Rivastigmine should not be used in delirious patients. If haloperidol is contraindicated or ineffective despite adequate dose, then benzodiazepines such as midazolam/lorazepam/diazepam maybe effective for short-term use. No pharmacological therapy has been shown to prevent delirium and haloperidol treatment has been shown recently not to improve outcomes in delirium.

Benzodiazepines remain the treatment of choice for alcohol withdrawal.

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Opioid Conversion Table

Drug	Dose	Route	Approximate equivalent oral morphine dose (mg)	Approximate conversion factor to oral morphine
Buprenorphine	200 µg	SL	12	× 60
Codeine phosphate	60 mg	PO	6	× 0.1
Dihydrocodeine	60 mg	PO	6	× 0.1
Dihydrocodeine	50 mg	SC/IM	15	× 0.3
Diamorphine	10 mg	SC/IM/IV	30	× 3
Hydromorphone	2.6 mg	PO	20	× 7.5
Morphine sulphate (immediate release)	10 mg	PO	10	× 1
Morphine sulphate M/R tablets (MST)	30 mg	PO	30	× 1
Morphine sulphate	5 mg	SC/IM	10	× 2
Morphine sulphate	5 mg	IV	10–15	× 2–3
Oxycodone	10 mg	PO	20	× 2
Pethidine	50 mg	PO	6.25	× 0.125
Pethidine	100 mg	SC/IM	25	× 0.25
Tramadol	100 mg	PO/IM/IV	20	× 0.2

Examples of conversion

Diamorphine SC injection to oral morphine liquid:

30 mg diamorphine daily by syringe driver: conversion factor = × 3
= 30 × 3 = 90 mg oral morphine daily
= 15 mg oral morphine immediate release every 4 hours

Morphine IM injection to oral tramadol:

40 mg morphine daily by injection: conversion factor = × 2
= 40 × 2 = 80 mg oral morphine daily

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Oral morphine 20 mg four times a day to oral Tramadol: conversion factor: divide by 0.2

= 80 mg of oral morphine divide by 0.2 = 400 mg tramadol total daily dose, i.e. 100 mg 6 hourly orally

Remember: When converting a patient from regular oral morphine (immediate release) to MST (modified release): Add up the total amount of morphine administered in 24 hours. Halve this amount to give a 12-hourly MST dose e.g. 10 mg 6-hourly immediate release morphine = 40 mg in 24 hours = 20 mg 12-hourly MST

Transdermal fentanyl

The initial fentanyl patch dose should be based on the patient's previous opioid history, including the degree of opioid tolerance, if any. The lowest dose 12 μg/h should be initiated in strong-opioid-naïve patients for dose titration. In opioid-tolerant patients, the initial dose of fentanyl should be based on the previous 24-hour opioid analgesic requirement. A recommended conversion scheme from oral morphine is given below. At lower doses, fentanyl conversions are less accurate.

Oral 24–hour morphine (mg/d)	Transdermal fentanyl dose (μg/h)
<60	12
61–90	25
91–134	37
135–224	50
225–314	75
315–404	100
405–494	125
495–584	150
585–674	175
675–764	200
765–854	225
855–944	250
945–1,034	275
1,035–1,124	300

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For both strong-opioid-naïve and opioid-tolerant patients the initial evaluation of the analgesic effect of the transdermal fentanyl should not be made before the patch has been worn for 24 hours, due to gradual increase in serum fentanyl concentrations up to this time. Previous analgesic therapy should therefore be phased out gradually from the time of the first patch application until analgesic efficacy with fentanyl is attained.

Remember: Fentanyl levels fall gradually once the patch is removed, taking up to 17 hours or more for the fentanyl serum concentration to decrease by 50%.

Antiretroviral Drugs: Alternatives for Swallowing Difficulties

Providing antiretroviral therapy for the HIV-infected population is a complex and challenging task. For critically ill patients the issue of bioavailability is of paramount importance for those patients who cannot swallow tablets, are unable to take anything by mouth before or after a procedure or those who need medication administration through a NG tube or PEG tube. This guide has been constructed to provide information on management of commonly used antiretrovirals in patients who have swallowing difficulties. Updated information may be available at the reference website.

Drug	Formulation	Administration instructions/ recommendations
Nucleoside reverse transcriptase inhibitors (nRTIs)		
Eviplera (emtricitabine, rilpivirine, tenofovir)	Tablets only	Do not crush; contact immune team for advice
Kivexa (abacavir, lamivudine)	Individual drugs available as liquids: Abacavir 20 mg/ml Lamuvidine 10 mg/ml	Do not crush; contact immune team for advice
Lamivudine	10 mg/ml solution	No dose adjustment between tablets and liquid
Stavudine	Capsules and 1 mg/ml liquid	Capsules can be opened and mixed with sorbital syrup; contact immune team for advice
Stribild (elvitegravir, cobicistat/emtricitabine, tenofovir)	Tablets only	Can be crushed

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Drug	Formulation	Administration instructions/ recommendations
Tenofovir disoproxil	Tablets	Tablets may be disintegrated in at least 100 ml of water, orange juice, or grape juice; caution – bitter taste[1]
Trizivir (abacavir, lamivudine, zidovudine)	Individual drugs available as liquids	No dose adjustment between tablets and liquid (applies to all three individual drugs)[1]
Truvada (tenofovir, emtricitabine)	Tablets only	Tablets may be disintegrated in at least 100 ml of water, orange juice, or grape juice and taken immediately; caution – bitter taste[1]
Zidovudine	10 mg/ml syrup	No dose adjustment between tablets and liquid[1]

Drug	Formulation	Administration instructions/ recommendations
Protease inhibitors		
Atazanavir	Capsules, oral powder	Do not crush – use oral powder
Darunavir	Tablets, 100 mg/ml oral suspension	No dose adjustment between tablets and liquid[1]; can crush tablets of use liquid
Evotaz (atazanavir, cobicistat)	Tablets only	Do not crush
Fosamprenavir	Tablets/50 mg/ml solution	Use solution but feed reduces absorption, so turn off feed before and after administration
Indinavir	Capsules only	Do not use; contact immune team for advice
Kaletra (ritonavir, lopinavir)	80/20 mg/ml solution	Use liquid; no dose adjustment between tablets and liquid[1]
Rezolsta (darunavir, cobicistat)	Tablets only	Crushed tablets should be ok
Ritonavir	Tablets or sachets	Use sachets

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Drug	Formulation	Administration instructions/ recommendations
Saquinavir	Capsules only	Open capsules and mix contents with simple syrup, strawberry-flavoured jelly, jam or baby food
Tipranavir	100 mg/ml solution	Use solution; dosing is the same between capsules and solution

Drug	Formulation	Administration instructions/ recommendations
Non-nucleoside reverse transcriptase inhibitors (nnRTI)		
Efavirenz	Capsules only	Open capsule and disperse contents in water or one to two teaspoons of food may be considered [1]; has peppery taste and food helps disguise this
Etravirine	Tablets only	Disperse the tablets in 5 ml of water (do not place the tablets in orange juice or milk without first adding water), drink immediately, and rinse the glass several times to ensure the entire dose is taken [1]
Nevirapine	10 mg/ml solution	No dose adjustment between tablets and liquid [1] but modified release will be lost if tablets are crushed; use twice daily dosing if body weight ≥90 kg to avoid sub-therapeutic levels
Rilpivirine hydrochloride	Tablets only	Do not crush; contact immune team for advice
Other antiretrovirals		
Enfuvirtide	90 mg solution for injection is the only form	
Maraviroc	Tablets only	Crush and disperse in water
Raltegravir	Tablets only	Crush and disperse in water

[1] ARV_Swallowing_2018_Mar.pdf [Internet]. [cited 2019 January 16]. Available from: https://liverpool-hiv-hep.s3.amazonaws.com/prescribing_resources/pdfs/000/000/011/original/ARV_Swallowing_2018_Dec.pdf?1543916096

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Management of Status Epilepticus

Status epilepticus is defined as continuous seizure activity lasting >30 minutes or more than two discrete seizures, between which the patient does not recover consciousness. About 50% of patients have known epilepsy, and status may be secondary to poor drug compliance with anticonvulsant therapy, a change in anticonvulsant therapy or alcohol withdrawal. Other causes of status epilepticus are listed below:

History of epilepsy:

- Poor compliance
- Recent change in medication
- Drug interactions
- Withdrawal of the effects of alcohol
- Pseudostatus

No history of epilepsy:

- Intracranial tumour/abscess
- Intracranial haemorrhage
- Stroke
- Head injury or surgery
- Infection – meningitis, encephalitis
- Febrile convulsions in children
- Metabolic abnormalities – hypoglycaemia, hypocalcaemia, hyponatraemia, hypomagnesaemia, hypoxia
- Drug toxicity
- Drug or alcohol withdrawal
- Use of antagonists in mixed drug overdoses

Status epilepticus is divided into four stages. There is usually a preceding period of increasing seizures – **the premonitory stage**, which can be treated with a benzodiazepine such as clobazam 10 mg. Early treatment at this stage may prevent the development of the next stage. **Early status epilepticus** can usually be terminated by an IV bolus of lorazepam 4 mg, repeated after 10 minutes if no response. If there is no response to benzodiazepine therapy after 30 minutes, **established status epilepticus** has developed and either phenobarbital, phenytoin or fosphenytoin should be given. If a patient is in **refractory status epilepticus** (when seizure activity has lasted 1 hour and there has been no response to prior therapy), the patient should be transferred to ICU and given a general anaesthetic to abolish electrographic seizure activity and prevent further cerebral damage.

The initial management of status epilepticus is directed at supporting vital functions. This is the same as that for any medical emergency, including assessment of airways, breathing and circulation.

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IV **lorazepam** may now be the preferred first-line drug for stopping status epilepticus. Lorazepam carries a lower risk of cardiorespiratory depression (respiratory arrest, hypotension) than **diazepam** as it is less lipid-soluble. Lorazepam also has a longer duration of anticonvulsant activity compared with diazepam (6–12 hours versus 15–30 minutes after a single bolus). If IV access cannot be obtained diazepam may be given rectally (Stesolid). It takes up to 10 minutes to work. The duration of action of diazepam in the brain is short (15–30 minutes) because of rapid redistribution. This means that, although a diazepam bolus is effective at stopping a fit, it will not prevent further fits.

If there is no response to benzodiazepine treatment after 30 minutes, either **phenobarbital, phenytoin** or **fosphenytoin** should be given. Fosphenytoin is a water-soluble phosphate ester of phenytoin that is converted rapidly after IV administration to phenytoin by endogenous phosphatases. An advantage of IV fosphenytoin is that it can be given up to three times faster than phenytoin without significant cardiovascular side effects (hypotension, arrhythmias). It can also be given IM, unlike phenytoin. Fosphenytoin may some day replace phenytoin. Patients with known epilepsy may already be on phenytoin. A lower loading dose should be given in these patients. Many of these patients will be having fits because of poor compliance. Oral **chlordiazepoxide** is particularly useful where fits are due to alcohol withdrawal.

If the patient has not responded to prior therapy and seizure activity has lasted 1 hour, the patient should be transferred to ICU and given a general anaesthetic (thiopentone or propofol) to abolish electrographic seizure activity and provide ventilatory support to prevent further cerebral damage. **Thiopentone** is a rapidly effective anticonvulsant in refractory status epilepticus and has cerebroprotective properties. Endotracheal intubation must be performed and the patient ventilated. Thiopentone has a number of pharmacokinetic disadvantages over propofol. Following an IV bolus, thiopentone is rapidly taken up in the brain, but high concentrations are not sustained due to its rapid redistribution into fatty tissues. For this reason an IV infusion should follow. Elimination of thiopentone may take days after prolonged infusion. Electroencephalographic monitoring is essential to ensure that the drug level is sufficient to maintain burst suppression. **Propofol**, although not licensed for the treatment of status epilepticus, has been used successfully. It certainly has pharmacokinetic advantages over thiopentone.

Paralysis with **suxamethonium, atracurium, vecuronium** or **rocuronium** is indicated if uncontrolled fitting causes difficulty in ventilation or results in severe lactic acidosis. Neuromuscular blockade should only be used in the presence of continuous EEG monitoring, as the clinical signs of seizure activity are abolished. Blind use of muscle relaxants without control of seizure activity may result in cerebral damage.

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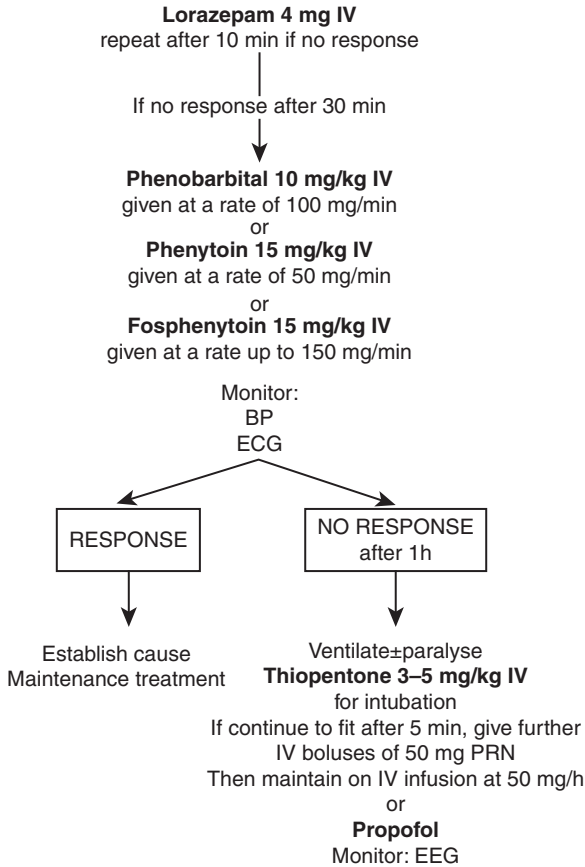
Initial measures

- Position patient to avoid pulmonary aspiration of stomach contents
- Establish on airway (oropharyngeal or nasopharyngeal) and give 100% oxygen
- Monitor vital functions
- IV access
- Send bloods for FBC, U&E, calcium, glucose, anticonvulsant levels
- Arterial blood gas



Further investigations after stablization

- Serum magnesium
- LFTs
- CT+ LP
- EEG

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Treatment of Status Epilepticus

Initial measures:

- Position patient to avoid pulmonary aspiration of stomach contents
- Establish an airway (oropharyngenal or nasopharyngeal) and give 100% oxygen
- Monitor vital functions
- IV access
- Send bloods for FBC, U&E, calcium, glucose, anticonvulsant levels
- Arterial blood gas

Further investigations after stabilization:

- Serum magnesium
- LFTs
- CT ± lumbar puncture
- EEG

Reasons for Treatment Failure

There are several possible reasons for failure of treatment, most of which are avoidable:

- Inadequate emergency anticonvulsant therapy
- Failure to initiate maintenance anticonvulsant therapy
- Metabolic disturbance, hypoxia
- Cardiorespiratory failure, hypotension
- Failure to identify or treat underlying cause
- Other medical complications
- Misdiagnosis (pseudostatus)

Pseudostatus

Up to 30% of patients ventilated for 'status epilepticus' may have pseudostatus. Clinical features suggestive of pseudostatus are:

- More common in females
- History of psychological disturbance
- Retained consciousness during 'fits'
- Normal pupillary response to light during 'fits'
- Normal tendon reflexes and plantar responses immediately after 'fits'

The diagnosis may be aided by EEG monitoring and serum prolactin level – raised following a true fit. A normal prolactin level is not helpful in that it does not exclude status epilepticus.

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Prevention of Delirium Tremens and Alcohol Withdrawal Syndrome

There are a variety of regimens available for this purpose. However, for many, **chlordiazepoxide** is the drug of choice. Sedative doses should be tailored to the individual requirements. This requires active titration at least once daily. Initial 30 mg four times daily should be adequate, but in severe cases, increase the dose to a maximum of 50 mg four times daily. For the night-time sedation, give a larger dose at bedtime for a quieter night!

Suggested oral regimen (titrate according to the patient's response):

	0800 hours	1200 hours	1800 hours	2200 hours
Day 1	30 mg	30 mg	30 mg	30 mg
Day 2	25 mg	25 mg	25 mg	25 mg
Day 3	20 mg	20 mg	20 mg	20 mg
Day 4	10 mg	10 mg	10 mg	10 mg
Day 5	5 mg	5 mg	5 mg	5 mg
Day 6	–	5 mg	5 mg	5 mg
Day 7	–	–	5 mg	5 mg
Day 8	–	–	–	5 mg

A smaller dose may be suitable (e.g. in the very elderly), in which case halve the doses. Prescribe 10–20 mg 'when required' in addition for breakthrough agitation.

Alternatives to chlordiazepoxide

- **Lorazepam** has a shorter duration of action than chlordiazepoxide and may be preferable in elderly patients or those with severe hepatic dysfunction (0.5 mg lorazepam ~15 mg chlordiazepoxide)
- **Diazepam** if the parenteral or rectal route is required (5 mg diazepam ~15 mg chlordiazepoxide)

Whatever drug and regimen is used, give a larger dose last thing at night, reduce doses if the patient is sleepy, and increase doses if signs of delirium tremens are increasing.

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Adjuncts to chlordiazepoxide

Continue any established anti-epileptic drugs. For patients not on any anticonvulsants but known to be susceptible to seizures, prescribe carbamazepine 200 mg PO 12 hourly during detoxification. Use diazepam 10 mg IV/PR if chlordiazepoxide does not adequately control seizures. Consider propranolol 40 mg PO 8–12 hourly (or higher) when required for reducing sweating, palpitations and tremor if the patient is particularly distressed.

Prevention of Wernicke–Korsakoff Syndrome

On admission, administer parenteral Pabrinex IVHP (p. 220) to all alcohol-dependent patients undergoing inpatient alcohol withdrawal, or to those patients who are thought to be severely thiamine deficient. Pabrinex contains vitamins B and C but we are using it for the thiamine content. Pabrinex should be administered before any parenteral glucose is given.

For prevention of Wernicke's encephalopathy, give ONE pair of Pabrinex IVHP 5 ml ampoules once or twice daily for 3–5 days. For therapeutic treatment for Wernicke's encephalopathy, give TWO pairs of Pabrinex IVHP ampoules three times daily for 3 days then review. If no response, discontinue therapy; if a response is seen, decrease dose to ONE pair daily given for as long as improvement continues.

When the Pabrinex course is finished give oral thiamine 50 mg 8 hourly and multivitamins one to two tablets daily, usually for the rest of the admission. For severe vitamin B group deficiency, give vitamin B compound strong tablets one to two 8 hourly. A short course of folic acid 5 mg PO daily may be beneficial.

Anti-Arrhythmic Drugs

The traditional Vaughan Williams' classification (based on electrophysiological action) does not include anti-arrhythmic drugs such as digoxin and atropine. A more clinically useful classification categorizes drugs according to the cardiac tissues that each affects, and may be of use when a choice is to be made to treat an arrhythmia arising from that part of the heart.

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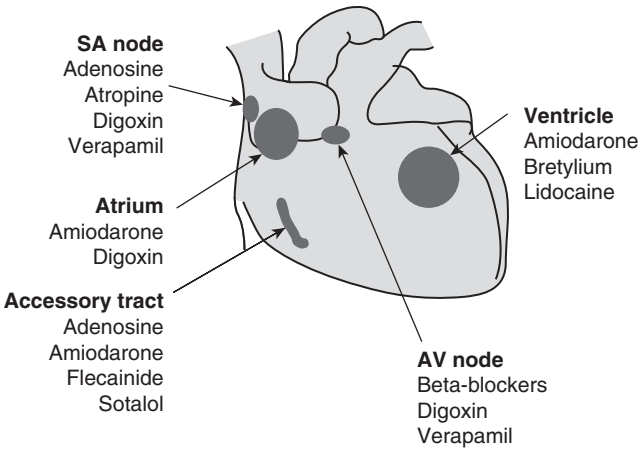

Inotropes and Vasopressors

Inotropes

Receptors Stimulated

Drug	Dose (μg/kg/min)	α_1	β_1	β_2	D_1
Dopamine	1–5				+ +
	5–10		+	+	+ +
	>10	+	+	+	+ +
Dobutamine	1–25	0/ +	+	+	
Dopexamine	0.5–6		0/ +	+ + + +	+
Adrenaline	0.01–0.2	+/ + +	+	+	
Noradrenaline	0.01–0.2	+ + +	+		

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Effects of Inotropes

Drug	Cardiac contractility	Heart rate	SVR	Blood pressure	Renal and mesenteric blood flow
Dopamine:	0	0	0	0	+
D_1	++	+	0/+	+	0
β	0	0	++	++	–
α	++	0	–	+	0
Dobutamine	0/+	+	–	0	+
Dopexamine	0/+	+	–	0	+
Adrenaline	++	+	+/–	+	0/–
Noradrenaline	+	–	++	++	–

+, increase; 0, no change; –, decrease

Which Inotrope to Choose?

The definition of a positive inotrope is an agent that will increase myocardial contractility by increasing the velocity and force of myocardial fibre shortening.

All inotropes will, therefore, increase myocardial oxygen consumption. In the case of a normal coronary circulation, the increased oxygen demand caused by the increased inotropic state of the heart and the increase in HR is met by increasing oxygen supply mediated by local mechanisms. In the presence of coronary artery disease, the increased oxygen demand may not be met by an increase in coronary blood flow. The tachycardia shortens the coronary diastolic filling time, reducing the coronary blood flow and making the ischaemia worse.

Therefore, inotropes have to be used with caution in patients with ischaemic heart disease.

The efficiency of the cardiac pump depends on preload, contractility, afterload and ventricular compliance. Each of these may be influenced by inotropes. In a patient with circulatory failure, an initial priority is to achieve an optimal preload by correcting any hypovolaemia. This may require the use of oesophageal Doppler monitoring or other minimally invasive monitoring techniques, which have largely superseded pulmonary artery catheterization. If circulatory failure persists after optimal volume loading, a positive inotrope may be used to increase myocardial contractility. If intravascular volume has been restored (PCWP 10–15 mmHg) but perfusion is still inadequate, the

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selection should be based on the ability of the drug to correct or augment the haemodynamic deficit. If the problem is felt to be inadequate cardiac output, the drug chosen should have prominent activity at β_1 receptors and little α activity. If the perfusion deficit is caused by a marked reduction in SVR, then a drug with prominent α activity should be used. The haemodynamic picture is often more complex than those presented above. Other special considerations such as oliguria, underlying ischaemic heart disease or arrhythmias may exist and affect the choice of drug.

Most inotropes increase contractility by increasing the intracellular Ca^{2+} concentration of cardiac cells. This may be achieved in three different ways.

- The catecholamines stimulate the β_1 receptor, which activates adenyl cyclase resulting in increased cAMP. This causes opening of Ca^{2+} channels.
- Phosphodiesterase (PDE) inhibitors prevent the breakdown of cAMP, thus facilitating Ca^{2+} entry and uptake by the sarcoplasmic reticulum.
- Digoxin acts by inhibiting the Na^+/K^+ pump and increasing intracellular Ca^{2+} concentration indirectly through Na^+/Ca^{2+} exchange mechanism.

The other way to increase contractility is by increasing the sensitivity of the contractile protein troponin C to Ca^{2+}. Stretch and α-adrenergic stimulation increase the sensitivity of troponin C for Ca^{2+}.

Acidosis, hypoxia and ischaemia, on the other hand, decrease the sensitivity of troponin C for Ca^{2+} and, therefore, the force of contraction.

There is no one ideal inotrope. The choice of inotrope will be influenced by the cause of the circulatory failure. The catecholamines are the most frequently used inotropes in the ICU. All act directly on adrenergic receptors. There are currently considered to be two α-, two β- and five dopaminergic receptors. Adrenaline, noradrenaline and dopamine are naturally occurring catecholamines. Dopamine is the immediate precursor of noradrenaline, and noradrenaline is the precursor of adrenaline. Dobutamine is a synthetic analogue of isoprenaline that acts primarily on β-receptors in the heart. Dopexamine is a synthetic analogue of dopamine, acting primarily on β_2-receptors.

Adrenaline (epinephrine) has α and β activities. In low dose, β predominates and SVR may be reduced. With high doses, α-mediated vasoconstriction predominates.

There is no stimulation of dopamine receptors. Adrenaline is useful when there is a severe reduction in cardiac output (e.g. cardiac arrest), in which the arrhythmogenicity and marked increase in HR and myocardial oxygen consumption that occur with this drug are not limiting factors. It is the drug of choice in anaphylactic shock, due to its activity at β_1- and β_2-receptors and its stabilizing effect on mast cells.

Noradrenaline (norepinephrine) is used to restore BP in cases of reduced SVR. The main haemodynamic effect of noradrenaline is predominantly α-

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mediated vasoconstriction. Noradrenaline can increase the inotropic state of the myocardium by α_1 and β_1 stimulation. The blood pressure is markedly increased due to vasoconstriction and the increase in myocardial contractility. However, cardiac output may increase or decrease due to the increase in afterload. The increase in blood pressure may cause reflex bradycardia. Noradrenaline will increase PVR. It is a potent vasoconstrictor of the renal artery bed. It also produces vasoconstriction in the liver and splanchnic beds with reduced blood flow. But in septic shock, noradrenaline may increase renal blood flow and enhance urine production by increasing perfusion pressure. It can be used to good effect in septic shock when combined with dobutamine to optimize oxygen delivery and consumption. It is essential that the patient is adequately filled before starting noradrenaline. Indiscriminate use of noradrenaline can aggravate the oxygen debt because of peripheral vasoconstriction.

Dopamine exerts its haemodynamic effects in a dose-dependent way. In low doses it increases renal and mesenteric blood flow by stimulating dopamine receptors. The increase in renal blood flow results in increased GFR and increased renal sodium excretion. Doses between 2.5 and 10 μg/kg/min stimulate β_1-receptors, resulting in increased myocardial contractility, stroke volume and cardiac output. Doses >10μg/kg/min stimulate α-receptors, causing increased SVR, decreased renal blood flow and increased potential for arrhythmias. The distinction between dopamine's predominant dopaminergic and α effects at low doses and β effects at higher doses is not helpful in clinical practice, due to marked interindividual variation. It may exert much of its effects by being converted to noradrenaline. However, because of overlap and individual variation, no dose is clearly only 'renal-dose' – dopaminergic effects may occur at higher doses, and vasoconstrictor effects at lower doses.

Dopamine tends to cause more tachycardia than dobutamine and unlike dobutamine usually increases rather than decreases pulmonary artery pressure and PCWP.

Dopamine has now been shown to have several adverse effects on other organ systems. On the respiratory system dopamine has been shown to reduce hypoxic respiratory drive and increase intra-pulmonary shunt leading to decreased oxygenation. Dopamine depresses anterior pituitary function except for adrenocorticotropic hormone Luteinising hormone (ACTH) secretion. Prolactin, luteinizing, growth and thyroid hormones are all suppressed. This will obtund the body's acute endocrine response to stress.

Dopamine may also alter immunological function via its inhibitory effect on prolactin secretion. Inhibition of prolactin causes humoral and cell-mediated immunosuppression.

With the lack of evidence for renal protection and the numerous potential adverse effects, the use of low-dose dopamine for prevention of renal failure is no longer considered appropriate (*Int Care Med* 2013; **39**: 165–225).

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Dobutamine has predominant β_1 activity. It is used when the reduced cardiac output is considered the cause of the perfusion deficit, and should not be used as the sole agent if the decrease in output is accompanied by a significant decrease in BP. This is because dobutamine causes reductions in preload and afterload, which further reduce the BP. If hypotension is a problem, noradrenaline may need to be added.

Dopexamine is the synthetic analogue of dopamine. Currently, it is not available worldwide. It has potent β_2 activity with one-third the potency of dopamine on the dopamine D_1 receptor, with little or no activity at α- and β_1-adrenoceptors. Dopexamine increases HR and CO, causes peripheral vasodilatation, increased renal and splanchnic blood flow, and decreased PCWP. The interest in dopexamine is centred on its dopaminergic and anti-inflammatory activity. The anti-inflammatory activity and improved splanchnic blood flow may be due to dopexamine's β_2 rather than D_1 effect. Studies, including one carried out in the ICU in York, have shown reduced mortality in patients undergoing major surgery in those pre-optimized to a protocol which included pre-operative fluid and inotrope administration to achieve a target oxygen delivery. Our study suggests that dopexamine is superior to adrenaline when used in the pre-optimized protocol. This may be attributable to improved organ perfusion and oxygen delivery to organs such as the gut and the kidneys. In comparison with other inotropes, dopexamine causes less increase in myocardial oxygen consumption.

This synthetic agonist has a number of different properties but is mainly a β_2-agonist. Dopexamine acts as a positive inotrope to increase the HR and decrease the SVR. In animals, dopexamine increases renal blood flow by D_1-agonism to cause intrarenal vasodilatation, an increased cortical but not medullary blood flow and an increase in urine output. However, in humans, the effects on diuresis and natriuresis are small, and may solely reflect the increase in renal blood flow from the increased cardiac output. This results in an improved oxygen supply–demand balance compared with dopamine where the increased natriuresis is secondary to D_2 activity, which increases oxygen requirements. Dopexamine also decreases gut permeability and may reduce bacterial translocation and endotoxinaemia.

There are two dopamine receptors with different functional activities (see table). Fenoldopam is a selective D_1-agonist, introduced principally as an antihypertensive agent. It reduces blood pressure in a dose-dependent manner while preserving renal blood flow and GFR. As a D_1-agonist, it acts post-synaptically to cause vasodilatation and so increase renal blood flow. Fenoldopam also improves CC. It does not act as an inotrope, but is a selective vasodilator of both renal and mesenteric beds. Increasing doses of fenoldopam do not cause tachycardia or tachyarrhythmias, as the agent has no action on β- or α-receptors. However, a tachycardia may occur if there is rapid vasodilatation. It is not presently licensed in the UK. Use of fenoldopam was approved

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by the US Food and Drug Administration (FDA) for the treatment of accelerated hypertension in 1998; there has been increasing use of its renoprotective effects in doses ranging from 0.03 to 0.05 μg/kg/min.

Sites of action of dopaminergic receptor drugs and their agonist effects

Receptor	Site	Effects
D_1	Renal and splanchnic beds	Vasodilatation, increased renal blood flow, natriuresis
D_2	Postganglionic sympathetic nerves	Inhibits presynaptic norepinephrine release, decreases renal blood flow

Vasopressin

Vasopressin (antidiuretic hormone) controls water excretion in kidneys via V_2 receptors and produces constriction of vascular smooth muscle via V_1 receptors. In normal subjects, vasopressin infusion has no effect on blood pressure but has been shown to significantly increase blood pressure in septic shock. The implication is that in septic shock there is a deficiency in endogenous vasopressin and this has been confirmed by direct measurement of endogenous vasopressin in patients with septic shock requiring vasopressors. In vitro studies show that catecholamines and vasopressin work synergistically. As its pseudonym antidiuretic hormone implies, vasopressin infusion might be expected to decrease urine output but the opposite is the case at doses required in septic shock. This may be due to an increase in blood pressure and therefore perfusion pressure. It is also worth noting that, whereas noradrenaline constricts the afferent renal arteriole, vasopressin does not affect renal function. Vasopressin does not cause vasoconstriction in the pulmonary or cerebral vessels, presumably due to an absence of vasopressin receptors. It does cause vasoconstriction in the splanchnic circulation, hence the use of vasopressin in bleeding oesophageal varices. The dose required in septic shock is much lower than that required for variceal bleeding. It has been shown that doses as high as 0.1 units/min (6 units/h) do reduce renal blood flow, so should be avoided. A dose of 0.04 units/min (2.4 units/h) is often efficacious and does not reduce renal blood flow. Anecdotally, use of 3 units/h is usually very effective and not associated with a reduction in urine output. In septic shock, its use is reserved for cases where the requirement for noradrenaline exceeds 0.3 g/kg/min. Vasopressin works synergistically with noradrenaline and as the patient's condition improves, the dose of vasopressin should be weaned down and off before the noradrenaline is stopped.

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Enoximone and **milrinone** are both potent inodilators, and because they do not act via adrenergic receptors, they may be effective when catecholamines have failed. The inhibition of PDE III isoenzyme is responsible for the therapeutic effects. They can increase CO by 30–70% in patients with heart failure. They may also show synergy with catecholamines and have the added advantage of causing less increase in myocardial oxygen consumption. Because they lower SVR and PVR, myocardial oxygen consumption is little increased compared with catecholamines. In addition they tend not to increase HR. There is also the added advantage of lusitropy – aiding relaxation of the ventricles and increasing coronary artery blood flow. The combination of inotropic support, vasodilatation, stable HR and improved diastolic relaxation is particularly advantageous in patients with ischaemic heart disease. Milrinone has an inotropy:vasodilatation ratio of 1:20 compared with 1:2 for enoximone. As a result, milrinone may need to be administered in combination with another inotrope or vasopressor.

The main use of enoximone and milrinone is the short-term treatment of severe congestive heart failure that is unresponsive to conventional therapy. In septic shock there is a significant risk of hypotension and they should be used with caution.

Digoxin has been used to treat heart failure for >200 years. The inotropic effect of digoxin is largely due to increase in intracellular calcium produced indirectly by inhibition of the Na/K pump. Its role in acute heart failure is restricted to patients in fast AF. In the presence of high sympathetic activity, its inotropic effect is negligible. It has a low therapeutic index. The potential for toxicity in the critically ill patient is increased by hypokalaemia, hypomagnesaemia, hypercalcaemia, hypoxia and acidosis. Toxicity does not correlate with plasma levels and is manifested by all types of arrhythmias, including AF.

Levosimendan is a unique, currently unlicensed, agent which is used in some centres for patients with acute decompensated congestive heart failure (CHF). Levosimendan enhances myocardial contractility without increasing oxygen requirements, and causes coronary and systemic vasodilation. Studies have shown that levosimendan increases cardiac output and lowers cardiac filling pressures and is associated with a reduction of cardiac symptoms, risk of death and hospitalization. Its action is independent of interactions with β-adrenergic receptors. Levosimendan's role in therapy remains unclear.

Bronchospasm

Causes of Wheezing in the ICU

- Pre-existing asthma/COPD
- Anaphylactic reaction
- Aspiration pneumonia

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- Kinked tracheal tube
- Tracheal tube too far – carinal/bronchial stimulation
- Bronchial secretions
- Pulmonary oedema
- Pneumothorax

Signs of Severe Asthma Needing Intensive Care

- Tachycardia (HR >130/min)
- Pulsus paradox >20 mmHg
- Tachypnoea (RR >30/min)
- Absent wheezing
- Exhaustion
- Inability to complete a sentence
- $PaCO_2$ normal or increased
- Hypoxia

The selective β_2-agonists such as salbutamol and terbutaline are the treatment of choice for episodes of reversible bronchospasm. Patients with chronic bronchitis and emphysema are often described as having irreversible airways obstruction, but they usually respond partially to the β_2-agonists or to the antimuscarinic drugs ipratropium or oxitropium. There is some evidence that patients who use β_2-agonists on a 'PRN' basis show greater improvement in their asthma than those using them on a regular basis. In the critically ill, these drugs will have to be given either nebulized or intravenously. The tracheobronchial route is preferable because the drug is delivered directly to the bronchioles; smaller doses are then required, which cause fewer side effects. If the bronchospasm is so severe that very little drug gets to the site of action via the tracheobronchial route, then the drug will have to be given intravenously.

Anti-Ulcer Drugs

Critically ill patients are highly stressed and this leads to an increased incidence of peptic ulceration. The risk of stress ulceration is increased in the presence of:

- Sepsis
- Head injury
- Major surgical procedures
- Multiple trauma
- Severe burn injuries

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- Respiratory failure
- Severe hepatic failure
- Severe renal failure

Routine use of anti-ulcer drugs to all patients in an ICU is unnecessary. Use should be restricted to those who have the risk factors described above and should be stopped when patients are established on enteral feeding. By maintaining adequate tissue perfusion in shock/sepsis and using enteral/NG feeding wherever possible prophylactic drug therapy should be unnecessary for the majority of patients.

Patients who have a coagulopathy or on NSAIDs, SSRIs, clopidogrel or steroids (whether or not enterally fed) should be covered with a PPI or ranitidine. If an NG PPI is needed, prescribe lansoprazole (others block NG tubes). The routine use of PPIs in the ICU is not justified; these are sometimes unintentionally continued long-term on discharge from the ICU and are associated with *Clostridium difficile* infection.

Immunonutrition in the ICU

Patients admitted to the ICU may be malnourished at the time of admission, and certainly become so under the catabolic stress of major illness. The malnourished patient suffers from a reduction in immunity and is predisposed to infections. The importance of providing nutrition to critically ill patients is now widely accepted. Recently there has been a move to introduce certain dietary compounds with immune-enhancing actions to the feed. Compounds that have been found to have such properties include glutamine, arginine, nucleotides and omega-3 polyunsaturated fatty acids. None of these compounds when added into immune-enhancing enteral feeds have been shown to improve survival when compared with standard enteral feeds. However, most studies have shown reduction in infection rate, number of days ventilated and length of hospital stay. All these immune-enhancing formulas are significantly more expensive than standard formulas.

Corticosteroids

While the normal physiological secretion of glucocorticoids from the adrenal cortex is about 30 mg cortisol per day, this can rise to 200–400 mg as part of the stress response to major surgery or trauma. Long-term therapy can suppress this adrenocortical response to stress. Patients on steroids or who have taken them within the past 12 months are also at risk of adrenal insufficiency. This may result in life-threatening hypotension, hyponatraemia and hyperkalaemia. The risk is greater when daily oral intake of prednisolone is >7.5 mg.

The aim in synthesizing new compounds has been to dissociate glucocorticoid and mineralocorticoid effects.

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	Relative potencies		Equivalent dose (mg)
	Glucocorticoid	Mineralocorticoid	
Hydrocortisone	1	1	20
Prednisolone	4	0.25	5
Methylprednisolone	5	±	4
Dexamethasone	25	±	0.8
Fludrocortisone	10	300	–

In the critically ill patient, adrenocortical insufficiency should be considered when an inappropriate amount of inotropic support is required. Baseline cortisol levels and a short synacthen test do not predict response to steroids. In patients who demonstrate a normal short synacthen test yet show a dramatic response to a steroid, it is possible that the abnormality lies in altered receptor function or glucocorticoid resistance rather than abnormality of the adrenal axis. Baseline cortisol levels and a short synacthen test are worthwhile to assess hypothalamic–pituitary–adrenal axis dysfunction versus steroid unresponsiveness.

However, the short synacthen test is no longer deemed necessary in septic shock management to identify those who might benefit from corticosteroid therapy. The use of steroids in septic shock remains controversial. The data suggest that hydrocortisone 50 mg IV 6 hourly is beneficial in resistant septic shock but not so in moderate septic shock. Higher doses of corticosteroids are associated with increased mortality in this indication.

Short Synacthen Test

Before starting corticosteroid treatment, it is worth confirming the diagnosis of adrenal insufficiency. Failure of plasma cortisol to rise after IM/IV tetracosactrin 250 μg indicates adrenocortical insufficiency.

Procedure:

- Take 5 ml blood in a plain tube for cortisol before and 30 minutes after IM/IV tetracosactrin 250 μg

Interpretation:

- A normal response requires an incremental rise of at least 200 nmol/l and a final result must be >500 nmol/l. In the critically ill, values should be much higher. We normally accept 1,000 nmol/l anywhere in the test as being a level sufficient for a septic patient needing ventilatory support

The test is impossible to interpret once hydrocortisone has been started. If urgent treatment is required before the test, use dexamethasone initially.

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Bone Marrow Rescue Following Nitrous Oxide

- Folic/folinic acid 15 mg IV for 2 days
- Vitamin B_{12} 1 mg IV for 2 days

The use of nitrous oxide for anaesthesia in excess of 2 hours inactivates vitamin B_{12} and may lead to impaired DNA synthesis and megaloblastic bone marrow haemopoiesis. In fit patients this is of little significance, but in the critically ill it may increase the mortality rate. Haemopoeitic changes induced by nitrous oxide can be reversed by folic/folinic acid. Vitamin B_{12} is given to replace that which has been inactivated. It is recommended by some authorities that both folic/folinic acid and vitamin B_{12} should be given to critically ill patients following surgery in which nitrous oxide was used as part of the anaesthetic for >2 hours.

Heparin-Induced Thrombocytopenia

Heparin induced thrombocytopenia (HIT) is a transient prothrombotic disorder initiated by heparin. It can occur with any type of heparin including LMWH. The main feature is thrombocytopenia caused by antibody-mediated platelet activation. It usually presents between days 4 and 14 of heparin therapy but can occur as early as day 2 if the patient has received any form of heparin in the preceding 3 months. Consider HIT if the platelet count falls by greater than 30% below baseline or below the normal range, and/or the patient develops new thrombosis or rash at the injection site.

NOAC/DOAC

Dabigatran was the first novel oral anticoagulant (NOAC) to be introduced in 2010. The term 'novel' was initially applied to dabigatran because of its mechanism of action. Unlike warfarin and heparin (binding to anti-thrombin III), it directly binds to clotting factor IIa (thrombin). Warfarin reduces the clotting factors by inhibiting the C1 subunit of vitamin K epoxide reductase enzyme complex and rendering the liver unable to produce vitamin K-dependant clotting factors II, VII, IX, X and the endogenous anticoagulant proteins C and S. Rivaroxaban, apixaban and edoxaban all bind directly to clotting factor Xa (the clotting factor responsible for activating prothrombin to thrombin).

After 7 years, the idea of these oral anticoagulants being novel doesn't seem applicable. In the most recent CHEST guidelines 2016, the 'N' stands for 'non-vitamin K.' Critics of the NOAC terminology cite that 'non-vitamin K' contains several letters not captured in the acronym, and NOAC may be misunderstood to mean 'NO AntiCoagulants.' DOAC, which stands for direct oral anticoagulant, reflects the mechanism of action of these anticoagulants and is set to replace NOAC to describe these anticoagulants.

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Antioxidants

The human body in health constantly produces potentially harmful reactive oxygen species. These are balanced by complex antioxidant systems. Tissue injury is probably due, at least in part, to local imbalances in the oxidant/antioxidant ratio. This imbalance is called 'oxidative stress' and can cause lipid peroxidation, damage to DNA and cell death. Sources of oxidative stress during critical illness include reactive oxygen species produced by leukocytes ('respiratory burst') and production of nitric oxide by vascular endothelium. Studies have suggested that the total antioxidant potential of the plasma is decreased in septic patients who go on to develop organ dysfunction.

A logical, if simplistic, approach to the oxidative stress of critical illness has been the administration of agents with free-radical scavenging properties. The hope is that the oxidant/antioxidant ratio will be restored towards normal and tissue damage will, therefore, be reduced. Agents that have been used for this purpose include acetylcysteine, vitamins A, C and E, zinc and selenium. There remains no confirmed benefit and the use of such agents must be viewed as speculative.

- Acetylcysteine (p. 5)
- Zinc (p. 302)
- Vitamin C (ascorbic acid)

  orally: 1 g daily dispersible tablets

  slow IV: 1 g daily (500 mg/5 ml)
- Vitamin E (tocopherol)

  orally: 100 mg 12 hourly (suspension 500 mg/5 ml)

  slow IV: 400 mg (oily injection 100 mg/2 ml)
- Selenium

  IV infusion: 400–800 μg sodium selenite daily in 50 ml sodium chloride 0.9%, given over 1–4 hours

  Normal range: 70–120 μg/l, 0.88–1.52 μmol/l

Guidelines for Patients with Absent or Dysfunctional Spleen

Patients with an absent or dysfunctional spleen (including sickle cell disease) are at risk of overwhelming infection. The length they remain at risk is unknown. Susceptibility is greatest in the first few years, but persists lifelong. Following splenectomy, patients have a significantly increased risk of infection, predominantly by encapsulated organisms such as *Streptococcus pneumoniae, Haemophilus influenzae* (Hib) and *Neisseria meningitidis*. Vaccinations and

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prophylactic antibiotics reduce but do not eliminate the risk of infection with these organisms. Patients should be educated about the potential risks of foreign travel, particularly with regard to malaria and unusual infections secondary to animal or tick bites. Patients should be given a UK Department of Health splenectomy-warning card and sign up for a 'Medic-Alert' bracelet.

Antibiotic prophylaxis

All patients should be given a stock of 'emergency' antibiotics. Lifelong prophylactic antibiotics should be offered to patients considered at continued 'high-risk' of pneumococcal infection. 'High-risk' patients are defined in current British Committee for Standards in Haematology (BCSH) guidelines as:

- children <16 years old
- adults >50 years old
- splenectomy for haematological malignancy rather than trauma
- poor/no response to pneumococcal vaccine
- previous invasive pneumococcal infection

Patients not at 'high-risk' should be counselled regarding the risks and benefits of lifelong antibiotics and may choose to discontinue them.

Oral penicillins remain the prophylactic drugs of choice in areas with low pneumococcal resistance. Specialist microbiological advice should be sought where this is not the case or for travel abroad. In patients with confirmed penicillin allergy, an appropriate macrolide may be substituted, depending on local practice.

Adults without penicillin allergy	Adults with penicillin allergy
Penicillin V 250 mg 12 hourly PO OR Benzylpenicillin 1.2 g 12 hourly IV	Clarithromycin 250 mg 12 hourly PO (if pregnant, use erythromycin 500 mg 12 hourly PO)

Children without penicillin allergy	Children with penicillin allergy
<1 year: Penicillin V 62.5 mg 12 hourly PO	1 month–2 years: Erythromycin 125 mg 12 hourly PO
1–5 years: Penicillin V 125 mg 12 hourly PO	2–8 years: Erythromycin 250 mg 12 hourly PO
>5 years: Penicillin V 250 mg 12 hourly PO OR Benzylpenicillin 25 mg/kg 12 hourly IV	8–18 years: Erythromycin 500 mg 12 hourly PO

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Vaccinations

Vaccine	Dose	Repeat dose
Pneumococcal	0.5 ml by IM injection	Repeat every 5 years
H. influenzae type b with meningococcal group C	0.5 ml by IM injection	No need
Meningococcal A, C, W135 and Y conjugate)	0.5 ml by IM injection	Repeat 1 year
Meningococcal B	0.5 ml by IM injection	Repeat once after1 month
Influenza	0.5 ml by IM injection	Repeat each year (September–November)

Where possible, the vaccines should be given 2 weeks before splenectomy. Otherwise, vaccination should optimally be given 2 weeks afterwards. This is because there is a dip in the immune response following major surgery. If it is not possible to organize this, a compromise is to vaccinate 3–5 days post-operatively (response suboptimal but adequate in most cases). It is preferable for each vaccine to be given into different limbs. Children less than 2 years of age respond poorly to the pneumococcal polysaccharide vaccine (PPV), so should receive pneumococcal conjugate vaccine (PCV).

Infection with serogroup C *N. meningitidis* accounts for around 40% of cases in the UK. No vaccine is currently available to protect patients against serogroup B *N. meningitidis*. The immunity conferred by the original meningococcal polysaccharide vaccine (Mengivac A+C) is not complete and is short-lived. Protection wanes rapidly and is generally gone by around 2 years from vaccination. The newer meningitis C (MenC) conjugate vaccines are more effective than polysaccharide vaccines and will provide long-term protection against infection. The meningococcal ACWY (MenACWY) conjugate vaccine (Menveo) is to be preferred over the meningococcal ACWY polysaccharide vaccine (ACWY Vax).

In the UK, the Department of Health (DoH) Green Book guidance 2013 suggests differing vaccination regimens depending on patient age and prior vaccination status:

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Patient age and vaccination status	DoH recommendation
Children <1 year of age	Two doses of MenACWY conjugate vaccine (Menveo) 1 month apart instead of the MenC vaccine in infancy FOLLOWED BY One dose of Hib/MenC vaccine at 12 months of age FOLLOWED BY One dose of MenACWY conjugate vaccine 2 months later
Children presenting when >1 year of age AND adults	One dose of Hib/MenC vaccine FOLLOWED BY One dose of MenACWY conjugate vaccine 2 months later
Children and adults who have been fully immunized with MenC vaccine as part of the routine programme	One additional dose of the combined Hib/MenC vaccine FOLLOWED BY One dose of the MenACWY conjugate vaccine 2 months later

When travelling to a high-risk area for serogroup A, W135 or Y meningococcal disease, patients should receive the MenACWY conjugate vaccine (Menveo).

Antimicrobial Drugs

Use of antimicrobial agents causes predictable adverse effects, which have to be considered as part of a risk/benefit analysis for each individual patient, the ICU as a whole and for the wider hospital environment. These effects include superinfection, selection of resistant micro-organisms and toxic side effects. Close liaison with a clinical microbiologist is important to ensure correct use of these agents in order to minimize these effects.

Antimicrobial agents may be used in the following ways:

- Prophylactic – to prevent an infective complication
- Empiric – to treat suspected infection before culture results are available
- Targeted – to treat established infection demonstrated by culture

Infection is only one of a number of causes of pyrexia in the ICU setting (see below). Administration of antimicrobial agents to all febrile patients is not appropriate and will lead to significant overuse of these agents, often with

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multiple changes of antimicrobials in a futile attempt to get the temperature to settle. A daily ward round with a clinical microbiologist or infectious disease physician can help to avoid this problem and provide an opportunity to evaluate the significance of new microbiological culture results. It is particularly worth bearing in mind the phenomenon of drug fever which is commonly caused by antibiotics and results in a pyrexia which only resolves when the provoking agent is discontinued.

Non-Infective Causes of Pyrexia

SIRS
Trauma
Burns
Pancreatitis
Acute hepatic failure

Thrombotic events such as DVT and PE

MI

Fibroproliferative phase of ARDS

Drugs

Antibiotics
Hypnotics
Diuretics
Antihypertensives
Anti-arrhythmics
NSAIDs
Phenytoin

Blood/blood-product transfusion

Cancer
Lymphoma
Leukaemia
Hypernephroma
Hepatoma
Pancreatic carcinoma

Connective tissue disease
Systemic lupus erythematosus

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(cont.)

Polyarteritis nodosa
Polymyalgia/cranial arteritis
Sarcoidosis
Rheumatoid disease
Malignant hyperpyrexia

Empiric therapy should be reserved for those patients with well-defined signs and symptoms of infection where delay in therapy would be expected to be harmful. It is essential to obtain appropriate specimens for microbiological examination, before starting empiric therapy. Requests for rapid tests, such as Gram stains and antigen detection techniques, and invasive sampling techniques, such as broncho-alveolar lavage (BAL) can be very helpful in guiding the need for empiric therapy and in modifying the choice of agents to be used.

The choice of agent(s) is also dependent on knowledge of the organisms likely to be involved. This should be based on previous experience within your own unit and should be designed to ensure coverage of the most likely pathogens, as failure to do so is associated with poorer patient outcomes. It should also take account of prior culture results for the individual patient concerned.

Antimicrobial therapy will not be successful in many infections associated with collections of pus or prosthetic devices without drainage or removal of the device as appropriate. Additional surgical intervention is not uncommonly required for ICU patients.

Empiric therapy should be modified or stopped, as appropriate, once culture results become available. It is also good practice to have stop dates or review dates to avoid unnecessarily prolonged treatment or side effects. Short course therapy of 5 to 7 days is adequate for most infections in the ICU.

Although the majority of antibiotics are relatively safe drugs, important toxic effects do occur particularly in the presence of other disease states. In addition, antibiotics may result in secondary bacterial, yeast or fungal infection (superinfection), and may facilitate the growth of *Clostridium difficile*, a cause of diarrhoea and pseudomembranous colitis.

Antibiotic Resistance

Bacterial resistance to antibiotics is an established and increasing problem. Many pathogens are now 'multiresistant'. Excessive and inappropriate use of antibiotics is believed to be one of the most important factors in increasing the

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prevalence of antibiotic resistance. In most hospitals, the ICU has the highest prevalence of such organisms.

Staphylococcus aureus can survive for long periods in the environment and colonizes the skin, nose or throat of approximately a third of patients and healthcare staff. If patients develop infections with *S. aureus*, this is usually by their own, commensal flora. *S. aureus* is readily spread either via hands or by contact with the inanimate environment. Methicillin-resistant *S. aureus* (MRSA), resistant to flucloxacillin, was first detected in Europe in the early 1960s.

Since 2008, data published by the European Antimicrobial Resistance Surveillance System (EARSS) have suggested a decreasing trend in the incidence of MRSA infections. This finding has been corroborated by the Health Protection Agency (HPA), which reports that counts and rates of MRSA bacteraemia continue to fall across the National Health Services in the UK (NHS). Between April 2011 and March 2012 (FY 2011/12), a total of 1,114 cases of MRSA bacteraemia were reported across the NHS. This equates to an MRSA bacteraemia rate of 2.1 per 100,000 bed-days and represents a 25% reduction on the 1,481 MRSA bacteraemia reports received in FY 2010/11. The introduction of routine screening for MRSA carriage was a significant turning point in the control of MRSA infection.

The majority of MRSA isolates in the UK belong to one of a relatively small number of epidemic strains, designated EMRSA-15 and EMRSA-16, which have spread widely throughout the country. In addition to inherent resistance to all beta-lactams (e.g. flucloxacillin), these strains usually express resistance to a number of antibiotics, including macrolides and quinolones. Traditionally, glycopeptides (e.g. vancomycin and teicoplanin) have been used to treat infections with these organisms, although alternative antibiotics, including linezolid and daptomycin, are now available. Vancomycin-resistant *S. aureus* (VRSA) isolates have not yet been reported from cases in the UK but have emerged in other parts of the world. EARSS reports that, as of 2008, the only European country to have reported a case of VRSA is Austria. However, there is evidence that the minimum inhibitory concentration (MIC) of glycopeptide against *S. aureus* is rising. Given the MIC-dependent response of *S. aureus* to glycopeptides, this trend is of significant concern for the future.

MRSA is no longer the most important threat in terms of multi-drug resistance. Enterobacteriaceae such as *Escherichia coli, Klebsiella* spp. and *Enterobacter* spp., expressing extended-spectrum beta-lactamases (ESBLs), are being identified with increasing frequency, and have caused outbreaks in hospitals and the community. These organisms have markedly reduced susceptibilities to most commonly used penicillins and cephalosporins. As a result of growing problems with these organisms in the ICU, empiric use of the carbapenems, including imipenem and meropenem, has increased. Unfortunately, resistance to the carbapenems is well established in *Pseudomonas aeruginosa*

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isolates, rising in *Acinetobacter* spp., and causing significant outbreaks in Enterobacteriaceae. There are few antibiotics left to treat significant infections with carbapenemase-producing Enterobacteriaceae, some of which are resistant to all beta-lactams, fluoroquinolones, tigecycline, polymyxins and aminoglycosides. As such, the rise in antimicrobial resistance in Gram-negative bacteria has recently led to significant media interest and has become a priority for the UK government. Quinolone-resistant strains of *Salmonella typhi* and *paratyphi* are being imported from the Indian subcontinent.

Penicillin-resistant *Streptococcus pneumoniae* are being isolated from cases of community-acquired pneumonia. In 2011, 0.8% of UK pneumococcal isolates tested resistant to penicillin, according to reports from the European Centre for Disease Prevention and Control (ECDC). Much higher rates of penicillin-resistant pneumococcal infections have been found in other European countries, particularly around the Mediterranean and in Eastern Europe. Five percent of UK isolates tested resistant to macrolides.

Enterococci form part of the normal human flora at multiple sites, particularly of the gastrointestinal tract, and can cause opportunistic infections. These organisms can grow and survive in harsh conditions and are inherently resistant to many classes of antibiotics, including cephalosporins and fluoroquinolones. *Enterococcus faecalis* is the most frequent species to be isolated, but *Enterococcus faecium* has the greater inherent resistance. Beta-lactams alone are ineffective against most strains of *E. faecium*.

EARSS reports that, over the last decades, enterococci have emerged as important nosocomial pathogens, paralleled by increases in glycopeptide and high-level aminoglycoside resistance. Vancomycin resistance in enterococci was first encountered in France and England but showed the most dramatic increase in the United States and was attributed to the widespread use of vancomycin. Since 2005, there has been a decreasing trend in glycopeptide resistance of enterococci in the UK. Conventional treatments of some serious enterococcal infections have involved the use of synergistic combinations of an aminoglycoside with a beta-lactam or a glycopeptide. Enterococci that are resistant to all synergistic combinations are now being reported. Carbapenem-resistant Enterobacteriaceae (CRE) or carbapenemase-producing Enterobacteriaceae (CPE) are increasingly prevalent worldwide. These are normal enteric bacteria (e.g. *E. coli, Klebsiella pneumoniae*) which carry genes for resistance to many antibiotics, including the carbapenems (meropenem/imipenem) – our usual last-line antibiotics. Infections with these organisms (urinary tract infections, intra-abdominal infections) become extremely difficult to treat, and can lead to high mortality.

Tuberculosis rates have been steadily rising in the UK. According to the HPA, there were 15.9 cases of tuberculosis per 100,000 population in the UK in 2011. Rates of multi-drug-resistant tuberculosis have been rising, accounting for 1.6% of new cases in 2011.

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Clostridium difficile Infection

Clostridium difficile is a Gram-positive, spore-forming, toxin-producing, obligate anaerobic bacillus that is ubiquitous in nature. The spectrum of illness ranges from asymptomatic colonization to diarrhoea (self-limiting to severe diarrhoea due to pseudomembranous colitis), toxic megacolon, colonic perforation and death. The increasing use of broad-spectrum antibiotics, suboptimal infection prevention and control-related practices and the expanding population of patients with depressed immunity (including renal, oncology, haematology and intensive care patients) have resulted in an increase in the frequency of outbreaks of infection, which may be prolonged and difficult to control. *C. difficile* ribotype 0127 appears to be associated with poor outcome. *C. difficile* was first recognized as a significant cause of diarrhoea in the 1970s, with subsequent rates of disease rising markedly. Data published by the HPA show that, since the introduction of mandatory *C. difficile* surveillance in the UK in 2007, disease rates have been declining.

Any antibiotic can cause *C. difficile* infection, including those used to treat the infection (i.e. vancomycin and metronidazole). Antibiotics particularly implicated include clindamycin, cephalosporins (particularly members of the third-generation cephalosporins), quinolones (including ciprofloxacin) and co-amoxiclav. The most frequently implicated antibiotics causing *C. difficile* infection in the UK are amoxicillin and ampicillin, although this may also be a reflection of their high prescription rates. The standard treatment is oral/NG metronidazole 400 mg 8 hourly or oral/NG vancomycin 125 mg 6 hourly. Fidaxomicin is a newly licensed, expensive drug for this indication. It is a novel bactericidal macrocyclic antibiotic that inhibits bacterial ribonucleic acid polymerase. It is effective against *C. difficile*, with limited activity against other Gram-positive bacteria. Two similar double-blind, randomized non-inferiority trials comparing oral vancomycin with fidaxomicin demonstrated no significant differences in clinical cure rates in the pre-specified subgroups of patients with severe or prior infection, but interestingly, recurrence rates were reduced with fidaxomicin. The high drug cost may be offset by the cost saved of treating additional episodes.

Bacterial Gram Staining

	Positive	Negative
Cocci	*Enterococcus* spp. *Staphylococcus* spp. *Streptococcus* spp. *Streptococcus pneumoniae*	*Moraxella catarrhalis* *Neisseria* spp.

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(cont.)

	Positive	Negative
Rods	*Actinomyces israelii* *Clostridium* spp. *Corynebacterium diphtheriae* *Listeria monocytogenes*	*Bacteroides* spp. *Burkholderia cepacia* *Enterobacter* spp. *Escherichia coli* *Haemophilus influenzae* *Klebsiella pneumoniae* *Legionella pneumophila* *Proteus mirabilis* *Pseudomonas aeruginosa* *Salmonella* spp. *Serratia marcescens* *Shigella* spp. *Stenotrophomonas*

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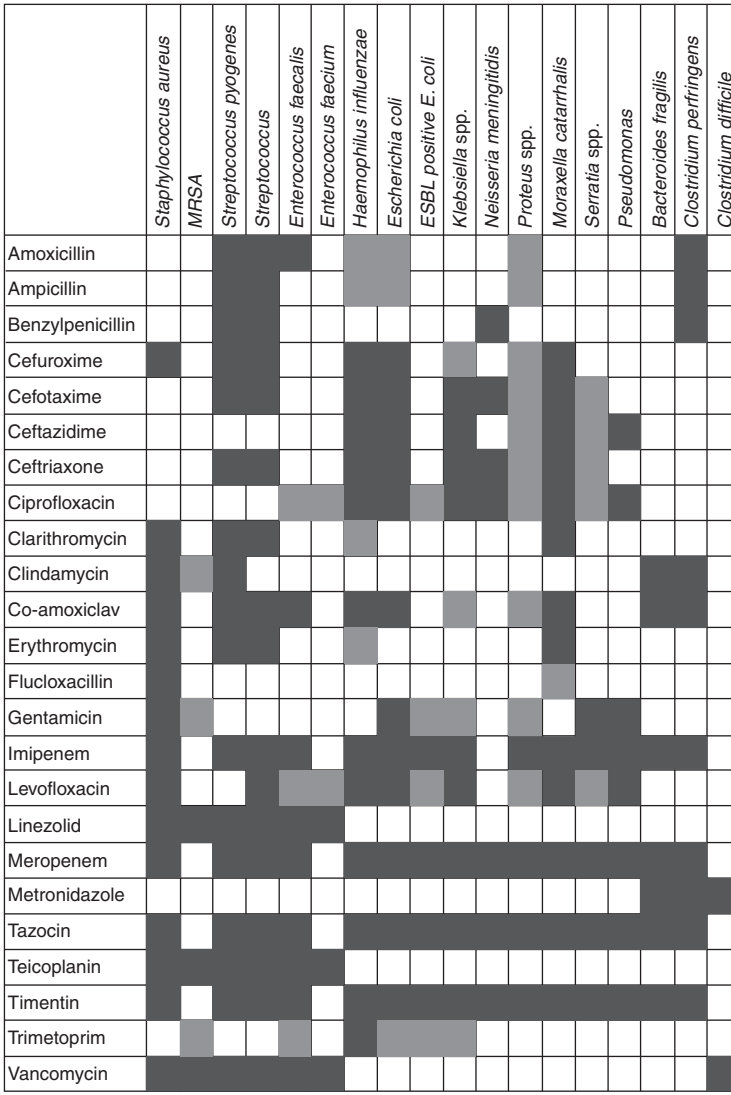
Antibiotics: Sensitivities



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When referring to this chart it is important to bear in mind the following:

- Antibiotic susceptibility is reducing in many organisms. There are great geographical variations in antibiotic resistance, not only between different countries, but also between different hospitals
- There may be a significant difference between antibiotic susceptibility determined in vitro and the clinical response, in vivo
- Gram-positive bacteria are intrinsically resistant to aztreonam, temocillin, polymyxin B/colistin and nalidixic acid
- Flucloxacillin may have activity against *Streptococcus pneumoniae* but it is not used to treat pneumococcal pneumonia
- Most staphylococci are penicillinase producers
- MRSA isolates are resistant to beta-lactam agents, including beta-lactamase inhibitor combinations, except for cephalosporins with approved anti-MRSA activity and clinical breakpoints (e.g. ceftaroline and ceftobiprole)
- Enterobacteriaceae are intrinsically resistant to benzylpenicillin, glycopeptides, fusidic acid, lincosamides, streptogramins, rifampicin, daptomycin and linezolid. They are also resistant to macrolides, although azithromycin is effective in vivo for the treatment of typhoid fever and erythromycin may be used to treat travellers' diarrhoea
- Extended-spectrum beta-lactamase (ESBL) producers are often categorized as susceptible to combinations of a penicillin and a beta-lactamase inhibitor. With the exception of urinary tract infections and bloodstream infections secondary to this origin, the use of these combinations in infections caused by ESBL producers remains controversial and should be approached with caution
- Non-fermentative Gram-negative bacteria are intrinsically resistant to benzylpenicillin, cefoxitin, cefamandole, cefuroxime, glycopeptides, fusidic acid, macrolides, lincosamides, streptogramins, rifampicin, daptomycin and linezolid
- *Burkholderia cepacia* and *Stenotrophomonas maltophilia* are intrinsically resistant to all aminoglycosides
- *S. maltophilia* is typically susceptible to trimethoprim–sulphamethoxazole but resistant to trimethoprim alone
- *Neisseria meningitidis* is susceptible to imipenem but it would not be used for treatment because of neurotoxicity (risk of convulsions)
- Although ciprofloxacin is not used for treatment of meningitis, HPA guidance for public health management of meningococcal disease in the UK recommends its use as prophylaxis for contacts (not licensed)

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Alterations to Drug Dosing in Renal Dysfunction and Haemo(dia)filtration

Acute kidney injury can dramatically alter the pharmacokinetics and pharmacodynamics of drug handling. Retention of water in all spaces, changes to the acid–base balance and therefore blood pH and the kidney's reduced ability to excrete and metabolize drugs are just some of the sequelae of acute kidney injury. Once patients go onto renal replacement therapy these alterations are compounded by the filter membrane's ability to remove and even bind some drugs, while leaving others unaffected. The following information relates to the table of common ICU drugs and how their doses need to be altered while undertaking continuous renal replacement therapy (CRRT).

There are several methods of dosing drugs while a patient is undergoing haemodiafiltration; however, the method that Univeristy College London Hospitals (UCLH) has adopted is as follows. Their guideline has drug dosing advice for different patient glomerular filtration rate (GFR) values. The patient's GFR is equated to the total fluid 'flux' within the filter circuit, by adding up all the fluids going through the filter circuit, i.e. citrate, dialysate fluid and replacement fluid and dividing it by 60, which gives a value in ml/min, equated to a patient GFR (see below).

For haemo(dia)filtration, the clearance achieved is variable and is dependent on the ultrafiltration rate, the blood flow rate, the amount of pre-dilution and the haematocrit count.

A more accurate calculation is as follows; however, since the sieving coefficient is usually equal to 1, it is pragmatic to use the simpler method described above.

$$\text{Clearance} = (\text{Sieving coefficient}) \times (\text{Total ultrafiltration rate})/[1 + (\text{Predilution flow rate})/(\text{Plasma flow rate})]$$

where

$$\text{Plasma flow} = \text{Blood flow} \times (1 - \text{Haematocrit})$$

Once the patient's GFR has been estimated by this method, then use the table to guide drug dosing according to the GFR range (see the example of aciclovir below). In this case a total haemodialfiltration rate of 2.2 l/h ~ GFR of 37 ml/min (2,200 ml/ 60 min). Consulting the table, an aciclovir dose in the GFR range of 25–50 ml/min is suitable.

The appropriate doses of drugs can be selected from the table below, on the basis of the patient's estimated GFR (eGFR). For a non-haemofiltered patient, this can be found from the blood results eGFR/CC (where appropriate), calculated using the Cockcroft–Gault equation or from a 24-hour urine collection. This estimated GFR may require interpretation in rapidly

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changing renal function and is especially necessary in acute oliguria, where an empiric estimation of GFR will be necessary. When a patient is on the filter and is also passing urine (suggesting additional clearance in addition to filter clearance) it is not possible to accurately state what this additional clearance will amount to. It is assumed here that haemodiafiltration will not produce significant additional clearance compared to haemofiltration. The dosing of some anti-infectives allows for some discretion and flexibility, taking into account severity of illness, weight of patient and beginning or later in therapy; this is indicated by an '*'.

For newly initiated antibiotics consider prescribing a full dose for the first 24 hours, irrespective of renal function, to ensure aggressive treatment. Subsequent doses should then be adjusted as per renal function. Loading doses are unaffected by renal failure and particularly with antibiotic dosing, other factors such as initial/later therapy, response, sepsis, extremes of weight and age should also be considered.

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GFR (ml/min)	<10	10–25	25–50	Dose in normal renal function
Aciclovir[1] (IV)	2.5–5 mg/kg every 24 hours depending on indication (i.e. 2.5 mg/kg for herpes simplex virus (HSV), herpes zoster virus (HZV); 5 mg/kg for HZV in immunocompromised, herpes simplex encephalitis (HSE))	5–10 mg/kg every 24 hours depending on indication (i.e. 5 mg/kg for HSV, HZV; 10 mg/kg for HZV in immunocompromised, HSE)	5–10 mg/kg every 12 hours depending on indication (i.e. 5 mg/kg for HSV, HZV; 10 mg/kg for HZV in immunocompromised, HSE)	**In obese patients use ideal body weight** 5–10 mg/kg every 8 hours depending on indication (i.e. 5 mg/kg for HSV, HZV; 10 mg/kg for HZV in immunocompromised, HSE)
GFR (ml/min)		**<10–50**		**Dose in normal renal function**
Adrenaline[1]		Dose as in normal renal function		0.01–1 mcg/kg/min
GFR (ml/min)	**<10**	**10–20**	**20–50**	**Dose in normal renal function**
Amikacin[1] (IV)	2 mg/kg every 24–48 hours	3–4 mg/kg every 24 hours	5–6 mg/kg every 12 hours	**In obesity use corrected body weight to calculate the dose** 7.5 mg/kg every 12 hours or
	Measure peak and trough levels. Do NOT withhold next dose awaiting results from laboratory as this risks underdosing			15 mg/kg every 24 hours; then adjusted according to levels

GFR (ml/min)	<10–50			Dose in normal renal function
Aminophylline[1]	IV and oral: dose as in normal renal function and adjust in accordance with blood levels			Modified release: 225–450 mg every 12 hours IV loading dose: 5 mg/kg (250–500 mg) Maintenance dose: typically 0.5–0.7 mg/kg/h adjusted according to levels
GFR (ml/min)	**<10**	**10–20**	**20–50**	**Dose in normal renal function**
Amiodarone[1]	Dose as in normal renal function	Dose as in normal renal function	Dose as in normal renal function	Oral: 200 mg three times a day for 1 week, then twice a day for 1 week, then 200 mg daily maintenance dose or minimum required to control arrhythmia IV: via central catheter – 5 mg/kg (maximum 1.2 g in 24 hours) Ventricular arrhythmias or pulseless ventricular tachycardias: 300 mg over at least 3 minutes

(cont.)

Amlodipine[1]	Dose as in normal renal function	Dose as in normal renal function	Dose as in normal renal function	Oral: 5–10 mg daily
GFR (ml/min)		**<10–50**		**Dose in normal renal function**
AmBisome (liposomal Amphotericin)[1] (IV)		Dose as in normal renal function		1–3 mg/kg/d maximum 5 mg/kg (unlicensed dose)
GFR (ml/min)	**<10**	**10–20**	**20–50**	**Dose in normal renal function**
Amoxicillin[1] (IV)	500 mg to 1 g every 8 hours (maximum 6 g per day in endocarditis)	Dose as in normal renal function	Dose as in normal renal function	500 mg to 1 g every 8 hours (maximum 6 g per day, up to 12 g in endocarditis)
GFR (ml/min)		**<10–50**		**Dose in normal renal function**
Azithromycin[1]		Dose as in normal renal function		*Prophylaxis for Pneumocystis jirovecii* pneumonia (*previously known as Pneumocystis carinii* pneumonia – PCP)/*Toxoplasma Gondii;* 250 mg IV/PO daily Monday – Friday

GFR (ml/min)	<10	10–20	>20	Dose in normal renal function
Benzylpenicillin[1]	600 mg to 1.2 g every 6 hours*	600 mg to 2.4 g every 6 hours*	Dose as in normal renal function	2.4–14.4 g daily in four to six divided doses
GFR (ml/min)	**<10–50**			**Dose in normal renal function**
Caspofungin[1]	Dose as in normal renal function (*In established renal failure the AUC is increased by 30–49% but a change in dose is not required*)[1]			70 mg loading dose on day 1 followed by 50 mg daily, thereafter If patient weighs >80 kg use 70 mg daily (no further dose increases required for obese patients) Moderate–severe liver failure use 35 mg daily [2]
GFR (ml/min)	**6–15**	**16–30**	**31–50**	**Dose in normal renal function**
Ceftazidime[1]	1 g every 24 hours (every 48 hours if *GFR <5 ml/min*)	1 g every 12 hours	2 g every 12 hours	2 g every 8 hours

GFR (ml/min)	<15	15–29	30–50	Dose in normal renal function
Ceftolozane 1 g/Tazobactam 0.5 g (Zerbaxa)[2]	No information	IV: 375 mg (to 750 mg)* 8 hourly	IV: 750 mg (to 1.5 g)* 8 hourly	IV: 1.5 g (to 3 g) 8 hourly Limited data – doses can be doubled in severe infections (unlicensed) [3]
GFR (ml/min)	**<10**	**10–20**	**20–50**	**Dose in normal renal function**
Ceftriaxone[1]	2 g every 24 hours	Dose as in normal renal function	Dose as in normal renal function	Severe infections: 2–4 g every 24 hours
Cefuroxime[1]	750 mg to 1.5 g every 24 hours*	750 mg to 1.5 g every 12 hours*	Dose as in normal renal function	IV: 750 mg to 1. 5 g every 6–8 hours Meningitis: 3 g every 8 hours
Cidofovir[4]	**GFR (ml/min)**	**Dose (mg/kg) weekly**		IV: 5 mg/kg weekly
	41–55	2.0		
	30–40	1.5		
	20–29	1.0		
	<19	0.5		

GFR (ml/min)	<10	10–50	Dose in normal renal function
Ciprofloxacin[1]	50% of normal dose (100% dose may be given for short periods under exceptional circumstances)	Dose as in normal renal function	Oral: 250–750 mg every 12 hours IV: 100–400 mg every 8–12 hours
GFR (ml/min)	**<10–50**		**Dose in normal renal function**
Clarithromycin (IV and oral)[1]	Dose as in normal renal function		Oral: 250–500 mg every 12 hours IV: 500 mg every 12 hours
Clindamycin[1]	Dose as in normal renal function		Oral: 150–450 mg every 6 hours Endocarditis prophylaxis: 600 mg 1 hour before procedure IV: 0.6–4.8 g every 24 hours in two to four divided doses Prophylaxis: 300 mg 15 minutes before procedure then 150 mg 6 hours later

GFR (ml/min)	<10	10–20	20–50	Dose in normal renal function
Clobazam[1]	Dose as in normal renal function. Start with low doses	Dose as in normal renal function	Dose as in normal renal function	Oral: 20–30 mg daily; maximum 60 mg daily
GFR (ml/min)	**<10**	**10–30**	**>30**	**Dose in normal renal function**
Co-amoxiclav[1]	IV: initial dose of 1.2 g and then 1.2 g 12 hourly or 600 mg every 8 hours or [1] Oral: dose as in normal renal function	IV: 1.2 g every 12 hours[1] Oral: dose as in normal renal function [1]	IV and Oral: dose as in normal renal function	IV: 1.2 g every 8 hours (increasing to every 6 hours in severe infections/obesity[1]) Oral: 625 mg every 8 hours
GFR (ml/min)	**<10**	**10–30**	**30–50**	**Dose in normal renal function**
Colistin[1]	NEB: Dose adjustment is not considered necessary[2] IV: 9 million units loading dose should be given as independent of renal function, then as below [1, 2]			IV: 9 million units loading dose, then 4.5 million units every 12 hours [1, 2] Nebulized solution: 1–2 million units two to three times daily (maximum 6 million units /d) [2]
	IV: 1.45 million units 12 hourly	IV: 2.25–2.75 million units 12 hourly	IV: 2.75–3.75 million units 12 hourly	

GFR (ml/min)	<15	15–30	30–50	Dose in normal renal function
Co-trimoxazole (80 mg trimethoprim/ 400 mg sulfamethoxazole)[1, 5]	*Pneumocystis jirovecii* pneumonia treatment: 30 mg/kg every 12 hours daily[1] This should only be given if haemodialysis facilities are available *Pneumocystis jirovecii* pneumonia prophylaxis/ other indication: 50% of normal dose[1]	*Pneumocystis jirovecii* pneumonia treatment: 60 mg/kg every 12 hours for 3 days, then 30 mg/kg every 12 hours[1] *Pneumocystis jirovecii* pneumonia prophylaxis/ other indication: 50% of normal dose[1]	Dose as in normal renal function	**Dosing based on ideal body weight** *Pneumocystis jirovecii* pneumonia treatment: 120 mg/kg/d divided in three to four doses for 3 days then 90 mg/kg/d for 18 days[5] *Pneumocystis jirovecii* pneumonia prophylaxis: Oral: 960 mg twice daily three times per week (Mondays, Wednesday, Friday) OR 480 mg daily Acute exacerbations of chronic bronchitis, *Stenotrophomonas* and urinary tract infections on microbiological advice: IV: 960 mg to 1.44 g every 12 hours; oral: 960 mg every 12 hours

GFR (ml/min)	<20	20–25	25–30	Dose in normal renal function
Dalteparin SC (treatment dose)[6]	***Must consult haemostasis team*** Consider half of treatment dose (split approximately 12 hourly)	Two-thirds of treatment dose (split approximately 12 hourly)	Three-quarters of treatment dose (split approximately 12 hourly)	**ROUND ALL DALTEPARIN DOSES AS PER BNF DOSE BANDING TABLE (use actual body weight)**
	Round doses to nearest available prefilled syringe size. This may result in asymmetrical dosing A suggested *empirical local guide (non evidence based)* is outlined above. These are unlicensed doses, difficult to monitor and significantly increase the risk of bleeding in renal impairment Anti-Xa level monitoring: discuss with haematology re the need for monitoring in these situations			**Therapeutic dose (standard risk of bleeding):** approximately 200 units/kg (maximum 18,000 units) SC ONCE daily **OR** **Therapeutic dose (increased risk of bleeding, unstable renal function etc):** approximately 100 units/kg (maximum 10,000 units) SC 12 hourly (*this may result in asymmetrical dosing; round to nearest available prefilled syringe*) (Above 110 kg contact haematology) **Acute coronary syndrome:** 120 units/kg 12 hourly (maximum licenced dose 10,000 units 12 hourly

GFR (ml/min)	<30	30–50	Dose in normal renal function
Daptomycin[1]	Usual dose (4–6 mg/kg) every 48 hours	Dose as in normal renal function	**Dose based on actual body weight [2]** IV: 4 mg/kg daily Specific indications as recommended by micro e. g. VRE, *Stenotrophomonas* and significant infections use 6 mg/kg daily Unlicensed doses of 10 or 12 mg/kg daily have been reported

GFR (ml/min)	<10	10–20	20–50	Dose in normal renal function
Digoxin[1]	62.5 μg alternate days or, 62.5 μg daily monitor levels	125–250 μg per day monitor levels	125–250 μg per day monitor levels	Digitalization: 0.75–1.5 mg over 24 hours in divided doses (IV) Maintenance: 125–250 μg every 24 hours
Dobutamine[1]	Dose as in normal renal function	Dose as in normal renal function	Dose as in normal renal function	2.5–10 μg/kg/min, increasing up to 40 μg/kg/min according to response

GFR (ml/min)	<10–50	Dose in normal renal function
Erythromycin[1]	Pro-kinetic: dose as in normal renal function But: increased risk of ototoxicity at high doses [1]	Prokinetic: IV: 250–500 mg every 6 hours Oral: 250–500 mg every 6 hours

GFR (ml/min)	<10	10–50	Dose in normal renal function
Fidaxomicin[1]	Dose as in normal renal function – use with caution	Dose as in normal renal function	200 mg every 12 hours for 10 days
Flucloxacillin[1]	Dose as in normal renal function up to a total daily dose of 4 g	Dose as in normal renal function	Oral: 250–500 mg every 6 hours IV: 250 mg to 2 g every 6 hours Endocarditis: maximum 2 g every 4 hours if >85 kg Osteomyelitis: maximum 8 g daily in divided doses
Fluconazole[1] (IV and oral)	Dose as in normal renal function	Dose as in normal renal function For haemofiltration: increase treatment dose to 800 mg every 24 hours[7]	50–400 mg every 24 hours Maximim 800 mg daily (unlicensed dose) In obesity a 12 mg/kg loading dose can be used,

(cont.)

			followed by 6 mg/kg daily (both doses capped at a maximum weight of 100 kg) (unlicensed practice)
Foscarnet Sodium[5]	**GFR (ml/min/kg)**	**Dose (mg/kg) CMV treatment every 12 hours**	90 mg/kg IV daily
	>1.6	90	
	1.5	85.5	
	1.4	79.5	
	1.3	73.5	
	1.2	69	
	1.1	63	
	1.0	58.5	
	0.9	52.5	
	0.8	48	
	0.7	42	
	0.6	37.5	
	0.5	31.5	
	0.4	27	
	<0.4	Do not use	

(cont.)

Fusidic acid/Sodium fusidate[1] (IV/NG/PO)	Dose as in normal renal function		Oral: 500 mg to 1 g (as sodium fusidate) every 8 hours Suspension: 750 mg every 8 hours (as fusidic acid)
Gabapentin[2]	**GFR (ml/min)**	**Total daily dose (mg)**	Day 1: 300 mg once daily, day 2: 300 mg 12 hourly, day 3: 300 mg 8 hourly – based on individual response and tolerability, can be increased in 300 mg/d increments every 2–3 days or faster in the ICU Epilepsy: 0.9–3.6 g in three divided doses Neuropathic pain: maximum 3.6 g daily in three divided doses Migraine prophylaxis: maximum 2.4 g daily in divided doses
	≥ 80	900–3,600	
	50–79	600–1800	
	30-49	300-900	
	15-29	150-600	
	<15	150-300	

Ganciclovir[5]	**GFR (ml/min)**	**Dose (mg/kg)**	**Dose interval (h)**	CMV infection: Treatment (IV infusion): Induction: 5 mg/kg every 12 hours for 14–21 days
	≥70	5	12	
	50–69	2.5	12	
	25-49	2.5	24	
	10-24	1.25	24	
	<10	1.25	24–after haemodialysis	
GFR (ml/min)	**5–10**	**10–20**	**20–50**	**Dose in normal renal function**
Gentamicin[1, 8, 9]	Loading dose 2 mg/kg then 1 mg/kg every 24 hours adjusted according to peak and trough levels[9]	Loading dose 2 mg/kg then 1–1.5 mg/kg twice daily[9] adjusted according to peak and trough levels. Use above for CWF rate <1.1 l/h	7 mg/kg (corrected body weight), adjusted according to levels (6–14 hours post-dose) CWF 1.2–3 l/h or CC 20–50 2 mg/kg loading dose then 1.5 mg/kg 12–24 h	7 mg/kg (corrected body weight), unless GFR <20 ml/min adjusted according to levels 6–14 hours post-dose OR 1–1.5 mg/kg every 8 hours (CBW) adjusted according to peak and trough levels
GFR (ml/min)		**<10–50**		**Dose in normal renal function**
Gentamicin IT (intrathecal)		Dose as in normal renal function		5 mg in 4 ml

(cont.)

Itraconazole[1]	Oral: dose as in normal renal function [1]; though oral bioavailability may be lower in renal insufficiency[2] IV: dose as in normal renal function [1] Hydroxypropyl-β-cyclodextrin is a component of the IV preparation, which is eliminated through glomerular filtration. If GFR is <30 ml/min, the IV formulation is contraindicated [2]; though in practice this is frequently ignored without apparent problems.			Oral: 100–200 mg every 12–24 hours according to indication IV: 200 mg every 12 hours for 2 days, then 200 mg every 24 hours
GFR (ml/min)	**<10**	**10–30**	**30–50**	**Dose in normal renal function**
Lacosamide[1]	Titrate slowly; maximum dose 250 mg daily	Maximum dose 250 mg daily	Dose as in normal renal function	Oral: 50–200 mg 12 hourly
GFR (ml/min)	**<10**	**10–20**	**20–50**	**Dose in normal renal function**
Lamotrigine[1]	Caution; start with low doses and monitor closely	Caution; start with 75% of dose and monitor closely	Caution; start with 75% of dose and monitor closely	Oral: 25–200 mg daily in one to two divided doses, according to clinical indication. Maximum: 500 mg daily; 700 mg with enzyme-inducing drugs
GFR (ml/min)	**<30**	**30–49**	**50–79**	**Dose in normal renal function**
Levetiracetam (Keppra)[1] (IV and oral)	250–500 mg every 12 hours	250–750 mg every 12 hours	250–1,000 mg every 12 hours	250 mg to 1.5 g every 12 hours

GFR (ml/min)		<10–50		Dose in normal renal function
Linezolid[1] (IV and oral)		Dose as in normal renal function (monitor closely if GFR<10 ml/min)		600 mg every 12 hours
GFR (ml/min)	**<10**	**10–25**	**26–49**	**Dose in normal renal function**
Meropenem[1]	500 mg to 1 g every 24 hours	500 mg to 1 g every 12 hours or 500 mg every 8 hours	500 mg to 1 g every 12 hours	500 mg to 1 g every 8 hours
	500 mg every 12[11]	500 mg 6 hourly[11]	500 mg 6 hourly[11]	**Majority of infections including neutropenic sepsis (unlicensed practice)** 500 mg 6 hourly (*initial bolus dose then subsequent doses given as three hour infusions*)
	1 g every 24 hours[10]	1 g 12 hourly	2 g 12 hourly	**Necrotising fasciitis/ meningitis/central nervous system infections;** 2 g 8 hourly

GFR (ml/min)	<10–50			Dose in normal renal function
Metronidazole[1]	Dose as in normal renal function			Oral: 200–500 mg every 8–12 hours IV: 500 mg every 8 hours PR: 1 g every 8–12 hours
Midazolam[1]	Use minimum dose and titrate to sedation score			
GFR (ml/min)	**<10**	**10–20**	**20–50**	**Dose in normal renal function**
Morphine[1]	Use small doses, e.g. 1.25–2.5 mg and extended dosing intervals Titrate according to response	Use small doses, e.g. 2.5–5 mg and extended dosing intervals Titrate according to response	75% of normal dose	5–20 mg every 4 hours (higher in very severe pain or terminal illness)
GFR (ml/min)	**<10**	**10–20**	**20–50**	**Dose in normal renal function**
Nimodipine[1]	Dose as in normal renal function	Dose as in normal renal function	Dose as in normal renal function	Oral: Prevention: 60 mg orally every 4 hours IV: Treatment via central catheter: 1 mg/h initially, increased after 2 hours to 2 mg/h. If BP unstable, weight <70 kg, start with 0.5 mg/h or less if necessary

GFR (ml/min)	<40	40–60	Dose in normal renal function
Nitrofurantoin[1]	Contraindicated	Dose as in normal renal function; use with caution – risk of treatment failure due to inadequate urine concentration	Acute uncomplicated infection: 50 mg every 6 hours for 7 days (3 days usually in women) Severe chronic recurrent infection: 100 mg every 6 hours for 7 days Prophylaxis: 50–100 mg at night
GFR (ml/min)		**<10 – 50**	**Dose in normal renal function**
Noradrenaline[1]		Dose as in normal renal function	(Doses expressed as noradrenaline base) Acute hypotension: 40 µg/ml solution, initially 0.16–0.33 ml/min; adjust according to response Cardiac arrest: 200 µg/ml solution, 0.5–0.75 ml

GFR (ml/min)	<10	10–30	30–60	Dose in normal renal function
Oseltamivir (oral)[1, 11]	Treatment: 30 mg once Prophylaxis: 30 mg once repeated after 7 days	Treatment: 30 mg once daily Prophylaxis: 30 mg every 48 hours	Treatment: 30 mg 12 hourly Prophylaxis: 30 mg once daily	Treatment: 75 mg every 12 hours for 5 days Prophylaxis: 75 mg every 24 hours for 10 days Discuss with Virology for prolonged courses No dose adjustments needed for obese patients [12]
GFR (ml/min)	**<10**	**10–30**	**30–50**	**Dose in normal renal function**
Perampanel[1]	Start with a low dose and titrate gradually	Start with a low dose and titrate gradually	Start with a low dose and titrate gradually	Oral: 2–12 mg once daily
GFR (ml/min)	**<10**	**10–20**	**20–50**	**Dose in normal renal function**
Phenobarbitone (Phenobarbital)[1]	Reduce dose by 25–50% Avoid very large single doses	Dose as in normal renal function but avoid very large doses	Dose as in normal renal function	Oral: 60–180 mg once a night Status epilepticus: IV: 10 mg/kg maximum 1 g

GFR (ml/min)	<10 – 50			Dose in normal renal function
Phenytoin[1]	Dose as in normal renal function – adjust to level			Oral: 150–500 mg/d or 3–4 mg/kg/d in one to two divided doses, higher doses can be used in exceptional cases Status epilepticus: IV: 20 mg/kg (maximum 2 g, at a rate of no more than 1 mg/kg/min) (with BP and ECG monitoring) then 100 mg every 6–8 hours according to levels
GFR (ml/min)	**<10**	**10–40**	**>40**	**Dose in normal renal function**
Piperacillin/ Tazobactam (Tazocin) (IV)[1]	4.5 g every 12 hours	4.5 g every 8 hours (including neutropenic sepsis)	Normal dosing	4.5 g every 8 hours (6 hourly for neutropenic sepsis or obesity[1,13])
GFR (ml/min)		**<10–50**		**Dose in normal renal function**
Posaconazole[1]		Dose as in normal renal function		400 mg every 12 hours with food or 240 ml of a nutritional supplement OR 200 mg every 6 hours without food

(cont.)

				Oropharyngeal candidiasis severe infection or in immunocompromised patients: Loading dose of 200 mg (5 ml) once on the first day then 100 mg (2.5 ml) every 24 hours for 13 days Prophylaxis of invasive fungal infections: 200 mg every 8 hours
Pregabalin[2]	**GFR (ml/min)**	**Starting dose (mg/d)**	**Maximum dose (mg/d)**	Neuropathic pain, epilepsy: 150 mg daily in two to three divided doses Based on response and tolerability may be increased to 300 mg per day after an interval of 3 to 7 days, and if needed, to a maximum dose of 600 mg per day after an additional 7-day interval
	≥60	150	600	
	30–59	75	300	
	15–29	25–50	150	
	<15	25	75	
	Haemodialysis	25	100	
Propofol[1]	Dose as in normal renal function			Sedation: 0.3–4 mg/kg/h

GFR (ml/min)	<10	10–50	Dose in normal renal function
Ranitidine[1]	50–100% of normal dose	Dose as in normal renal function	Oral: 150–300 mg every 12–24 hours Zollinger–Ellison syndrome: 150 mg every 8 hours (up to 6 g/d) IV injection: 50 mg every 6–8 hours
GFR (ml/min)	**10–30**	**30–50**	**Dose in normal renal function**
Ribavirin (IV: 1.2 g in 12 ml) [unlicensed preparation]	IV/PO: No recommendation can be given although some experts use 200 mg once a day under close clinical and laboratory monitoring[14]	IV/PO: 200 mg 8 hourly	Respiratory syncytial virus (RSV) treatment [15] IV: 10–30 mg/kg body weight in three divided doses PO: 30 mg/kg/d in three divided doses for 7 days

GFR (ml/min)	<10	10–20	20–50	Dose in normal renal function
Sodium valproate[1]	Dose as in normal renal function	Dose as in normal renal function	Dose as in normal renal function	Oral: 600 mg to 2.5 g daily in divided doses IV: For continuation of existing oral therapy, IV and oral doses are

(cont.)

				equivalent, give the same dose For initiation of new therapy: give a loading dose of 400–800 mg (up to 10 mg/kg), followed by either a constant infusion or intermittent doses up to a cumulative daily dose of 2.5 g
GFR (ml/min)	**<10**	**10–20**	**>20**	**Dose in normal renal function**
Teicoplanin[1]	Dose reduction not necessary until day 4, then normal dose every 72 hours[9]	Dose reduction not necessary until day 4, then normal dose every 48 hours [9]	Dose as in normal renal function[9]	Dose based on actual body weight < 70 kg: initially 400 mg 12 hourly for three doses, then 400 mg daily > 70 kg: 6 mg/kg 12 hourly for 3 doses, then 6 mg/kg once a day (maximum 1 g per dose) Endocarditis: 10 mg/kg (maximum 1 g per dose) 12 hourly for three doses, then 10 mg/kg (maximum 1 g per dose) once a day

(cont.)

				Bone and joint infections: 800 mg IV or 12 mg/kg every 12 hours for three to five doses, then 12 mg/kg once a day (UCLH: three loading doses)
GFR (ml/min)	**<10**	**10–20**	**20–50**	**Dose in normal renal function**
Thiopental[2]	No specific guidance on renal doses It is metabolized almost entirely in the liver			
GFR (ml/min)	**<10**	**10–20**	**20–50**	**Dose in normal renal function**
Topiramate[1]	Initially 50% of normal dose and increase according to response	Initially 50% of normal dose and increase according to response	Dose as in normal renal function	Oral: Monotherapy: epilepsy: 50–500 mg daily in two divided doses Adjunctive treatment: 200–400 mg daily in two divided doses

GFR (ml/min)	<10	10–20	20–50	Dose in normal renal function
Tranexamic acid[1]	IV: 5 mg/kg every 24 hours Oral: 12.5 mg/kg every 24 hours	IV: 10 mg/kg every 24 hours Oral/NG: 25 mg/kg every 12–24 hours	IV: 10 mg/kg every 12 hours Oral: 25 mg/kg every 12 hours	Oral: 1–1.5 g every 8–12 hours (15–25 mg/kg every 8–12 hours) IV: 0.5–1 g every 8 hours (25–50 mg/kg daily in divided doses)

GFR (ml/min)	<10	10–24	25–39	40–59	Dose in normal renal function
Valganciclovir[1,5]	Treatment: 200 mg three times a week or 450 mg two to three times a week Prophylaxis: 100 mg three times a week or 450 mg one to two times a week[1]	Treatment: 225 mg daily or 450 mg every 48 hours Prophylaxis: 125 mg every 24 hours or 450 mg twice weekly	Treatment: 450 mg every 24 hours Prophylaxis: 225 mg every 24 hours[5] or 450 mg every 48 hours[1]	Treatment: 450 mg every 12 hours Prophylaxis: 450 mg daily	Induction/treatment: 900 mg every 12 hours for 21 days Maintenance/prophylaxis: 900 mg every 24 hours[5]

GFR (ml/min)	<20	20–29	30–39	40–54	55–74	75–89	90–110	Dose in normal renal function
Vancomycin [16,17]	Oral: 100% of normal dose IV: 500 mg every 48 hours	Oral/NG: 100% of normal dose IV: 500 mg every 24 hours	Oral/NG: 100% of normal dose IV: 750 mg every 24 hours	Oral/NG: 100% of normal dose IV: 500 mg every 12 hours	Oral/NG: 100% of normal dose IV: 750 mg every 12 hours	Oral/NG: 100% of normal dose IV: 1 g every 12 hours	Oral: 100% of normal dose IV: 1.25 g every 12 hours	IV: Loading dose (independent of renal function) based on actual body weight: <60 kg 1.5 g, 60–90 kg 1.5 g, >90 kg 2 g, then maintenance dose: if CC >110 1.5 g 12 hourly, if CC <110 then according to table Oral: 125 mg or 500 mg every 6 hours (Higher dose for resistant cases of *Clostridium difficile*)
Vancomycin IT	Dose as in normal renal function							20 mg in 4 ml
Voriconazole[1]	Dose as in normal renal function							Use ideal body weight for most obese patients – consider using adjusted body weight in life-threatening infections [18] IV: 6 mg/kg every 12 hours for 24 hours, then 3–4 mg/kg every 12 hours Oral:<40 kg, 200 mg (5 ml) every 12 hours for 24 hours, then 100–150 mg every 12 hours >40 kg, 400 mg (10 ml) every 12 hours for 24 hours, then 200–300 mg every 12 hours

GFR (ml/min)	<15	15–30	30–50	50–79	Dose in normal renal function
Zanamivir (IV)[1,2]	Initial dose: 600 mg and 48 hours later, maintenance dose: 60 mg every 12 hours	Initial dose: 600 mg and 24 hours later, maintenance dose: 150 mg every 12 hours	Initial dose: 600 mg and 12 hours later, maintenance dose: 250 mg every 12 hours	Initial dose: 600 mg and 12 hours later, maintenance dose: 400 mg every 12 hours	IV: 600 mg every 12 hours

* Optimized dosing dependent upon severity of infection and weight of patient

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Chemical Pleurodesis of Malignant Pleural Effusion

Until recently, tetracycline was the most widely used but is now no longer available worldwide. Doxycycline and talc are now the two recommended sclerosing agents. They are thought to work by causing inflammation of the pleural membranes. This procedure can be painful. In the awake patient, administer 15–25 ml lidocaine 1% (maximum dose 3 mg/kg, with a ceiling of 250 mg) via the chest drain immediately prior to the sclerosing agent. IV opioids and paracetamol may be required. Anti-inflammatory drugs, such as NSAIDs and steroids, should be avoided for up to 2 days before and after the procedure if possible. Talc has a high success rate and is usually well tolerated. Pleuritic chest pain and mild fever are the commonest side effects. However, ARDS is associated with the use of talc in less than 1% of cases. The major disadvantages of bleomycin are the cost and the need for trained personnel familiar with the handling of cytotoxic drugs.

Procedure

- Inset small-bore chest drain (10–14 F) – ensure drainage of the effusion and lung re-expansion
- Analgesics in the awake patient
- Clamp drain at patient's end and insert 50 ml bladder syringe filled with 3 mg/kg lidocaine (20 ml 1% solution for 70 kg patient)
- Release clamp and inject the lidocaine slowly into the pleural space
- Clamp drain and in the same manner inject either talc 4–5 g or doxycycline 500 mg or bleomycin 60,000 units (four vials) diluted in up to 50 ml sodium chloride 0.9% with the bladder syringe
- Flush drain with 10 ml sodium chloride 0.9%
- Clamp the drain for 1–2 hours, observing for signs of increasing pneumothorax (tachycardia, hypotension, falling oxygen saturation, decreased tidal volumes)
- Unclamp the drain and leave on free drainage
- In the absence of excessive fluid drainage (>250 ml/d), the drain should be removed within 2 days of sclerosant administration
- If excessive fluid drainage persists (>250 ml/d), repeat pleurodesis with alternative sclerosant

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Sclerosing agent	Dose	Success rate (%)	Side effects	Cost
Talc	4–5 g	90	Chest pain (7%), fever, ARDS (<1%)	4 g £25
Doxycycline	500 mg	76	Chest pain (60%), fever	£105
Bleomycin	60000 units	61	Chest pain, fever, nausea	£91

Patient rotation is not necessary after intrapleural instillation of sclerosant. It is time-consuming, inconvenient, uncomfortable and made no difference to the success rate.

Reference: Management of a malignant pleural effusion: British Thoracic Society Pleural Disease Guideline. *Thorax* 2010; **65** (suppl II); ii32–ii40.

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Appendices

Appendix A Creatinine clearance

Severity of renal impairment is expressed in terms of glomerular filtration rate, usually measured by creatinine clearance (CC). This may be estimated from the serum creatinine.

Estimating CC from serum creatinine:

For men:

$$\text{CC (ml/min)} = \frac{\text{weight (kg)} \times (140 - \text{age}) \times 1.23}{\text{serum creatinine } (\mu\text{mol/l})}$$

For women:

$$\text{CC (ml/min)} = \frac{\text{weight (kg)} \times (140 - \text{age}) \times 1.03}{\text{serum creatinine } (\mu\text{mol/l})}$$

Normal range (based on an adult with a body surface area of 1.73 m^2):

Age	Sex	CC (ml/min)
20–29	Male	94–140
	Female	72–110
30–39	Male	59–137
	Female	71–121

For each decade thereafter values decrease by 6.5 ml/min.

Renal impairment is arbitrarily divided into three grades:

Grade	CC (ml/min)
Mild	20–50
Moderate	10–20
Severe	<10

Renal function declines with age; many elderly patients have a glomerular filtration rate <50 ml/min, which, because of reduced muscle mass, may not be indicated by a raised serum creatinine. It is wise to assume at least mild renal impairment when prescribing for the elderly.

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Appendix B Weight conversion (stones/lb to kg)

	lb								
		0	2	4	6	8	10	12	13
Stones	6	38.1	39.0	40.0	40.8	41.7	42.6	43.5	44.0
	7	44.5	45.4	46.3	47.2	48.1	49.0	49.9	50.3
	8	50.8	51.7	52.6	53.5	54.4	55.3	56.2	56.7
	9	57.2	58.1	59.0	59.9	60.8	61.7	62.6	63.0
	10	63.5	58.1	65.3	66.2	67.1	68.0	68.9	69.4
	11	69.9	70.8	71.7	72.6	73.5	74.4	75.4	75.7
	12	76.2	70.8	78.0	78.9	79.8	80.7	81.6	82.1
	13	82.6	70.8	84.4	85.3	86.2	87.0	88.0	88.4
	14	88.9	89.8	90.7	91.6	92.5	93.4	94.3	94.8
	15	95.3	96.2	97.1	98.0	98.9	99.8	100.7	101.1
	16	101.6	102.5	103.4	104.3	105.2	106.1	107.0	107.5
	17	108.0	108.9	109.8	110.7	111.6	112.5	113.4	113.8
	18	114.3	115.2	116.1	117.0	117.9	118.8	119.7	120.2

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Appendix C Body mass index (BMI) calculator

$$\text{BMI} = \frac{\text{Weight (kg)}}{\text{Height (m)}^2}$$

To use the table:

First convert weight to kg (1 lb = 0.45 kg)

Then read across from patient's height until you reach the weight (kg) nearest to the patient's

Then read up the chart to obtain the BMI

Height												
(Feet/inches)	(metres)	20	21	22	23	24	25	26	27	28	29	30
5′0″	1.52	46	49	51	53	55	58	60	62	65	67	69
5′1″	1.55	48	50	53	55	58	60	62	65	67	70	72
5′2″	1.58	50	52	55	57	60	62	65	67	70	72	75
5′3″	1.60	51	54	56	59	61	64	67	69	72	74	77
5′4″	1.63	53	56	58	61	64	66	69	72	74	77	80
5′5″	1.65	54	57	60	63	65	68	71	74	76	79	82
5′6″	1.68	56	59	62	65	68	71	73	76	79	82	85
5′7″	1.70	58	61	64	66	69	72	75	78	81	84	87
5′8″	1.73	60	63	66	69	72	75	78	81	84	87	90
5′9″	1.75	61	64	67	70	74	77	80	83	86	89	92
5′10″	1.78	63	67	70	73	76	79	82	86	89	92	95
5′11″	1.80	65	68	71	75	78	81	84	87	91	94	97
6′0″	1.83	67	70	74	77	80	84	87	90	94	97	100
6′1″	1.85	68	72	75	79	82	86	89	92	96	99	103
6′2″	1.88	71	74	78	81	85	88	92	95	99	102	106

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Height												
(Feet/inches)	(metres)	20	21	22	23	24	25	26	27	28	29	30
6′3″	1.90	72	76	79	83	87	90	94	97	101	105	108
6′4″	1.93	74	78	82	86	89	93	97	101	104	108	112
6′5″	1.96	77	80	84	88	92	96	99	103	107	111	115
		Desirable						Moderately obese				

<20 = underweight
20–24.9 = desirable
25–29.9 = moderately obese
>30 = obese

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Appendix D Lean body weight charts

For men:

Height in feet and inches (cm)	Weight (kg)		
	Small frame	Medium frame	Large frame
5′6″ (168)	62–65	63–69	66–75
5′6″ (168)	63–66	65–70	68–76
5′8″ (173)	64–67	66–71	69–78
5′9″ (175)	65–68	69–74	70–80
5′10″ (178)	65–70	69–74	72–82
5′11″ (180)	66–71	70–75	73–84
6′0″ (183)	68–73	71–77	75–85
6′1″ (185)	69–75	73–79	76–87
6′2″ (188)	70–76	75–81	78–90
6′3″ (191)	72–78	76–83	80–92
6′4″ (193)	74–80	78–85	82–94

For women:

Height in feet and inches (cm)	Weight (kg)		
	Small frame	Medium frame	Large frame
5′0″ (152)	47–52	51–57	55–62
5′1″ (155)	48–54	52–59	57–64
5′2″ (158)	49–55	54–60	58–65
5′3″ (160)	50–56	55–61	60–67
5′4″ (163)	52–58	56–63	61–69
5′5″ (165)	53–59	58–64	62–70
5′6″ (168)	55–60	59–65	64–72

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Height in feet and inches (cm)	Weight (kg)		
	Small frame	Medium frame	Large frame
5′7″ (170)	56–62	60–67	65–74
5′8″ (173)	57–63	62–68	66–76
5′9″ (175)	59–65	63–70	68–77
5′10″ (178)	60–66	65–71	69–79
5′11″ (180)	61–67	66–72	70–80
6′0″ (183)	63–69	67–74	72–81

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Appendix E Ideal tidal volume (ITV) 6 ml/kg Based on Height/Predicted Body Weight (PBW)

MALE			FEMALE		
Height (m)	PBW (kg)	ITV (ml)	Height (m)	PBW (kg)	ITV (ml)
1.46	44	260	1.40	34	205
1.48	46	275	1.42	36	215
1.50	48	290	1.44	37	220
1.52	50	300	1.46	39	235
1.54	51	310	1.48	41	245
1.56	53	320	1.50	43	260
1.58	55	330	1.52	45	270
1.60	57	340	1.54	46	275
1.62	59	355	1.56	48	290
1.64	61	365	1.58	50	300
1.66	62	370	1.60	52	315
1.68	64	385	1.62	54	325
1.70	66	395	1.64	56	335
1.72	68	410	1.66	57	340
1.74	70	420	1.68	59	355
1.76	71	425	1.70	61	370
1.78	73	440	1.72	63	380
1.80	75	450	1.74	65	390
1.82	77	460	1.76	66	395
1.84	79	475	1.78	68	410
1.86	80	480	1.80	70	420
1.88	82	490	1.82	72	430

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MALE			FEMALE		
Height (m)	PBW (kg)	ITV (ml)	Height (m)	PBW (kg)	ITV (ml)
1.90	84	505	1.84	74	445
1.92	86	515			
1.94	88	530			

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Appendix F Estimated height from ulna length

Measure between the point of the elbow (olecranon process) and the midpoint of the prominent bone of the wrist (styloid process) – left arm if possible

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Men (<65 years)	1.94	1.93	1.91	1.89	1.87	1.85	1.84	1.82	1.80	1.78	1.76	1.75	1.73	1.71
Men (>65 years)	1.87	1.86	1.84	1.82	1.81	1.79	1.78	1.76	1.75	1.73	1.71	1.70	1.68	1.67
Ulna length (cm)	32.0	31.5	31.0	30.5	30.0	29.5	29.0	28.5	28.0	27.5	27.0	26.5	26.0	25.5
Women (<65 years)	1.84	1.83	1.81	1.80	1.79	1.77	1.76	1.75	1.73	1.72	1.70	1.69	1.68	1.66
Women (>65 years)	1.84	1.83	1.81	1.79	1.78	1.76	1.75	1.73	1.71	1.70	1.68	1.66	1.65	1.63
Men (<65 years)	1.69	1.67	1.66	1.64	1.62	1.60	1.58	1.57	1.55	1.53	1.51	1.49	1.48	1.46
Men (>65 years)	1.65	1.63	1.62	1.60	1.59	1.57	1.56	1.54	1.53	1.51	1.49	1.48	1.46	1.45
Ulna length (cm)	25.0	24.5	24.0	23.5	23.0	22.5	22.0	21.5	21.0	20.5	20.0	19.5	19.0	18.5
Women (<65 years)	1.65	1.63	1.62	1.61	1.59	1.58	1.56	1.55	1.54	1.52	1.51	1.50	1.48	1.47
Women (>65 years)	1.61	1.60	1.58	1.56	1.55	1.53	1.52	1.50	1.48	1.47	1.45	1.44	1.42	1.40

Appendix G Infusion rate/dose calculation

To calculate the infusion rate in ml/h:

$$\text{Infusion rate (ml/h)} = \frac{\text{Dose (μg/kg/min)} \times \text{Weight (kg)} \times 60}{\text{Concentration of solution (μg/ml)}}$$

To calculate the dose in μg/kg/min:

$$\text{Dose (μg/kg/min)} = \frac{\text{Infusion rate (ml/h)} \times \text{Concentration of solution (μg/ml)}}{\text{Weight (kg)} \times 60}$$

For example: adrenaline infusion (4 mg made up to 50 ml) running at 6 ml/h in a patient weighing 80 kg:

$$\text{Dose (μg/kg/min)} = \frac{6 \text{ ml/h} \times \frac{4{,}000 \text{ μg}}{50 \text{ ml}}}{80 \text{ (kg)} \times 60}$$

$$= 0.1 \text{ μg/kg/min}$$

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Appendix H Drug compatibility chart

Ideally, all drugs given intravenously should be given via a dedicated line or lumen, and not mixed at any stage. However, if this is not possible, then compatibility data must be obtained before co-administering drugs. In general, drugs should not be added to parenteral nutrition, or to blood products. Sodium bicarbonate and mannitol solutions should not be used as diluent for IV drug administration.

As a general guide, line compatibility of different drugs often depends on the pH of the drugs concerned. This will vary depending on how the drug is reconstituted or diluted. Drugs with widely differing pH will almost certainly be incompatible. However, the converse is not necessarily true, and lines should always be checked regularly for any gross signs of incompatibility (e.g. precipitate formation).

This chart indicates whether two drugs can be run in through the same IV access. It assumes normal concentrations and infusion rates for each drug, and data may vary depending on the diluent used. It should be used as a guide only, and not taken as definitive.

Please refer to the table at the back of the book.

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Appendix I Sodium content of oral medications

The normal daily requirement of sodium for an adult is 100 mmol. ICU patients are frequently administered effervescent or soluble tablets and these can contribute a significant sodium load. Below is a list of commonly used oral medications in the ICU with their sodium content. The precise values given for generic products may differ slightly between manufacturers.

Preparation	Approximate sodium content, per dose unit
Aciclovir 200 mg/400 mg/800 mg tablets (manufacturer Actavis)	<1 mmol
Aspirin 75 mg dispersible tablets	<1 mmol
Co-beneldopa (Madopar) 62.5 mg/125 mg dispersible tablets	None
Co-codamol 8/500 dispersible/effervescent/soluble tablets	16.7–19 mmol per tablet
Diclofenac (Voltarol) 50 mg dispersible tablets	<1 mmol
Gastrocote liquid	2.1 mmol in 5 ml
Lansoprazole (Zoton FasTab) orodispersible tablets	None
Mirtazipine 15 mg/30 mg/45 mg orodispersible tablets	None
Olanzapine 5 mg/10 mg/15 mg/20 mg orodispersible tablets	None
Paracetamol 500 mg soluble tablets	16.9–19.1 mmol per tablet
Phosphate-Sandoz effervescent tablets	20.4 mmol per tablet
Piroxicam (Feldene Melt) 20 mg orodispersible tablets	None
Potassium effervescent tablets (Sando-K)	0.1 mmol per tablet
Prednisolone soluble tablets	1.5 mmol per tablet
Ranitidine 150 mg effervescent tablets	5.2 mmol per tablet
Risperidone 0.5 mg/1 mg/2 mg/3 mg/4 mg generic orodispersible tablets	None
Sandocal-400 effervescent tablets	None
Sandocal-1000 effervescent tablets	6 mmol per tablet

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Preparation	Approximate sodium content, per dose unit
Sodium bicarbonate 500 mg capsules	6 mmol per tablet
Tramadol (Zamadol Melt) 50 mg orodispersible tablets	None
Zinc (Solvazinc) effervescent tablets	4.6 mmol per tablet

Source: National Electronic Library for Medicines

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Appendix J Drug management of the brain-stem-dead donor

- Initially, **methylprednisolone** 15 mg/kg IV bolus, as soon as possible. Methylprednisolone is associated with reduced lung water and renders the lungs more suitable for transplant
- Continue **antibiotics** as indicated
- **Insulin** ≥1 unit/h, blood glucose target 4–9 mmol/l
- **Inotropes and vasopressors** may be indicated (p. 343). If response to catecholamine infusion is inadequate, a trial of **hydrocortisone** 50–100 mg intravenously may improve cardiovascular parameters
- Diabetes insipidus is a common problem and may need treatment with **vasopressin** (p. 293) or **desmopressin (DDAVP)** (p. 90)
- Recent studies suggest that **tri-iodothyronine** (T_3) supplementation may add little to an intensive donor management protocol which includes vasopressin and methylprednisolone, and suggest using it only if cardiac performance is unresponsive to volume loading and vasopressors. T_3 4 μg IV bolus, followed by IV infusion of 3 μg/h
- If hypernatraemia is a problem, use Ringer's lactate solution (**Hartmann's**) or a **glucose-containing** solution. Glucose solution and methylprednisolone may lead to hyperglycaemia, requiring an increase in insulin infusion
- Electrolyte disturbance with low **potassium, magnesium, calcium** or **phosphate** should be corrected
- Bradycardia will be unresponsive to atropine, use **isoprenaline** or **dobutamine** infusion
- Maintenance **IV fluids** should be limited if ongoing losses are not excessive; enteral route can be considered

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Appendix K Vancomycin by continuous infusion

Underdosing and problems associated with the sampling and the timing of serum level monitoring are problems which may result in decreased efficacy of vancomycin in the treatment of infection. The efficacy of vancomycin depends on the time for which the serum level exceeds the minimum inhibitory concentration (MIC) for the micro-organism rather than on the attainment of high peak levels. Administration of vancomycin as a continuous infusion is therefore an ideal method of administration for optimum efficacy. Once the infusion reaches a steady state, the timing for serum level monitoring is not crucial, and samples can be taken at any time.

Administration – day 1

Weight-related loading dose followed immediately by continuous infusion. Ideal body weight should be used for patients who are overweight or fluid-overloaded. Use patient's actual body weight if this is lower than the ideal body weight.

IV loading dose:

<70 kg:	1 g in 100 ml sodium chloride 0.9% over 2 hours via central line OR
	1 g in 250 ml sodium chloride 0.9% over 2 hours via peripheral line
≥70 kg:	1.25 g 100 ml sodium chloride 0.9% over 2 hours via central OR 1.25 g in 250 ml sodium chloride 0.9% over 2 hours via peripheral line

Continuous IV infusion: Start continuous IV infusion (over 24 hours) immediately after the loading dose has been given. The starting dose is based on an estimate of the patient's renal function (see table below).

For **central** administration: Reconstitute 500 mg vancomycin in 10 ml WFI, and further dilute with sodium chloride 0.9% to make up to 50 ml total volume.

For peripheral administration: Reconstitute 500 mg vancomycin in 10 ml WFI, and further dilute with sodium chloride 0.9% to make up to 100 ml total volume.

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Renal function	Starting vancomycin infusion dose (over 24 hours)
Normal (serum creatinine <120 μmol/l)	1.5 g
Impaired (serum creatinine >120 μmol/l)	1 g
CVVH	1 g

Measure serum levels every day at 06:00 hours from day 2 onwards, and adjust dose according to levels (as below).

Adjustment of daily infusion dose – day 2 onwards

Target vancomycin levels are between 15–25 mg/l). The adjustment of the infusion dose is dependent on the vancomycin level:

Vancomycin level (mg/l)	Dosage change required	Rate adjustment
<15	Increase the dose by 500 mg	Increase infusion rate to next level up in subsequent table
15–25	No change	No change
>25	Decrease the dose by 500 mg*	Reduce infusion rate to next level down in subsequent table
>30	Stop infusion for minimum of 6 hours	Restart at a reduced dose

* If the patient is receiving only 500 mg/d, the dose should be decreased to 250 mg/d (as outlined in table below)

Vancomycin dose over 24 hours	Infusion rate (ml/h)	
	via central line (500 mg in 50 ml)	via peripheral line (500 mg in 100 ml)
2.5 g	10.4	20.8
2 g	8.3	16.7
1.5 g	6.3	12.5
1 g	4.2	8.3
500 mg	2.1	4.2
250 mg	1.1	2.1

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Adjustment of daily infusion dose on coming off CVVH

If the patient has been on CVVH, and a decision is made to withhold CVVH, there is a risk of an increased plasma vancomycin level. Please ensure the levels are checked on a daily basis and the daily dose adjusted appropriately.

Once CVVH is to be resumed, the daily dose should be back to what it was before coming off CVVH.

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Appendix L Child–Pugh score

The Child–Pugh score is used to assess the prognosis of chronic liver disease, mainly cirrhosis. Although it was originally used to predict mortality during surgery, it is now used to determine the prognosis, as well as the required strength of treatment and the necessity of liver transplantation. This score is to guide dose reduction in liver failure for certain drugs, such as caspofungin and tigecycline.

Scoring

The score employs five clinical measures of liver disease. Each measure is scored 1–3, with 3 indicating most severe derangement.

Measure	1 point	2 point	3 point
Bilirubin (μmol/l)	<34	34–50	>50
Serum albumin (g/l)	>35	28–35	28–35
INR	<1.7	1.71–2.20	>2.20
>2.20	None	Suppressed with medication	Refractory
Hepatic encephalopathy	None	Grade I–II (or suppressed	Grade III–IV (or refractory)

In primary sclerosing cholangitis (PSC) and primary biliary cirrhosis (PBC), the bilirubin references are changed to reflect the fact that these diseases feature high conjugated bilirubin levels. The upper limit for 1 point is 68 μmol/l and the upper limit for 2 points is 170 μmol/l.

Interpretation

Chronic liver disease is classified into Child–Pugh classes A to C, employing the added score from above.

Points	Class	1-year survival (%)	2-year-survival (%)
5–6	A	100	85
7–9	B	81	57
10–15	C	45	35

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Appendix M Severe sepsis algorithm

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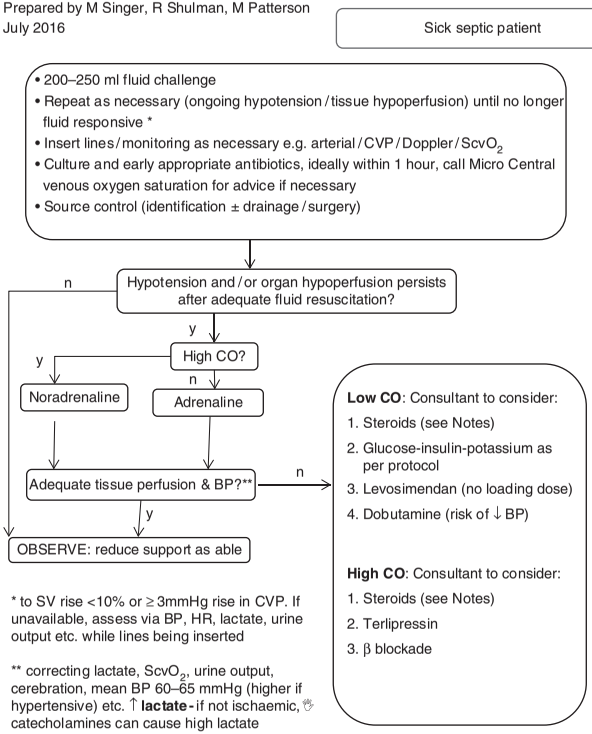
Prepared by M Singer, R Shulman, M Patterson
July 2016



NOTES

Steroid: If noradrenaline / adrenaline > 0.4 µg / kg / min - hydrocortisone IV 50 mg four times a day 5/7 then 50 mg twice a day 3/7, then 50 mg once a day 3/7 then stop

Terlipressin: IV 0.25 mg bolus prn or IV infusion 0.1 mg/h (can increase to 0.3 mg/h). Will take 20 mins for first effect.
Avoid in low CO states, as can cause ischaemia.

If **dusky digits** appear, review vasopressors and start epoprostenol infusion 10 ng / kg / min and titrate

IV immunoglobin dose for toxic shock / necrotizing fasciitis fas: 2g / kg IV stat immediately or if fluid restricted: 1 kg/d 1, then 0.5 g / kg for days 2 and 3, then stop

Levosimendan needs cardiologist consultant approval, 0.1µg/kg / min IV for 24 hours, once only.

Beta-blockers: if HR > 95, on high dose noradrenaline, volume resuscitated, titrate to HR 80–95. If haemodynamic unstable consultant to consider esmolol initially then change to metoprolol. If stable start with metoprolol. Start with low rates and titrate up til HR 80–95

Fluids Give against an adequate tissue perfusion target. Try to avoid excessive fluid. Use Geloplasma for the initial resuscitation only (maximum 2l). After the resuscitation period, aim for neutral balance unless clinically indicated e.g. ↑ output from fistula loss.

Blood glucose avoid hypo and hyperglycaemia (target range 4–10 mmol/l), as per unit insulin guidelines.

Antibiotics review depending on culture sensitivities. review need after 5 days. Dosing in relation to severity, renal function, size etc.

Appendix N Insulin guidelines

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UCLH Critical Care Insulin Guidelines

Check blood glucose (BG) on admission to ICU: target BG 4.4–10 mmol/l

If BG > 10 mmol/l start insulin (Actrapid) infusion 50 µg in 50 ml sodium chloride 0.9%

Blood glucose (mmol/l)	Initial rate for insulin infusion (units/hour)
8–9.9	0.5 if BG is rising
10–14.9	1
15–17.9	2
18–21	3
>21	4

- IV glucose (G), enteral (EN) or TPN must accompany any insulin infusion.
- If using G infusion, rate should be at least 3 g/h (i.e. G10% at 30 ml/h or G5% at 60ml/hr)
- Stop insulin infusion when interrupting EN and/or TPN for more than 2 hours; if BG still high after that period, restart insulin infusion with a G infusion background (see above). More frequent BG checks should be performed when changing the EN or TPN
- Insulin doses may need to be higher when steroid or inotropes are co-administered

Check BG at 1 hour

BG < 4.4 mmol/l

Stop insulin for 1 hour.

Notify doctor

Check BG at 15–30 minutes

BG 2.5–3.9 mmol/l

give 25 ml G50% (if no central line, give 60 ml of G20%)

BG <2.5 mmol/l

give 50 ml G50% (if no central line, give 125 ml of 20%)

BG 4.4 mmol/l

Check BG at 1 hour

Consider reducing insulin infusion rate if BG decreasing by >3 mmol/l in previous hour

BG remains 4.4–10mmol/l

Check BG every 2 hours

BG > 10 mmol/l

Increase infusion rate by 1–2 units/h if BG stable or rising

If BG decreasing by >3mmol/l in previous hour

Consider reducing insulin infusion rate

- Signs of hypoglycaemia include adrenergic activation (sweating, tremor tachycardia, agitaiton)
- If BG remains in range for 12 hours, then measure BG 4-hourly
- Revert to hourly BG checks if:
  - BG outside target range
  - Change in clinical condition
  - Change to nutrition

Prepared by Dr Rob Shulman (Pharmacy), based on guideline from Peter MacCallum Cancer Centre, ICU

Drug Index

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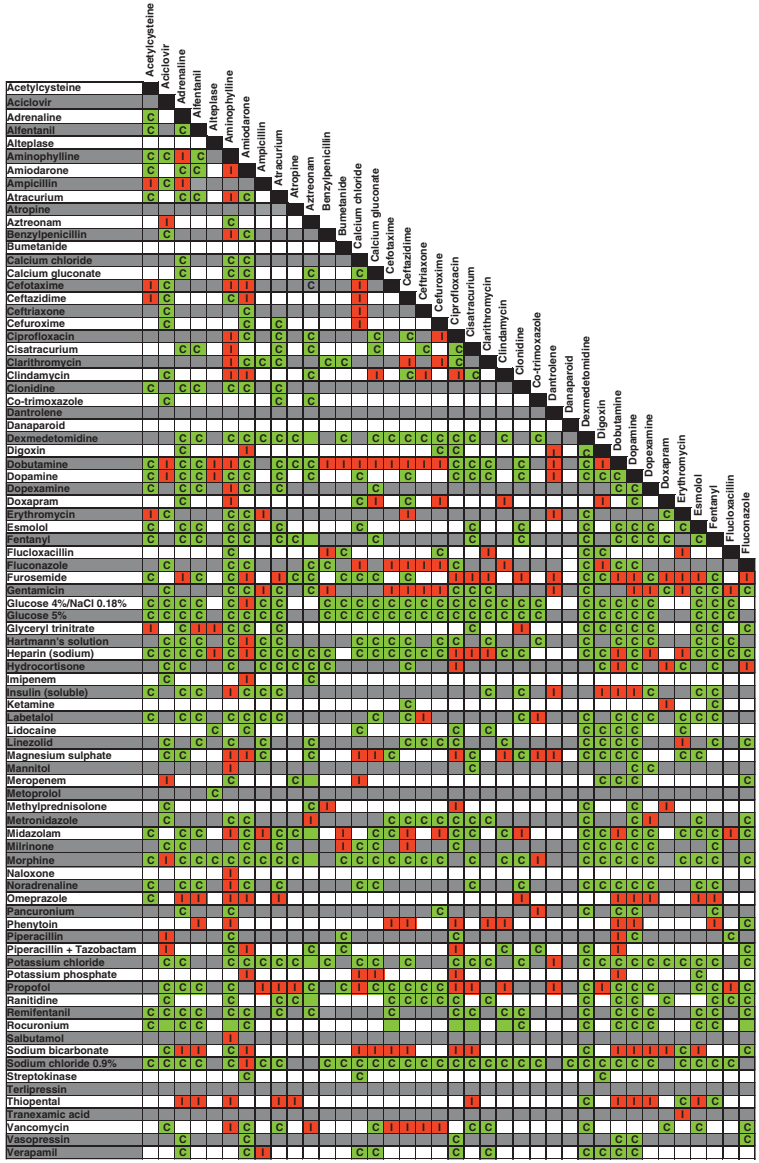
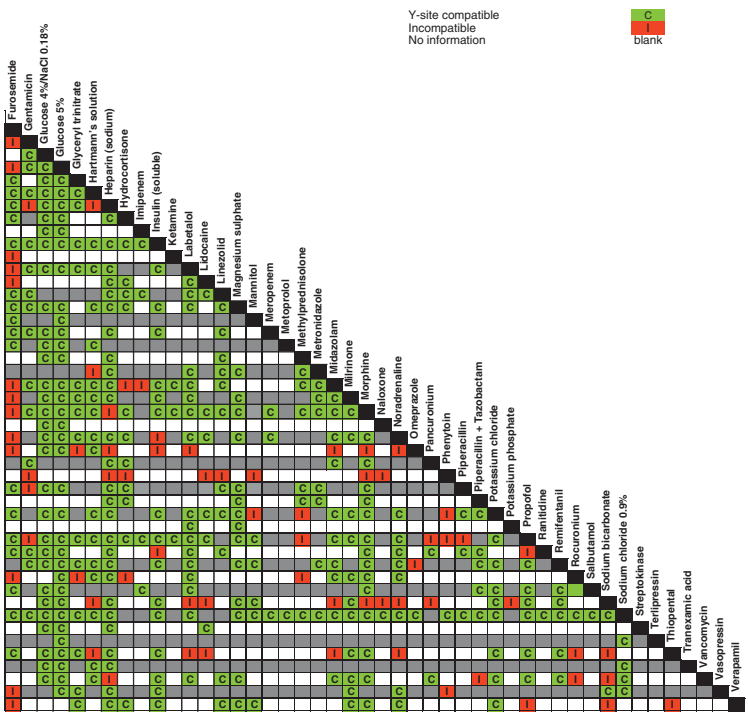


IV COMPATIBILITY CHART

Check clarity of solution before any administration



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