



# Guidance for patient with septic shock

Guidance to support the multidisciplinary team manage a critically ill patient with septic shock.

Supporting complex decision-making in critical care



**Critical Illness**

Available through

 **Medicines  
Complete**



# Guidance for patient with septic shock

Using essential knowledge at the point of care



**AK, a 42-year-old male, is transferred from a surgical ward to the intensive care unit (ICU) with septic shock. He had abdominal surgery five days earlier.**

Critical Illness drug monographs are intended to provide comprehensive guidance to support the care of acutely unwell adult patients, managed in ICU. Monographs are presented in a standardised format including information on indication and dose, administration, dose adjustments, pharmacokinetics (PK) and pharmacodynamics (PD) observed in critical illness, as well as other important considerations in this patient group. The evidence-based recommendations consider the effects of acute illness and organ failures, as well as the impact these have on optimising drug therapy.

Medicines Complete

Co-amoxiclav

**Critical Illness**

Publication last updated on 14-Sep-2021

Essential medicines information to support complex decision-making and dynamic prescribing in critical care.

Evidence grading ■

Subsections

Related Content

- Introduction
- Indications in critical illness
- Administration
- Dose adjustments
- Pharmacology
- Pharmacokinetics
- Important considerations in the critically ill
- References

## Co-amoxiclav

Last Update: 03-Aug-2021

### Introduction

Co-amoxiclav is a combination beta-lactam antibiotic (amoxicillin) and beta-lactamase inhibitor (clavulanic acid) with a broad spectrum of activity against gram-positive and gram-negative bacteria. Maintaining drug concentration above the minimum inhibitory concentration (MIC) of the target organism is associated with treatment success.

Inadequate beta-lactam antibiotic exposure (free concentrations maintained above the MIC of the pathogen for less than 50% of the dosing interval [T<sub>f</sub> < 50% MIC]) in critically ill patients has been associated with the need for escalation of antibiotic therapy or prolonged treatment course; higher PK/PD targets (higher drug exposure) should be considered.<sup>1</sup> This reinforces the need to optimise dosing in critically ill patients.

Amoxicillin is active against gram-positive organisms—*Staphylococcus aureus*, *Streptococcus* spp. (including *S. pneumoniae* and alpha-haemolytic streptococci), *Enterococcus* spp. (e.g. *Enterococcus faecalis*), and *Listeria monocytogenes*—and gram-negative organisms—*Haemophilus influenzae*, *Escherichia coli*, *Helicobacter pylori*, *Neisseria* spp. and *Salmonella* spp.—so long as they are strains that do not produce beta-lactamases. Clavulanic acid is a beta-lactamase inhibitor and extends the spectrum of amoxicillin to include the beta-lactamase-producing strains of many organisms including many anaerobic bacteria otherwise resistant to amoxicillin. Clavulanic acid has some limited intrinsic antibacterial effect; it irreversibly inhibits beta-lactamase therefore protecting the amoxicillin. Co-amoxiclav is not active against *Pseudomonas* spp. or ESCAPPM bacteria (*Enterobacter* spp., *Serratia* spp., *Citrobacter freundii*, *Hafnia* spp., *Aeromonas* spp., *Proteus* spp., *Providencia* spp., and *Morganella morganii*).

For details on general use of co-amoxiclav, see [British National Formulary](#).



## Dosing

Suspecting a severe Enterobacteriaceae infection, the team review the latest evidence to guide the dosing of co-amoxiclav.

The dosing information is immediately accessible and adapted for reference at the patient bedside. Where dosing information is unlicensed, this is clearly indicated with the relevant references cited.

The screenshot displays the Medicines Complete interface for 'Co-amoxiclav' under the 'Critical Illness' section. The page is titled 'Indications in critical illness' and includes a table of contents on the left with sections like Introduction, Indications in critical illness, Administration, Dose adjustments, Pharmacology, Pharmacokinetics, Important considerations in the critically ill, and References. The main content area provides detailed information on indications, infection types, and dosing regimens. A 'Rationale' section is expanded, showing dosing simulations and clinical commentary on side-effects and adjustments.

**Indications in critical illness**

Community-acquired pneumonia/respiratory-tract infections; exacerbations of chronic obstructive pulmonary disease (COPD); intra-abdominal infections (community acquired); dental infections; Group A streptococcal pharyngitis; diabetic foot infection; skin and soft tissue infections, in particular cellulitis, animal bites, and severe dental abscess with spreading cellulitis; bone and joint infections, in particular osteomyelitis; prophylaxis against infections associated with major surgical procedures in adults, such as those involving the: gastrointestinal tract, pelvic cavity, head and neck, and biliary tract (after surgery).

A loading or initial dose of antimicrobial therapy should be administered as soon as possible in sepsis or septic shock (ideally within the first hour of presentation). Blood cultures should be taken before antimicrobial administration.<sup>4</sup> **Even in renal dysfunction, the full dose should be used for at least the first dose and potentially the first 24 to 48 hours unless patient is frail, elderly, or has very low body-weight.** [E]

**Infection**

By intravenous injection

**Dose**

1.2 g every 6 to 8 hours (6 hourly dosing is unlicensed in UK) or  
1.2 g every 6 hours (plus amoxicillin 1 g every 12 hours) in patients with severe Enterobacteriaceae infections due to high MIC, or intra-abdominal infection, and CrCl greater than 130 mL/minute [unlicensed]<sup>2</sup>

**Rationale**

Dosing simulations support 1.2 g every 6 hours or 2.4 g every 8 hours with low to normal CrCl (30 to 130 mL/minute) using a target MIC of 8 mg/L and a PK-PD target of 50% fT>MIC.<sup>3</sup> 1.2 g every 8 hours also met the target for MIC of 8 mg/L and a PD target of 50% fT>MIC, up to and including CrCl of 50 mL/minute.

Dosing simulations demonstrated little accumulation of clavulanic acid for patients with normal to high CrCl with high doses of co-amoxiclav.<sup>3</sup>

Co-amoxiclav can cause more gastrointestinal side-effects than amoxicillin. As the beta-lactamase inhibition of clavulanic acid lasts 8 to 12 hours, dosing could be adjusted to amoxicillin/clavulanic acid 1.2 g every 6 hours plus amoxicillin 1 g intravenously every 12 hours, which may be an alternative to high dosing.<sup>2</sup>

## Rationale

Comprehensive information is available through the expandable rationale section that provides a detailed clinical commentary. The rationale explains the evidence behind the recommendations and provides expert critical appraisal of the literature, to inform further review and study.

## Expert opinion

While the evidence-based literature in critical care has strengthened over the last few years, there are many situations where evidence is lacking or inconclusive. In these situations, recommendations reflect best-practice and the consensus opinion of the Critical Illness editorial team, comprised of



world-renowned critical care, renal and antimicrobial experts working in clinical practice. These recommendations are identified clearly as expert opinion and have been evidenced-graded within the drug monograph.

## Dose adjustments

There is a high clinical suspicion that AK has augmented renal clearance (ARC) and the Minimum Inhibitory Concentration (MIC) for Enterobacteriaceae is anticipated to be high. To account for the changes in clearance, AK's co-amoxiclav is increased to optimise dosing.

Drug monographs have been specifically designed to consider PK and PD changes observed in critical illness. The risk in critical illness, especially with some antimicrobials in the acute phase, is that insufficient doses are given. This can be due to changes associated with critical illness PK or because doses are incorrectly adjusted in acute kidney injury, renal replacement therapy, or other extracorporeal circuits.

Critical care patients are at high risk of adverse reactions and side effects from drugs, with some easier to predict than others. Toxicity caused by the accumulation of drugs is often considered and drug interactions are well recognised, although not always acted upon in clinical practice. Therefore, a balance between toxicity and undertreatment has to be made. Ideally, this should be done on a daily basis.

Critical Illness provides detailed recommendations on dose adjustments including those required for acute kidney injury, chronic kidney disease, ARC and extra-corporeal membrane therapies.



## Pharmacokinetics

The ICU pharmacist wants to learn more about the other potential differences in PK parameters to consider.

To provide effective and safe treatment, it is crucial to understand the PK of a drug, and how the PK will be affected by critical illness.

Critical Illness provides information on PK parameters, including key differences between healthy, hospitalised, and the critically ill. These differences can be significant and standard drug information is often not suitable in critical care.

Curated by international experts and supported by recent PK studies, the information gives the multidisciplinary team the knowledge to make decisions on drug selection, dosing, monitoring, and aids in identifying the risk of an adverse effect.

The screenshot shows the Medicines Complete interface for Co-amoxiclav. The 'Pharmacokinetics' section is active, displaying a table comparing standard pharmacokinetics with pharmacokinetics in critically ill patients. The table includes parameters like Volume of distribution (L/kg) and Mean volume of distribution standardised to 70 kg patient.

Parameter	Standard pharmacokinetics	Pharmacokinetics in the critically ill
Volume of distribution (L/kg) <sup>8</sup>	Healthy volunteer: amoxicillin: 0.318 L/kg, clavulanic acid: 0.33 L/kg	Amoxicillin: 0.317 L/kg Clavulanic acid: 0.30 L/kg
	Hospital inpatient: amoxicillin: 0.26 L/kg	
	Mean volume of distribution standardised to 70 kg patient	Mean volume of distribution standardised to 70-kg patient

## Monitoring

72 hours later, a fluconazole-resistant candida infection is reported in AK's results. The Infectious Diseases team recommend voriconazole with therapeutic drug monitoring (TDM) to ensure treatment is within the optimal range. The team would like to confirm the best practice for voriconazole TDM.

Critically ill patients are at risk of drug-related harm, both from toxicity as well as therapeutic failure. Drug monographs provide actionable monitoring recommendations, including TDM targets where relevant. Like other monograph sections, recommendations are based on evidence, are fully referenced, and include an expandable rationale section with detailed clinical commentary.



The screenshot shows the Medicines Complete interface for Voriconazole. The search bar contains 'Voriconazole'. The page is titled 'Critical Illness' and 'Evidence grading' is shown as a green bar. The left sidebar has 'Subsections' and 'Related Content' tabs. Under 'Subsections', 'Important considerations in the critically ill' is selected. The main content area is titled 'Important considerations in the critically ill' and includes sections for 'Monitoring' and 'Rationale'.

**Monitoring**

Liver function tests at start of and during therapy; renal function; monitor patients for the development of pancreatitis.<sup>1,2</sup>

Electrolyte imbalances should be corrected prior to treatment to minimise the risk of cardiac instability in QTc prolongation.

The expert ESICM panel recommends TDM using  $C_{min}$  monitoring. The sample should be taken 30 minutes prior to the next dose and monitoring should occur between 2 and 5 days of therapy. Aim  $C_{min}$  2 to 6 mg/L for prophylaxis or treatment.<sup>2,4</sup>

**Rationale**

In critically ill patients, there is a wide variation in serum voriconazole levels that can lead to therapeutic failure and toxicity.<sup>15,16,19</sup>

Resistance of aspergillus to azoles is increasing.<sup>20</sup> Target levels of voriconazole for invasive aspergillus are at least 1.5 mg/L and ideally greater than 2 mg/L. Levels lower than this are associated with treatment failure.<sup>4,19</sup>

Toxicity usually becomes apparent once levels are above 4.5 to 5 mg/L.<sup>4,15,16,19</sup>

Timely access to TDM shortens the time to therapeutic levels and increases the time in the therapeutic range, and is essential.<sup>4,15,16</sup>

A week later AK is improving, and the team considers switching the voriconazole from IV to oral. The team are unclear on when this change should be made.

Decisions on drug dosing and administration should be made regularly as a patient's clinical status can rapidly change. Critical Illness provides dosing recommendations to support dynamic prescribing, in this case including advice on how and when to approach a change in route or formulation.

The screenshot shows the Medicines Complete interface for Voriconazole. The search bar contains 'Voriconazole'. The page is titled 'Critical Illness' and 'Evidence grading' is shown as a green bar. The left sidebar has 'Subsections' and 'Related Content' tabs. Under 'Subsections', 'Important considerations in the critically ill' is selected. The main content area is titled 'Notes' and 'Rationale'.

**Notes**

Oral/enteral dosing based upon pharmacokinetics in the management of invasive infections in critically ill patients should be considered only as a step-down option once there is a satisfactory global improvement, e.g. radiological/serological response. [E] If the patient is no longer shocked/critically ill, use standard licensed dosing.

**Rationale**

Enteral absorption of voriconazole in critically ill patients can be erratic, with bioavailability as low as 50% suggested in some reviews.<sup>5</sup>

Suspension available.

When dosing using body-weight use ideal body-weight or adjusted body-weight rather than actual body-weight.<sup>6</sup> [E]

A feed-break is required for administration, to improve absorption.<sup>7</sup>

TDM is recommended when voriconazole is used for the treatment of invasive infections.<sup>4</sup>

When making dose adjustments, consider the non-linear kinetics of voriconazole.

## Administration

While reviewing the patient's chart, the nurse is concerned about any incompatibilities with his other medicines which include fentanyl, omeprazole and midazolam. They plan to run several drugs through a Y-site.



Delivering multiple drugs intravenously is common in this setting and introduces challenges with administration and timing. Essential compatibilities/incompatibilities are included in the drug monograph, saving time by removing the need to consult a separate resource.

**Medicines Complete** Fentanyl

**Critical Illness** Evidence grading ■

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**Important compatibilities/incompatibilities**

The following is a simplified list of compatibility considerations in critically ill patients. As such this is not an exhaustive list; please refer to the [Injectable Drugs Guide](#) for more detailed information.

Via Y-site:<sup>14</sup>

Aciclovir, amikacin, atracurium, aztreonam, bivalirudin, calcium gluconate, caspofungin, ceftazidime, cefazolin, cefotaxime, cefoxitin, ceftaroline, ceftazidime, ceftriaxone, cisatracurium, clindamycin, daptomycin, dexamethasone, dexmedetomidine, dobutamine, dopamine, doripenem, doxycycline, epinephrine, eptifibatid, esmolol, fluconazole, furosemide, gentamicin, heparin, hydrocortisone, imipenem, insulin, labetalol, levofloxacin, linezolid, lorazepam, magnesium sulfate, mannitol, methylprednisolone, metoclopramide, metronidazole, midazolam, morphine, nicardipine, nitroglycerin, nitroprusside, norepinephrine, octreotide, phenylephrine, piperacillin-tazobactam, potassium chloride, propofol, lactated ringers, sodium bicarbonate, tacrolimus, tigecycline, tobramycin, vancomycin, vasopressin, vecuronium, voriconazole

**Fentanyl is incompatible with: omeprazole [E].**

## Related content

AK's condition has stabilised and he is transferred back to the general surgical ward. The ward pharmacist reviews AK's medication chart using MedicinesComplete.

MedicinesComplete makes it easy for healthcare professionals to access essential medicines information at the point of care. Related content suggestions are provided so that users can easily move between trusted evidence-based resources including British National Formulary, Stockley's Drug Interactions and Martindale: The Complete Drug Reference.

**Medicines Complete** Fentanyl

**Critical Illness** Evidence grading ■

Publication last updated on 14-Sep-2021  
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**Fentanyl** Last Update: 03-Aug-2021

**Introduction**

Fentanyl is a synthetic opioid, used as an analgesic and a respiratory depressant in mechanically ventilated patients in critical care. Intravenous opioids are first-line agents for the treatment of non-neuropathic pain in critically ill patients.<sup>1,2</sup>

Pain management is challenging in critically ill patients as they often experience moderate to severe pain at rest and during standard care procedures<sup>1</sup>. Intubated ICU patients have complicated analgesic requirements due to medical, surgical or trauma-related conditions. A standardised approach to the assessment and management of pain in critically ill patients is vital owing to the difficulties inherent in managing this patient group, such as impaired consciousness, delirium, and communication difficulties.<sup>1</sup> Severe pain can affect the clinical status of the patient, resulting in cardiac instability, respiratory depression (a concern in non-intubated patients) and immunosuppression. Analgesic requirements can be compounded by anxiety or pre-existing depression or chronic pain syndromes. The well-validated ICU-specific pain scores Behavioral Pain Scale (BPS) and Critical Care Pain Observation Tool (CPOT) are used to evaluate pain in critically unwell sedated patients.

Pain left undetected or not effectively managed is associated with the development of chronic pain, PTSD and patients' lower health-related quality of life after their ICU stay.<sup>2</sup>

For details on general use of fentanyl, see [British National Formulary](#).



## Critical Illness

An indispensable resource to guide the most effective treatment for adult patients in intensive care. Critical Illness provides practical, evidence-based information and dosing guidance to support the complex needs of the critically ill.

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