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Pharmacokinetics in sepsis

M. Charlton[1,2] and J.P. Thompson[1,2,*]

[1]University Hospitals of Leicester NHS Trust, Leicester, UK and [2]University of Leicester, Leicester, UK

*Corresponding author: jt23@le.ac.uk

Learning objectives

By reading this article you should be able to:

- Describe the effects of sepsis on drug absorption, distribution, metabolism, and elimination.
- Detail the potential effects of sepsis-associated organ dysfunction on pharmacokinetics.
- Explain the practical implications of sepsis on the pharmacokinetics of drugs used commonly in anaesthesia and critical care.

Key points

- Sepsis can cause changes in physiology and organ function that have important consequences for drug handling.
- Drug absorption, distribution, metabolism and elimination are all altered in sepsis even when organ failure is not apparent.
- Treatment may increase or decrease pharmacokinetic variability in sepsis.
- Specific data are limited, but drug doses and regimens can be adjusted based on first principles.
- Dosage and route of administration may need altering to avoid harm.

Sepsis is a heterogeneous syndrome caused by a dysregulated host response to systemic infection whereby uncontrolled pro- and anti-inflammatory processes lead to tissue injury, immune suppression, and organ dysfunction.[1] The response to sepsis has profound effects on many physiological processes and body systems. These can have significant effects on absorption, distribution, metabolism, and elimination of drugs, with potential implications for treatment regimens and the incidence of adverse effects. Furthermore, these adverse effects may be increased or decreased by our therapeutic interventions. In addition to requiring treatment in critical care, many patients with sepsis undergo anaesthesia and surgery.

This article reviews the pathophysiology of sepsis in relation to its effects on the pharmacokinetics of the drugs commonly used in anaesthesia and critical care. This is needed to predict pharmacodynamic effects, ensure correct dosing, and avoid harm. Altered pharmacokinetics in sepsis also has implications for drug–drug interactions, but this is outside the scope of this article.

Effects of sepsis on pharmacokinetics—general principles

Sepsis is characterised by the widespread release of cytokines, proteases, and reactive oxygen species, which lead to both direct and indirect cellular damage.[2] Vasodilatation and capillary leak ensue, resulting in relative and absolute intravascular hypovolaemia in the first instance, followed by the potential for considerable increase in total body fluid after resuscitation.[3] Microcirculatory blood flow is impaired leading to heterogeneous organ perfusion, mitochondrial dysfunction, cellular hypoxia, and subsequently organ dysfunction and failure.[2] The extent to which these changes occur depends on the complex interplay between infectious factors (causative organisms and microbial load), patient factors (age, physiological status/fitness, comorbidities, genetic characteristics, and treatment interventions) and treatment factors (volume of fluid resuscitation, use of vasoactive agents).[1,2] Because these processes are both dynamic and interacting, pharmacokinetics may be altered to a variable extent that can be difficult to predict.

***Matthew Charlton** FRCA FFICM is a specialty trainee and clinical lecturer in anaesthesia and critical care at the University of Leicester and University Hospitals of Leicester NHS Trust.*

***Jonathan Thompson** BSc (Hons), MD, FRCA, FFICM is honorary professor of anaesthesia and critical care at the University of Leicester and a consultant at Leicester Royal Infirmary. He is a former editor of the British Journal of Anaesthesia, current editorial board member of the BJA and Perioperative Medicine, and current editor-in-chief of BJA Education.*

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In addition, there are few available data on the specific effects of sepsis on drug handling, with most pharmacokinetics studies performed in healthy volunteers and results extrapolated to clinical practice in a variety of situations. The specific pharmacokinetic aspects are discussed in more detail below. It is important to remember that clinical pharmacy services form an integral part of the multidisciplinary team in critical care. Their knowledge and expertise is invaluable: advice from a clinical pharmacist should be sought when prescribing for complex patients with potentially altered pharmacokinetics, both within and outside the critical care unit.

Absorption

Gastric emptying is delayed to some extent in almost all critically ill patients, with many having intestinal ileus, particularly after surgery. This may be compounded by opioids used for analgesia or sedation, which further reduce gastric emptying and gut peristalsis. Other factors affecting gastrointestinal (GI) absorption include hypoperfusion, venous congestion, mucosal oedema, motility dysfunction, continuous feeding regimens, nasogastric suctioning, and alterations of intraluminal pH (alkalinisation).[4] The use of vasoactive agents for circulatory support may also decrease splanchnic blood flow, gut perfusion, and therefore absorption. Together these may pose significant problems for medicines only available in an enteral formulation (e.g. many antiretroviral, psychoactive, anticoagulants, antiparkinsonian, and antiplatelet drugs). In practice it may be possible to withhold certain medications until the enteral route is available or utilise an intravenous formulation if one exists. If unavailable, alternate routes may be considered (e.g. rotigotine patches for patients with Parkinson's disease) as an alternative or in addition to the oral preparation if toxicity is unlikely.

Drug absorption via other non-enteral routes may also be altered in sepsis. Decreased skin and muscle perfusion caused by redistribution of blood flow in shock and compounded by vasopressor drugs can lead to unpredictable absorption after subcutaneous or intramuscular drug administration. For example, several studies have shown variability in anti-factor Xa activity after administration of low molecular weight heparins (LMWH) at doses used for thromboprophylaxis.[5,6] Conversely, transdermal drug absorption may be increased during fever because of peripheral vasodilatation and increased cutaneous blood flow.

Distribution

Drug distribution depends on regional blood flow, cardiac output, body composition, age, and the physiochemical properties of the drug, such as lipid solubility, protein binding, molecular size, pKa, and degree of ionisation.

Sepsis and common therapies cause several pathophysiological changes that alter drug disposition, the effects of which can be significant. Redistribution of blood away from peripheral tissues with or without reduction in cardiac output can decrease the volume of distribution (V_D) of some fat-soluble medications leading to higher plasma concentrations and the potential for adverse effects. This is particularly important in critical care for rapidly acting medications with concentration-dependent adverse effects such as intravenous anaesthetic, analgesic or sedative agents.

Endothelial damage, altered capillary permeability, and fluid leak in combination with fluid resuscitation may significantly increase the V_D of hydrophilic medications (e.g. beta-lactam and aminoglycoside antibiotics), which can lead to decreased plasma concentrations and potential underdosing. Other factors that increase V_D include extracorporeal circuits and comorbidities such as liver cirrhosis and heart failure.

The degree of ionisation is determined by pK_a and affects lipophilicity, the extent to which a drug can cross membranes and its V_D. Weak bases are more ionised at pH values below their pK_a; the opposite is true for weak acids. Acidaemia, frequently found in sepsis, therefore leads to an increased degree of ionisation of drugs that are weak bases (e.g. opioids, local anaesthetics) and a decreased volume of distribution.

Albumin and α_1-acid glycoprotein (AAG) are the two main drug binding proteins in the plasma. Albumin, an anion, predominately binds proton donors (acidic drugs) in contrast to α_1-acid glycoprotein, which predominantly binds basic drugs. Hypoalbuminaemia is common in sepsis, and the relationship between hypoalbuminaemia and drug pharmacokinetics is complex.[7] Low serum albumin concentrations initially lead to an increase in the free fraction of highly protein-bound drugs with the potential for toxicity. However, as volume of distribution and clearance are increased, free drug concentrations may decrease to subtherapeutic levels. Highly protein-bound drugs requiring a minimal plasma concentration for clinical effect (such as antimicrobials) may require increased loading and maintenance doses to achieve the desired therapeutic effect.[8] Conversely, drugs extensively bound to albumin with an immediate clinical effect may require reduced dosing. Midazolam, for instance, has a more rapid onset in the presence of hypoalbuminaemia.[9] Therefore drugs should be prescribed in patients with sepsis and hypoalbuminaemia on a case-by-case and agent-by-agent basis.

Alpha$_1$-acid glycoprotein is an acute-phase reactant that is increased in sepsis and other critical illness, leading to increased binding and decreased free drug concentrations of basic protein-bound molecules. The clinical effect of drugs such as opioids may therefore be decreased.

Metabolism

Most drugs are metabolised predominantly in the liver, but extrahepatic sites may be important. For example, propofol has a clearance in excess of hepatic blood flow, as it is metabolised in the lungs and kidneys.[10]

Hepatic drug metabolism depends on three factors: hepatic blood flow, free unbound fraction of the drug, and the intrinsic enzymatic capacity of hepatocytes. Hepatic extraction ratio (ER) is the fraction of drug cleared from the blood after a single pass through the liver (intrinsic clearance ÷ hepatic blood flow). Drugs can be classified as having high (>0.7), intermediate (0.3–0.7), or low (<0.3) ERs. Examples are given in Table 1.

Drugs with a high hepatic ER are rapidly cleared by the liver, and so their clearance depends on adequate hepatic blood flow and less so on enzyme function. Conversely, drugs with a low hepatic ER are relatively flow independent; clearance is related to hepatic enzyme activity and the proportion of free drug in plasma.

The pathophysiology of hepatic dysfunction in sepsis is complex and not fully understood. Two clinical entities may be observed. An imbalance in hepatic oxygen delivery and demand accompanied by a reduced ability of hepatocytes to extract oxygen leads to *hypoxic hepatitis*, characterised by increased aminotransferase concentrations. Impaired cellular

Table 1 Examples of drugs with a high, intermediate and low extraction ratio (ER)

High ER (<0.7)	Morphine
	Fentanyl
	Propofol
	Ketamine
	Lidocaine
	Dexmedetomidine
Intermediate ER (0.3–0.7)	Aspirin
	Midazolam
	Alfentanil
	Vecuronium
Low ER (<0.3)	Anti-epileptic agents: carbamazepine, phenytoin, valproic acid, phenobarbital
	Diazepam
	Lorazepam
	Rocuronium
	Clonidine
	Thiopental
	Theophylline

function and bile handling leads to intrahepatic cholestasis (*sepsis-induced cholestasis*). These features may have a significant impact on both drug delivery to hepatocytes and cellular oxygenation required for their metabolism, as cytochrome P450 (CYP450) systems located in the pericentral area of the liver lobule are at risk of cellular hypoxia. In addition, pro-inflammatory cytokines such as tumour necrosis factor (TNF)-α and interleukin (IL)-1β and IL-6 directly affect CYP450 function, leading to reduced clearance of low ER drugs.[11] Organ dysfunction in one system may also induce dysfunction in another by a process known as 'organ crosstalk'. For example, acute kidney injury (AKI) may lead to a reduction in CYP450 activity by cytokine- and non-cytokine-mediated mechanisms ('renohepatic crosstalk').[12]

Adrenaline (epinephrine), vasopressin, and positive pressure ventilation all reduce hepatic blood flow, and therefore the clearance of drugs with a high ER such as fentanyl and propofol. Therapeutic hypothermia and drug interactions (e.g. with proton pump inhibitors, macrolides, fluoroquinolones, and azole antifungals), decrease enzymatic function. Prone positioning may effect hepatic blood flow and function,[13] although evidence from studies in critical care suggests that when performed correctly, using appropriate supports and cushioning, its effects are limited.[14]

Elimination

Elimination comprises metabolism to inactive compounds by the liver and other body systems and excretion of drugs either in their unchanged form or as active and inactive metabolites. Most drugs are excreted via the kidney with larger molecules excreted in bile, although other routes of excretion also occur (skin, faeces, and lungs).

AKI is common in sepsis with a reported incidence between 15% and 38% depending on the definition used.[15] The pathophysiology of AKI is multifactorial, including ischaemia, cellular hypoxia, inflammation, and toxic injury. The risk of AKI is increased by positive pressure ventilation probably because of decreased renal blood flow.[16]

Renal excretion comprises filtration, secretion, and reabsorption, with filtration being the primary mechanism. Drugs that are primarily filtered have a linear relationship between the adequacy of renal function and clearance, with a risk of drug accumulation when renal function is impaired. This may be particularly important in the case of hydrophilic antimicrobials such as β-lactams, aminoglycosides, and glycopeptides.[17] In contrast, renal drug clearance may be augmented by increased renal blood flow associated with a hyperdynamic circulation in early sepsis, leading to increased clearance of hydrophilic molecules and under-dosage.[18] Active secretion of drugs by the renal tubule is an energy-dependent process requiring adequate renal blood flow, and so elimination may be reduced in AKI and sepsis. Drugs with significant renal secretion include β-lactam antibiotics, digoxin, and furosemide.

During continuous renal replacement therapy, clearance is determined by the prescribed dialysate and filtrate flow rates, and protein binding. Only the free unbound portion of the drug is cleared, so highly protein-bound molecules are not eliminated effectively by haemofiltration.

Dose adjustment in renal failure is a complex topic. Pharmacokinetics may be altered as a consequence of reduced renal clearance and alterations in plasma protein binding, acid–base balance, and volume of distribution, together with the accumulation of organic acids such as uric and lactic acid. Generally, loading dosages do not require adjustment but the dosing interval should often be increased, ongoing doses reduced, or a combination of the two. Care should be taken in drugs with a narrow therapeutic index and in those with active or toxic metabolites that may accumulate in renal failure. Propofol, atracurium, and paracetamol require no dose adjustment. Rocuronium, morphine, and fentanyl have reduced clearance and therefore a prolonged therapeutic action. The *Renal Drug Handbook* provides an excellent resource on the prescribing of medications in renal failure, and advice from pharmacists should be sought.

Table 2 provides an overview of the pharmacokinetic changes in sepsis, with the potential clinical effects of these changes.

Implications for drugs used in anaesthesia and critical care

Intravenous anaesthetic agents

Propofol, thiopental, and etomidate are highly lipid-soluble molecules with extensive protein binding (propofol 98% bound to albumin). In severe sepsis, V_D is initially decreased as a consequence of centralisation of blood flow. This combined with a decreased serum albumin can lead to significantly higher free plasma concentrations in patients with sepsis, causing pronounced cardiovascular effects. Decreased cardiac output also prolongs time to induction of anaesthesia, and doses should be reduced, given slowly, and titrated to effect.

Thiopental has a pKa of 7.6, and is 61% unionised at physiological pH. Acidosis may therefore increase the unionised fraction and theoretically increase its clinical effects, including a greater risk of cardiovascular depression. Administration by continuous infusion can lead to zero-order hepatic metabolism of thiopental, and the clinical effects become significantly prolonged. This may be compounded in the presence of impaired hepatic function, although renal dysfunction has limited effects.

Renal and hepatic dysfunction have limited effects on the metabolism and clearance of propofol, and its metabolites are inactive. Accumulation in peripheral compartments during prolonged infusions leads to a long context-sensitive half-time and therefore prolonged effects. Critically ill patients are

Table 2 Overview of pharmacokinetic alterations in sepsis, with examples of potential clinical effects

Pharmacokinetic process	Alteration in sepsis	Potential clinical effect
Absorption	• Decreased for most routes • Potentially increased transdermal absorption	• Potential for subtherapeutic effects of all enterally administered medications • Potential increased absorption of transdermal preparations (fentanyl)
Distribution	• Lipophilic medications—decreased V_D • Hydrophilic medication—increased V_D • Hypoalbuminaemia—increased free drug concentration of acidic protein bound drugs • Increased α_1 acid glycoprotein—decreased free drug concentration of basic protein bound drugs • Acidaemia—decreased V_D of weak bases	• Increased plasma concentration of intravenous anaesthetic agents, opioids and sedatives leading to adverse effects (e.g. cardiovascular depression) • Potential for subtherapeutic levels of commonly used hydrophilic antimicrobial agents such as beta-lactams and aminoglycosides • Midazolam may have a more rapid onset because of decreased protein binding in hypoalbuminaemia • Decreased clinical effect of opioids because of increased binding by the acute phase reactant α_1 acid glycoprotein
Metabolism	• Generally decreased	• Prolonged clinical effect and risk of toxicity
Excretion	• Generally decreased	• Prolonged clinical effect and risk of toxicity

at an increased risk of propofol infusion syndrome, and infusions exceeding 4 mg kg^{-1} h^{-1} should be avoided.[19]

Ketamine, unlike the other i.v. agents, can be administered via several routes. Protein binding is 25% and therefore hypoproteinaemia has little effect. Ketamine is metabolised by the cytochrome P450 system to an active metabolite, norketamine, with approximately one-third the potency of the parent compound, and so clinical effect may be prolonged in severe hepatic impairment. Norketamine is conjugated to inactive metabolites that are excreted in the urine. Ketamine is unusual in comparison with other i.v. anaesthetic agents in that it produces sympathetic stimulation via endogenous catecholamine release, offsetting its intrinsic myocardial depressant activity. However, in septic shock endogenous catecholamine release may already be maximal, so the intrinsic cardiovascular depressant effects of ketamine can predominate, leading to cardiovascular collapse. Dose adjustment is therefore required (usually 0.25–0.5 mg kg^{-1} i.v. for induction of anaesthesia).[20]

Inhalation anaesthetic agents

The solubility of an inhalation anaesthetic agent is determined by its blood:gas (B:G) partition coefficient, with larger partition coefficients equating to increased solubility and prolonged induction time. Lower B:G coefficients occur with haemodilution, hypoalbuminaemia, and pyrexia, leading to more rapid onset of anaesthesia. Increased cardiac output leads to slower induction of anaesthesia caused by washing out of the alveolar concentration gradient, with the converse being true when cardiac output is reduced; both situations can occur in sepsis. In animal models, the minimum alveolar concentration (MAC) is reduced in sepsis.[21] Inhalation agents in current use undergo minimal metabolism and are eliminated unchanged via the lungs.

Benzodiazepines

Benzodiazepines are lipophilic and >95% bound to albumin. Hypoalbuminaemia causes a significant (up to three-fold) increase in V_D, allowing free drug to distribute throughout adipose tissue, prolonging half-life and pharmacodynamic effect. Despite increased V_D, the decrease in protein binding leads to higher initial free plasma concentrations, with a rapid pharmacological response. Both midazolam and diazepam are metabolised in the liver to active compounds (midazolam to 1-hydroxymidazolam and 4-hydroxymidazolam; diazepam to desmethyldiazepam, oxazepam, and temazepam). 1-Hydroxymidazolam has a potency similar to that of midazolam, and therefore the clinical effects of these agents can be prolonged in liver and renal failure. Lorazepam is metabolised to an inactive compound. For these reasons, it is recommended that doses of benzodiazepines are reduced in sepsis, titrated to clinical effect, and administered as boluses rather than continuous infusion.

Neuromuscular blocking agents

Non-depolarising neuromuscular blocking drugs

Both benzylisoquinolinium and aminosteroid non-depolarising neuromuscular blocking agents (NMBAs) contain one or more quaternary ammonium groups. They are positively charged with small volumes of distribution, which may be increased in cases of hepatic dysfunction prolonging half-life. The benzylisoquinolinium compounds (e.g. atracurium) are unaffected by hepatic and renal dysfunction, and this is a potential advantage in the critically ill patient with sepsis. Atracurium is metabolised by non-specific plasma esterases and Hofmann elimination, a spontaneous non-enzymatic process that is delayed by hypothermia and acidosis. Conversely, aminosteroid compounds such as rocuronium, pancuronium, and vecuronium undergo hepatic metabolism to a variable extent (more so vecuronium), to active metabolites which are subsequently excreted via the kidneys. Rocuronium undergoes minimal metabolism, being predominantly excreted unchanged in the bile (~40%) with hepatic dysfunction leading to a reduced clearance and prolonged action. Hypoproteinaemia will prolong the duration of all non-depolarising NMBAs because of an increase in V_D. Hypokalaemia, hypocalcaemia, hypermagnesaemia, acidosis, and hypothermia (particularly with atracurium) prolong the effect of NMBAs. Neuromuscular monitoring is advisable when NMBAs are used in any patient in critical care, and this may be especially important in sepsis.

Succinylcholine

Succinylcholine is rapidly hydrolysed by plasma cholinesterases after administration, to the extent that approximately only 20% of an administered dose reaches the neuromuscular

junction. Acquired plasma cholinesterase deficiency occurs in sepsis; renal, hepatic, and cardiac failure; and protein malnutrition (amongst many other causes), with the potential for prolonged neuromuscular block.[22]

Neostigmine and sugammadex

Neostigmine is a highly ionised molecule with low protein binding. Dose adjustment is not required.

Sugammadex and the sugammadex–NMBA complex do not bind to plasma proteins and are not metabolised. The complex is 96% excreted via the kidneys and is cleared by renal replacement therapy. The sugammadex–NMBA complex has been shown to be present 7 days after administration in patients with severe renal impairment, and so it is not recommended in AKI. It is not recommended in hepatic failure because it has spurious effects on clotting when administered at high doses. Molecules with a high affinity for sugammadex, such as flucloxacillin, toremifene, and intravenous fusidic acid, may displace rocuronium or vecuronium from the sugammadex–NMBA complex. This may lead to a delay in recovery of train-of-four, or the potential for recurarisation, although this has not been observed in clinical practice.[23]

Opioids

Opioids are weak bases, with variable degree of ionisation depending on the pKa of the drug and plasma pH. Absorption and distribution are related to the degree of ionisation, with weak bases demonstrating increased ionisation at lower pH levels, and therefore reduced absorption and distribution. Weak bases (such as opioids) are bound to AAG, an acute phase reactant whose concentration increases in cases of critical illness. An increase in AAG leads to a decreased V_D and decreased clearance, prolonging duration of action in sepsis. Apart from remifentanil, opioids are metabolised in the liver to active and inactive metabolites. The morphine metabolite morphine-6-glucoronide is 13 times more potent than the parent compound and, along with the other major metabolite (morphine-3-glucoronide), is excreted via the kidneys leading to accumulation in renal failure. Morphine and fentanyl have high hepatic ERs, and decreased clearance occurs when hepatic blood flow is decreased. Tramadol is also primarily metabolised in the liver and excreted by the kidney. It should be avoided in renal failure and the dosing interval prolonged in cases of hepatic or renal dysfunction.

Remifentanil is rapidly metabolised by non-specific plasma esterases to a metabolite that is essentially inactive (1/4600th potency). As a consequence of rapid metabolism and a low volume of distribution, there is negligible accumulation of remifentanil irrespective of the duration of an i.v. infusion, so it has a 'context in-sensitive' half-time. Its pharmacokinetics are unaffected by hepatic and renal dysfunction.

Transdermal preparations of opioids are probably best avoided in sepsis because skin blood flow and absorption are unpredictable; either low therapeutic effect or toxicity could occur.[24]

Vasoactive agents

Pharmacokinetic variability may be a less important concept when considering the vasoactive agents given their short half-lives and clinically titratable effects, but tachyphylaxis does occur. Patients with sepsis and acidaemia often require increased concentrations of exogenous (and endogenous) catecholamines to produce the same increase in arterial pressure when compared with patients without sepsis, a phenomenon known as vascular hyporesponsiveness.[25]

Vascular hyporesponsiveness describes a decreased dose–response relationship, and its aetiology is multifactorial. In patients with sepsis it includes downregulation of catecholamine receptors, increased nitric oxide and prostacyclin production, generation of oxygen free radicals and peroxynitrite, and the activation of ATP-sensitive potassium channels caused by acidaemia and increased circulating lactate; this leads to hyperpolarisation of cell membranes and vasodilatation.[3]

It should be noted that vasoactive agents may also affect the absorption, distribution, and elimination of other drugs because of their effects on cardiac output, regional and tissue blood flow.

Antimicrobial drugs

Early and appropriate antimicrobial therapy forms a cornerstone of the management of sepsis. Adequate dosing is essential to provide sufficient pharmacodynamic effect whilst avoiding harm.

Hydrophilic antimicrobials (Table 3) are greatly affected by the pathophysiological changes of sepsis. They are principally confined to the extracellular space with a relatively low V_D and are mostly excreted by the kidneys. Endothelial dysfunction, altered protein binding, and the administration of large volumes of intravenous fluids lead to an increase in the V_D, leading to subtherapeutic plasma concentrations and therefore ineffective microbial clearance. This is particularly problematic with antimicrobials whose therapeutic effects are determined by the minimum time above a desired plasma concentration ('time-dependent killing'), such as the β-lactams. Therefore it is advisable to deliver the maximal appropriate loading dose of hydrophilic antimicrobial in the initial instance, accounting for the risks of toxicity on a patient-by-patient basis, followed by appropriate titration of maintenance doses.[26] Maintenance doses and frequency may need to be increased, particularly with commonly used β-lactam antibiotics and carbapenems, and may be better administered by continuous infusion rather than intermittent doses.[27] Highly protein-bound antimicrobials may conversely have a reduced V_D, but the subsequently increased free plasma concentrations lead to increased clearance, and subtherapeutic concentrations. Lipophilic antimicrobials (Table 4) may also require dose adjustment in cases of hepatic failure.[8] For example metronidazole should be reduced to one-third of the normal dose and administered once daily.

In the case of AKI, dosages may require further adjustment because of the risk that molecules excreted mostly by the kidney may accumulate as a result of decreased clearance, leading to the risk of toxicity. Dosages may require further

Table 3 Classes of hydrophilic antimicrobials and examples of drugs in each class

Class of hydrophilic antimicrobial	Examples
Aminoglycosides	Gentamicin, tobramycin, amikacin
Beta-lactams	
• Carbapenems	• Meropenem, ertapenem
• Penicillins	• Flucloxacillin, amoxicillin, piperacillin
• Cephalosporins	• Cefuroxime, ceftriaxone, ceftazidime
Glycopeptides	Vancomycin, teicoplanin

Table 4 Classes of lipophilic antimicrobials and examples of drugs in each class

Class of lipophilic antimicrobial	Examples
Nitroimidazoles	Metronidazole
Fluoroquinolones	Ciprofloxacin, moxifloxacin, levofloxacin
Oxazolidinones	Linezolid
Macrolides	Clarithromycin, erythromycin, azithromycin
Lincosamides	Clindamycin
Tetracyclines	Doxycycline, tigecycline, minocycline

review should the patient be commenced on renal replacement therapy, with many hydrophilic antimicrobials being filtered. Input from a dedicated critical care pharmacist is essential in this scenario.

Given the complexity of the host response in sepsis, therapeutic drug monitoring should be used whenever available to ensure adequate drug concentrations and therapeutic effect, and avoid toxicity. This is particularly important for drugs with a narrow therapeutic window such as gentamicin and vancomycin, both of which are commonly used in the management of sepsis.

Summary

It is difficult to predict the precise effects of sepsis on pharmacokinetics because of diverse pathophysiology, differences in host response, and the effects of treatment. Absorption, metabolism, and excretion are generally reduced. The effects on distribution are more variable and depend on the pharmacokinetic properties of the drug in question, acid–base balance, plasma protein concentrations, and the effects of illness and resuscitation on total body water.

For most drugs commonly used in anaesthetic practice, dosages should be adjusted according to the pharmacokinetic principles outlined above and titrated to clinical effect. For drugs with narrow therapeutic indices or where maintenance of a minimum concentration is essential for therapeutic effect, assays should be used to monitor plasma concentrations where available. Published data are limited, but an understanding of the effects of sepsis based on first principles is essential in order to adjust doses appropriately.

Declaration of interests

JPT is editor-in-chief of *BJA Education*. This article was originally commissioned and submitted before his appointment and the reviewing process has been handled by other members of the editorial board.

MC declares no conflict of interest.

MCQs

The associated MCQs (to support CME/CPD activity) will be accessible at www.bjaed.org/cme/home by subscribers to *BJA Education*.

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