PHARMACEUTICAL PRESS
Essential Knowledge

PATIENT CASE STUDY

Managing a patient in respiratory arrest

Guidance to support the multidisciplinary team manage a critically ill patient in respiratory arrest.

Part 1 of 2

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Supporting complex decision-making in critical care

Critical Illness

Available through

Medicines Complete

Managing a patient in respiratory arrest

Supporting complex decision-making in critical care

Abbreviations

IV	intravenous	**PO**	*per os* (by mouth)
MIC	Minimum inhibitory concentration	**RRT**	Renal replacement therapy
NG	Nasogastric tube	**SC**	Subcutaneous
PD	Pharmacodynamic	**TDM**	Therapeutic drug monitoring
PK	Pharmacokinetic		

Background

JD is a 20-year-old man who presents to the Intensive Care Unit (ICU) in respiratory arrest, after a rapid response call from the surgical ward. He was admitted to the ward six days earlier after being assaulted during an evening out with friends. His X-ray reports multiple rib fractures associated with the original injury.

Past medical history

- Alcohol intake and recreational drug use: five to six pints after work during the week most nights. Higher quantities of alcohol during the weekend, along with the recreational drug, methamphetamine.
- Smoker: 20 pack/day for approximately three years.
- Weight: 150 kg.
- Height: 170 cm (5 foot 9 inches).
- BMI: 52 kg/m^2.
- Medicines: nil of note.

Ward stay

- **Day one:** stable but in severe pain, commenced morphine patient-controlled analgesia (PCA) and paracetamol (oral).
- **Day two:** added pregabalin 75 mg PO twice daily, struggling with pain relief and difficulty mobilising.
- **Day three:** refusing to mobilise because of severe pain. Confused and aggressive.
- **Day four to five:** becoming more aggressive and unmanageable, prescribed and administered haloperidol 2.5 mg IV as required up to 4 hourly.

- **Day six:** increasingly unmanageable on ward, aggressive, and desaturating (SaO_2 88%) on supplementary oxygen, with raised temperature (38.5°C), increased respiratory rate 35 breaths per minute). A lower respiratory tract infection (LRTI) is suspected. The critical care outreach team is contacted and a decision is made to transfer JD to the ICU.

On admission to ICU (via computerised tomography (CT) scan)

- **Oxygen saturation (SaO2):** 82% on Non-Invasive Ventilation (NIV) FiO_2 0.4 (40%).
- **Arterial blood gasses:** PaO_2 7.2 kPa, $PaC0_2$ 7 kPa.
- **Arterial blood pH:** 7.29.
- **Respiratory rate:** 28-32 breaths per minute.
- **Arterial blood pressure:** 103/45 mmHg, mean arterial pressure 60 mmHg.
- **Heart rate:** 140 beats per minute.
- **CT chest:** lower respiratory tract infection (LRTI).

Laboratory results

- Sodium 135 mmol/L.
- Potassium 3.5 mmol/L.
- Creatinine 60 micromol/L.
- Haemoglobin 110 g/L.
- White blood count (WBC) 22 $x10^9$/L.
- Neutrophils 20 $x10^9$/L.
- Platelets 200 $x10^9$/L.
- Albumin 20 g/L.
- Phosphate 0.6 mmol/L.
- Magnesium 0.6 mmol/L.
- Calcium (adjusted) 2.1 mmol/L.

Medicines reconciliation on ICU admission

- Enoxaparin 40 mg SC once daily.
- Pregabalin 75 mg PO twice daily.
- Co-amoxiclav 1.2 g IV every 8 hours.
- Morphine 1 mg IV every 6 minutes, with 1 mg per hour background infusion (patient-controlled analgesia, PCA).
- Haloperidol 2.5 mg IV every 4 hours as required (4 doses in previous 24 hours).
- Paracetamol 1 g PO every 6 hours (maximum 4 g in 24 hours).

Intensive Care Unit (ICU) admission

JD was diagnosed with a severe lower respiratory tract infection (LRTI) and severe respiratory distress, and was intubated and ventilated.

After intubation, JD was reviewed by the multi-disciplinary ICU team, led by the consultant intensivist.

Medicines commenced after intubation

- Propofol up to 300 mg per hour by continuous IV infusion, to achieve Richmond Agitation Sedation Score (RASS) of -1 to -2.
- Fentanyl 30 – 250 micrograms per hour by continuous IV infusion according to pain score.
- Pantoprazole 40 mg IV once daily.
- Enoxaparin 70 mg SC every 12 hours.
- Meropenem 2 g IV once only (as a loading dose), then 2 g IV every 8 hours, by continuous infusion.

- Pabrinex IV (B vitamins, including thiamine 250 mg, and vitamin C) 2 pairs three times a day for five days.
- Paracetamol 1 g IV every 8 hours.
- Senna 15 mg PO twice daily.
- Docusate sodium 100 mg PO/NG every 8 hours.
- Chlorhexidine skin cleanser for Methicillin Resistant Staphylococcus Aureus (MRSA).
- Consideration was also given to using regional analgesia for pain relief, for rib fractures.
- Potassium and magnesium supplementation was also prescribed for electrolyte deficiencies.

Using the example of patient JD, this case study aims to breakdown the complexity of therapeutic decisions that need to be considered, often on a daily basis, to provide clinical care for a critically ill patient. This includes:

- Assessment of patient, drug, environment.
- Evaluation of available evidence base.
- Continuous evaluation of multiple factors throughout the patient's ICU stay.

All prescribing choices and decisions, including antimicrobial choice (meropenem), and thromboprophylaxis (enoxaparin), are explained in detail throughout the case. The FAST HUGS process is included as a method to give order to JD's pharmacotherapy review.

FAST HUGSBID

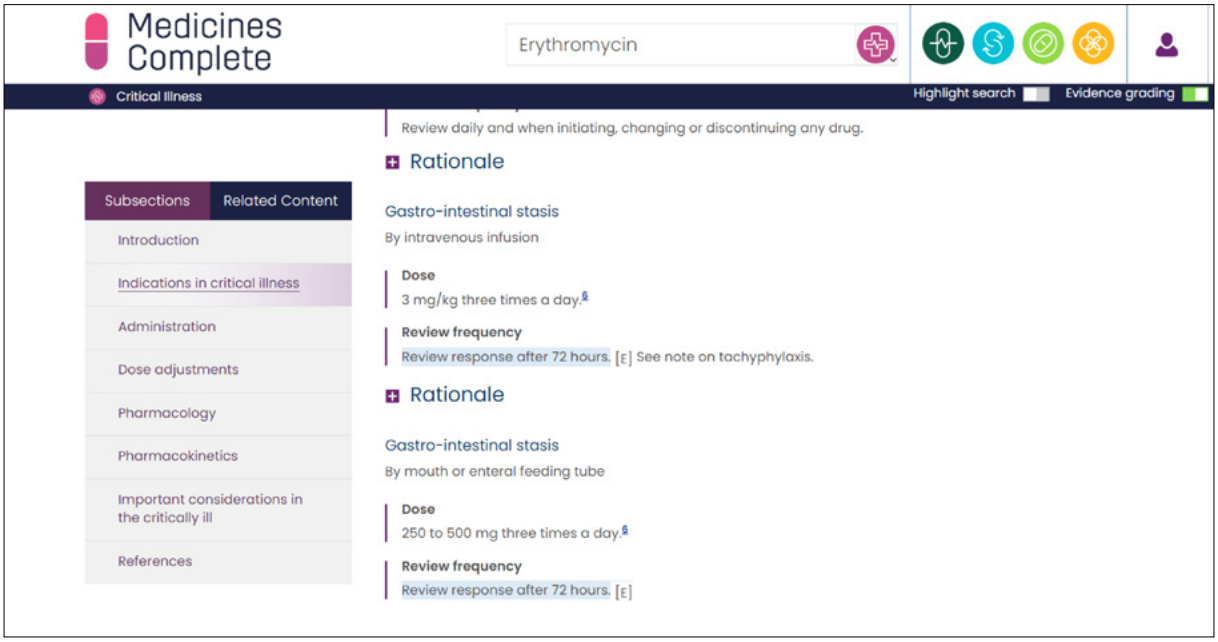
JL Vincent popularised the FAST HUGS mnemonic for critically ill patients.[1] These 'FAST-HUGS' or similar ensure consistency in the care of critically ill patients, and the idea is that the process undertaken daily for every patient. There is some variation in what the acronym stands for. Below are some suggestions:

F = FEEDING or fluids
A = ANALGESIA and/or aperients
S = SEDATION
T = THROMBOPROPHYLAXIS
H = HEAD angle of BED ELEVATED or hydration
U = ULCER PROPHYLAXIS
G = GLUCOSE CONTROL
S = SPONTANEOUS BREATHING TRIAL or sugar

There are now several versions of this mnemonic in use, including extensions such as FAST HUGS BID, where the BID stand for Bowels, Indwelling catheter, and Delirium.[2] An ICU pharmacist version known as FASTHUG-MAIDENS was designed to support pharmacists working in ICU.[3] Published in Canadian Journal of Hospital Pharmacy in 2011, it adds Medication reconciliation, Antimicrobials, Indications, Drug dosing, Electrolytes, haematology and other laboratory results, No drug interactions, allergies, duplications or side effects, and Stop dates to the FASTHUG mnemonic.

SECTION 1: FEEDING

Patients should ideally be fed by the enteral route and as early as feasible. Enteral feeding improves intestinal blood flow and maintains the gut mucosal barrier. High gastric aspirates, along with vomiting, constipation, abdominal distension, or diarrhoea can be the result of an intolerance to enteral feeding or paralytic ileus. This can be a result of the pathophysiological process of critical illness (e.g. cardiogenic shock) and/or medication (including vasopressors, opioid analgesics and alpha-2 agonists). Patients intubated and sedated can require concomitant prokinetics, typically metoclopramide and/or erythromycin to reduce gastroparesis and laxatives or aperients to minimise constipation.



The ICU multi-disciplinary team elected to prescribe and administer erythromycin as a prokinetic. For JD a weight-based erythromycin dose of 3 mg per kg is 450 mg IV. This is a high dose and would place him at greater risk of adverse effects including QTc prolongation and drug-drug interactions. In clinical practice, an erythromycin dose of 250 mg IV would be sufficient.

SECTION 2: ANALGESIA/PAIN CONTROL

JD has multiple rib fractures, his management on the ward was suboptimal. His poor pain management meant that he was not comfortable to mobilise or take full breaths, resulting in his severe LRTI and ICU admission; JD's morbid obesity will also have hampered mobility. The majority of acute hospital trusts that have an emergency department (ED) will have a trauma pathway, with the option to provide multimodal analgesia techniques, including spinal epidural and thoracic-lumbar blocks for this type of admission.

The management of JD's pain control during his ICU stay will be critical to facilitate recovery and to enable weaning from the ventilator and early mobilisation. Alongside acute pain from his multiple rib fractures, he will experience pain at rest from his endotracheal tube and during early mobilisation.[4] Experiencing pain while sedated in ICU can lead to long term psychological consequences including poor sleep and the development of chronic pain and post-traumatic stress syndrome (PTSD).[5,6]

While JD remains sedated, he is unable to self-report pain. The Society of Critical Care Medicine (SCCM) recommend maintaining a light level of sedation, which can improve the detection and management of pain.[5,7] Pain in sedated critically ill patients should be assessed using a validated tool; for example, critical care pain observation tool (CPOT) or behavioural pain scale (BPS) for monitoring pain in medical, postoperative, or trauma patients (excluding brain injury) unable to communicate.[5,7]

Practice point

Use a validated pain scale to assess pain in an intubated patient

Behavioural pain scale[8]

Table 1. Behavioral pain scale

Item	Description	Score
Facial expression	Relaxed	1
	Partially tightened (e.g., brow lowering)	2
	Fully tightened (e.g., eyelid closing)	3
	Grimacing	4
Upper limbs	No movement	1
	Partially bent	2
	Fully bent with finger flexion	3
	Permanently retracted	4
Compliance with ventilation	Tolerating movement	1
	Coughing but tolerating ventilation for most of the time	2
	Fighting ventilator	3
	Unable to control ventilation	4

Critical care pain observation tool[9]

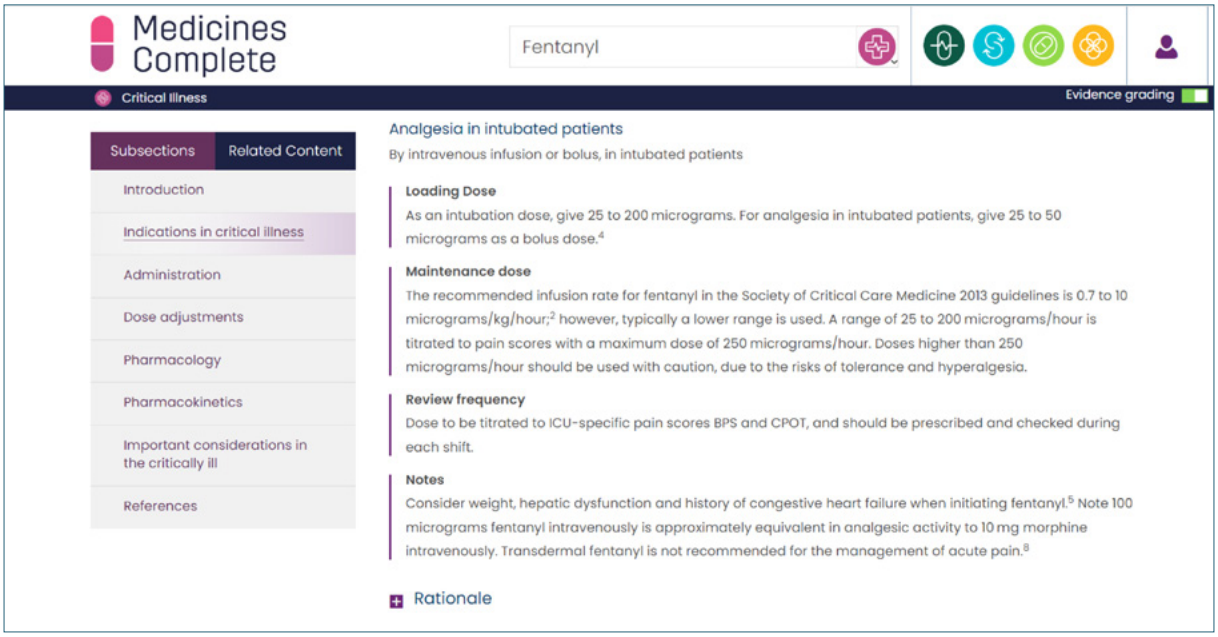
Table 1 Description of the Critical-Care Pain Observation Tool

Indicator	Description	Score	
Facial expression	No muscular tension observed	Relaxed, neutral	0
	Presence of frowning, brow lowering, orbit tightening, and levator contraction	Tense	1
	All of the above facial movements plus eyelid tightly closed	Grimacing	2
Body movements	Does not move at all (does not necessarily mean absence of pain)	Absence of movements	0
	Slow, cautious movements, touching or rubbing the pain site, seeking attention through movements	Protection	1
	Pulling tube, attempting to sit up, moving limbs/ thrashing, not following commands, striking at staff, trying to climb out of bed	Restlessness	2
Muscle tension Evaluation by passive flexion and extension of upper extremities	No resistance to passive movements	Relaxed	0
	Resistance to passive movements	Tense, rigid	1
	Strong resistance to passive movements, inability to complete them	Very tense or rigid	2
Compliance with the ventilator (intubated patients)	Alarms not activated, easy ventilation	Tolerating ventilator or movement	0
	Alarms stop spontaneously	Coughing but tolerating	1
OR	Asynchrony: blocking ventilation, alarms frequently activated	Fighting ventilator	2
Vocalization (extubated patients)	Talking in normal tone or no sound	Talking in normal tone or no sound	0
	Sighing, moaning	Sighing, moaning	1
	Crying out, sobbing	Crying out, sobbing	2
Total, range			0-8

Opioids and paracetamol remain the mainstay of pain management in ICU, and the Society of Critical Care Medicine (SCCM) guidelines recommend using the lowest effective opioid dose to avoid the incidence of adverse effects. Overuse of opioids in this population can contribute to prolonged sedation, mechanical ventilation, and a prolonged ICU admission. High cumulative doses of opioids rapidly cause tolerance, driving dose escalation, and can lead to iatrogenic withdrawal and dependence.[10,11,12] High doses of strong opioids have also been associated with hyperalgesia and chronic neuropathic pain.[11,13] Opioids additionally increase the incidence of delirium; this risk is dose dependent. The association between opioid risk and delirium was stronger in surgical patients than in medical patients.[14,15] This can contribute to delayed long term recovery.[4,16]

The choice of opioid will depend on the patient's clinical scenario along with the unit practice or policy, and clinical pharmacist or consultant intensivist preference. The most commonly used agents are fentanyl, alfentanil, morphine, or remifentanil.[17] Newer agents include oxycodone. Refer to Critical Illness through MedicinesComplete for comprehensive drug information and dosing guidance including dose adjustments in extremes of body-weight, organ dysfunction, hemofiltration, sustained low efficiency dialysis (SLED), and extra-corporeal membrane oxygenation (ECMO).

The ICU multi-disciplinary team has elected to prescribe and administer a fentanyl infusion as the background opioid.



Fentanyl appears to be a good choice from a pharmacokinetic perspective with a rapid onset of action however, it has a context sensitive half-life. This means, when prescribed as a continuous infusion, fentanyl can accumulate in adipose tissue when infusions are used for a prolonged period.[18] This is particularly likely to occur in patients with hepatic dysfunction, reduced cardiac output, and hypothermia where distribution can take hours to days.[19] Bolus doses are rapidly cleared, although they are very short acting and can result in severe rebound pain and distress. Transdermal fentanyl should be avoided for pain control in critically ill patients, as they are more suited to chronic pain control with less variation in dosing than in ICU. Further, transdermal absorption can be unpredictable in critical illness.

Opioid titration in critical illness

JD's poor pain management has contributed to his deterioration on the ward and resulting ICU admission. It takes 4 to 5 elimination half-lives to reach steady state; an effective strategy is to give bolus doses alongside the opioid infusions to control initial pain.[20,21,22] Constantly increasing infusion doses can result in accumulation of parent drug and metabolites.[20,23] Emphasis should be placed on regular pain assessment and administration of IV bolus doses (if feasible), rather than increasing infusion rates during procedures predicted to be painful. This minimises the risk of accumulation and excessive exposure to strong opioids. Bolus dosing however is challenging in patients who are haemodynamically compromised which can be common in critical illness.

The fentanyl infusion is continued for the management of JD's analgesia, with close monitoring of his pain score.

The use of a multimodal analgesic approach using non-opioid agents is recommended in severe pain, as this approach can modulate the pain response and reduce opioid requirements.[5,7,24]

Consideration should be given to commencing an alternative analgesic alongside the opioid infusion. Options include local anaesthetic blocks, epidurals, and in some instances ketamine. Using an opioid infusion as the sole analgesic could result in JD remaining on the ventilator for longer and place him at greater risk of iatrogenic withdrawal syndrome. In ICU, there is a continuous plan to wean from the ventilator with a plan to extubate. Paracetamol is an effective adjuvant and in short term may need to be given intravenously to ensure effective levels for pain control in critical illness.[25]

Pain control should be a daily dynamic process in critical illness and is an important aspect of the daily ICU management plan. Rib fractures can be painful for a long period of time; non-neural blocks can be safely performed in ICU and can be effective in rib fractures.[11] These blocks can be managed in general ward areas, although this very much depends on institutional preference and policy.

Practice point

Nonopioid analgesics may decrease the amount of opioid administered (or eliminate the need for IV opioids altogether). Their use also decreases opioid-related side effects including reduction of gastric motility and euphoria.

How to wean opoid agents will be covered in Part 2 of the patient case study - coming soon.

SECTION 3: SEDATION

Sedating JD while he is intubated and ventilated supports mechanical ventilation optimisation, reduces distress, anxiolysis, and somnolence. The 2013 Pain, Agitation/Sedation, Delirium, Immobility, and Sleep disruption (PADIS) guidelines recommend that sedation is titrated to a Richmond agitation sedation scale (RASS) of 0 to -2. A RASS in this range means that JD is lightly sedated and should be able to keep his eyes open for approximately 10 seconds on arousal. Lighter sedation reduces overall exposure to sedative agents and is reported to reduce ICU length of stay. The SCCM recommend maintaining light levels of sedation along with lung protective mechanical ventilation strategies and compliance with ABCDEF bundle protocols.[7,26,27,28]

The two tools validated for measuring the quality and depth of sedation in adult ICU patients are the Richmond agitation sedation scale (RASS) and the sedation agitation scale (SAS).[5] Of the two validated tools, the RASS is the most commonly used.[17]

The Richmond Agitation Sedation Score (RASS)[29]

Table 1. The Richmond Agitation-Sedation Scale (RASS)

Score	Term	Description	
+4	Combative	Overtly combative, violent, immediate danger to staff	
+3	Very agitated	Pulls or removes tube(s) or catheter(s); aggressive	
+2	Agitated	Frequent nonpurposeful movement, fights ventilator	
+1	Restless	Anxious but movements not aggressive or vigorous	
0	Alert and calm		
−1	Drowsy	Not fully alert, but has sustained awakening (eye opening/eye contact) to voice (>10 seconds)	Verbal stimulation
−2	Light sedation	Briefly awakens with eye contact to voice (<10 seconds)	
−3	Moderate sedation	Movement or eye opening to voice (but no eye contact)	
−4	Deep sedation	No response to voice, but movement or eye opening to physical stimulation	Physical stimulation
−5	Unarousable	No response to voice or physical stimulation	

Procedure for RASS Assessment

1. Observe patient
   - Patient is alert, restless, or agitated. — Score 0 to +4
2. If not alert, state patient's name and say to open eyes and look at speaker.
   - Patient awakens with sustained eye opening and eye contact. — Score −1
   - Patient awakens with eye opening and eye contact, but not sustained. — Score −2
   - Patient has any movement in response to voice but no eye contact. — Score −3
3. When no response to verbal stimulation, physically stimulate patient by shaking shoulder and/or rubbing sternum.
   - Patient has any movement to physical stimulation. — Score −4
   - Patient has no response to any stimulation. — Score −5

Adapted with permission.[29]

ABCDEF Bundle of Care[30]

A: Assess, prevent and manage pain
B: Both spontaneous awakening trials (SAT) and spontaneous breathing trials (SBT)
C: Choice of sedation and analgesia
D: Delirium
E: Early mobility and exercise
F: Family engagement and empowerment

Practice point

Use a validated tool to assess sedation depth.

Practice point

Lighter sedation depth is generally associated with better clinical outcome, although the relationship is inconsistent.[31]

Which drug to choose?

It's easy to overlook the importance of the choice of sedative agent, the dose used, and monitoring requirements. Propofol or alpha-2 adrenoceptor agonists are the preferred sedative agents over benzodiazepines in critically ill, mechanically ventilated adults,[7] although many ICUs still use benzodiazepines as part of their sedative policy.[17]

Propofol is a short acting intravenous gamma-amino-butyric acid (GABA) agonist. It is the drug of choice for sedated and ventilated patients and its rapid onset and offset make it easily titratable.

Propofol infusion syndrome (PRIS) can result in hyperkalaemia, metabolic acidosis, and raised creatine kinase (CK), and can be fatal. PRIS has also been associated with doses higher than 4 mg per kg per hour and longer propofol infusion duration.[32]

JD is morbidly obese; he weighs 150 kg and 170 cm tall with a BMI of 52 kg/m^2.

Is the recommended maximum dose for JD 150 kg x 4 mg/kg/hour = 600 mg/hour?

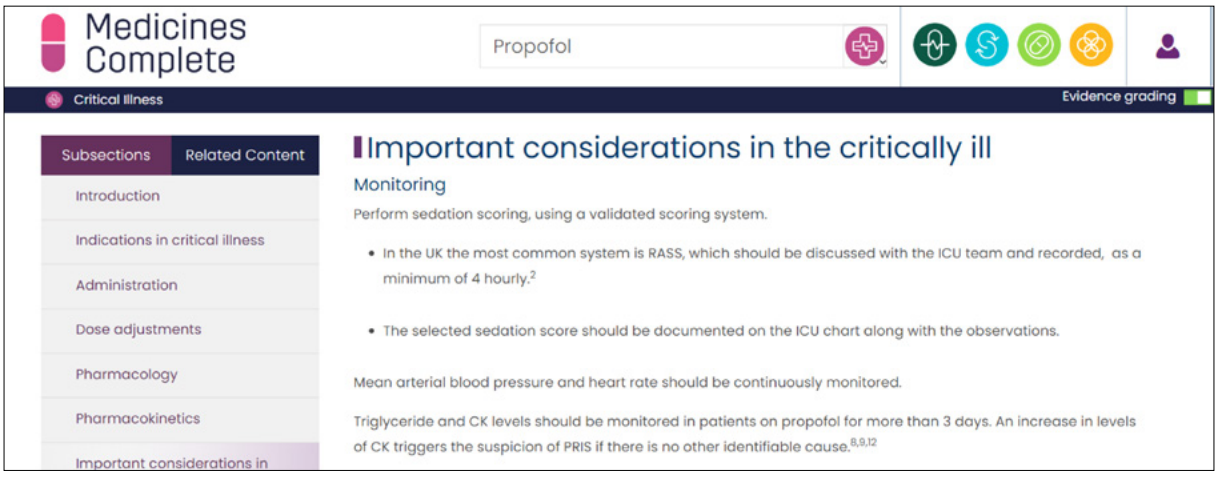
Critical illness provides dose adjustments, including for extremes of body-weight, and recommends:

Using ideal body-weight (66 kg) the maximum dose would be 264 mg/hour
Using adjusted body-weight (99 kg) the maximum dose would be 400 mg/hour

Both of these doses are on the high side. The dose of 400 mg IV per hour is very high and would result in hypotension, bradycardia, and increased serum triglycerides. Doses as high as 400 mg IV per hour are very rarely seen in critical care clinical practice. In a patient like JD, adding a small dose of a second sedative agent may be necessary (e.g. midazolam) to achieve the desired RASS of 0 to -2.

For JD the **ideal body weight dose** of **propofol** of 264 mg IV per hour should be used to protect JD from unnecessary harm, although JD may still need a second agent should he become bradycardic and/or hypotensive.

If JD required intubation and sedation with propofol for longer than three days, serum triglycerides and creatine kinase (CK) should be monitored. An increasing CK could suggest the early development of PRIS, but should be interpreted in the context of the patient's clinical status.[32,33]



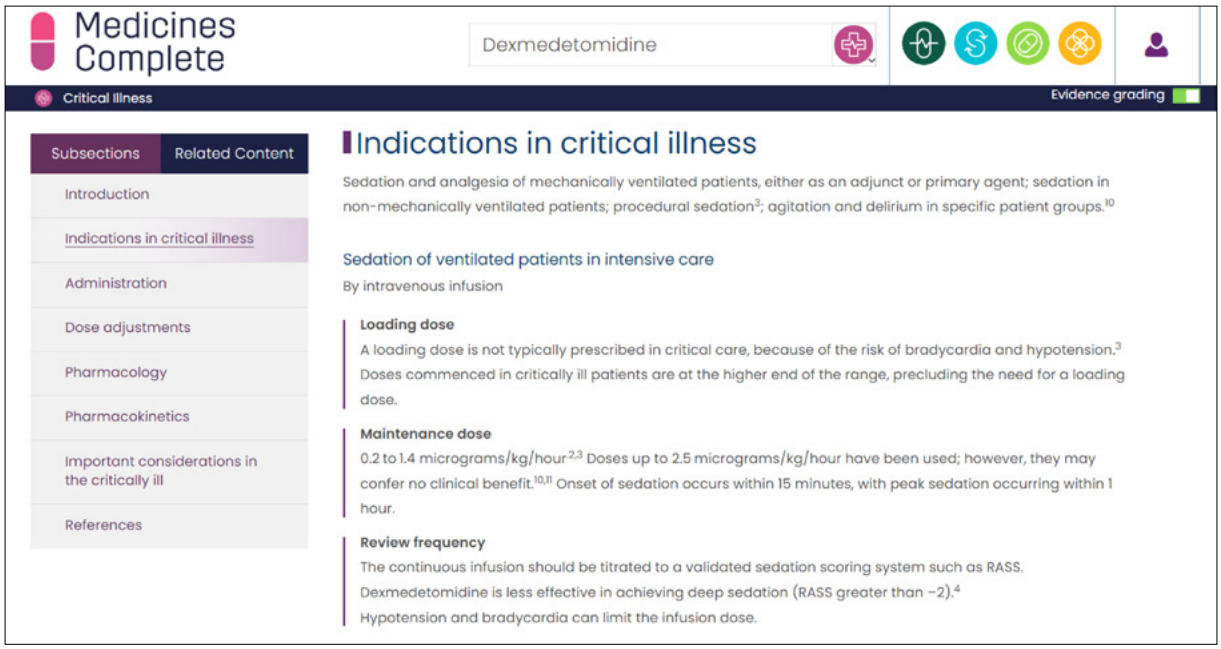
Another option for JD is **dexmedetomidine**. Dexmedetomidine has the advantage of providing additional analgesia and anxiolysis with minimum respiratory depression. However, findings from the Sedation Practice in Intensive Care Evaluation (SPICE) (III) study reported a higher mortality in patients <65 years old who received dexmedetomidine early in their ICU stay.[34] A secondary analysis of the SPICE III study was published in 2021 which reported that the higher mortality was particularly

found in non-surgical patients with a higher severity of illness. Given that JD is a non-surgical ICU admission and is severely unwell, the dosing of dexmedetomidine will be challenging because of JD's high BMI. It's sensible to avoid dexmedetomidine in the short term and reconsider later, when hopefully JD will be less severely unwell.[34]

Dexmedetomide will be covered in Part 2 of the patient case study - coming soon.

JD requires additional pain control analgesia and is at risk of developing delirium due to predisposing factors including alcohol and recreational drug use, in combination with precipitating factors including sepsis and severe pain.[35] In these circumstances, the addition of dexmedetomidine to his sedation and analgesic regimen could be of benefit, although, as described earlier it must be weighed up against the risks. Dexmedetomidine can be helpful in preventing ICU delirium and in pain management. However, its effect is not consistently predictable.[33,36,37]

Delirium will be covered in Part 2 of the patient case study - coming soon.



Benzodiazepines are no longer recommended for routine use in sedating critically ill patients, although they are still used regularly in ICU, especially during the Covid 19 pandemic.[38,39] Use of benzodiazepines are associated with longer ICU length of stay and a higher incidence of delirium. A combination of propofol and benzodiazepine may still be required for deep sedation (RASS < -2), however it is unlikely that JD would require deep sedation. JD may need a small dose of midazolam to reduce his propofol dose, plus JD has a history of alcohol dependence and therefore an indication for a small dose of benzodiazepine. Unfortunately, sedation practices in critical care changed during the COVID-19 pandemic, where many patients required deep sedation to allow ventilator synchrony, to tolerate prone positioning and because of shortage of nursing staff. This has resulted in an increase in the incidence of delirium that persists for several days. Benzodiazepine use and lack of family visitation were identified as modifiable risk factors.[39]

Practice point

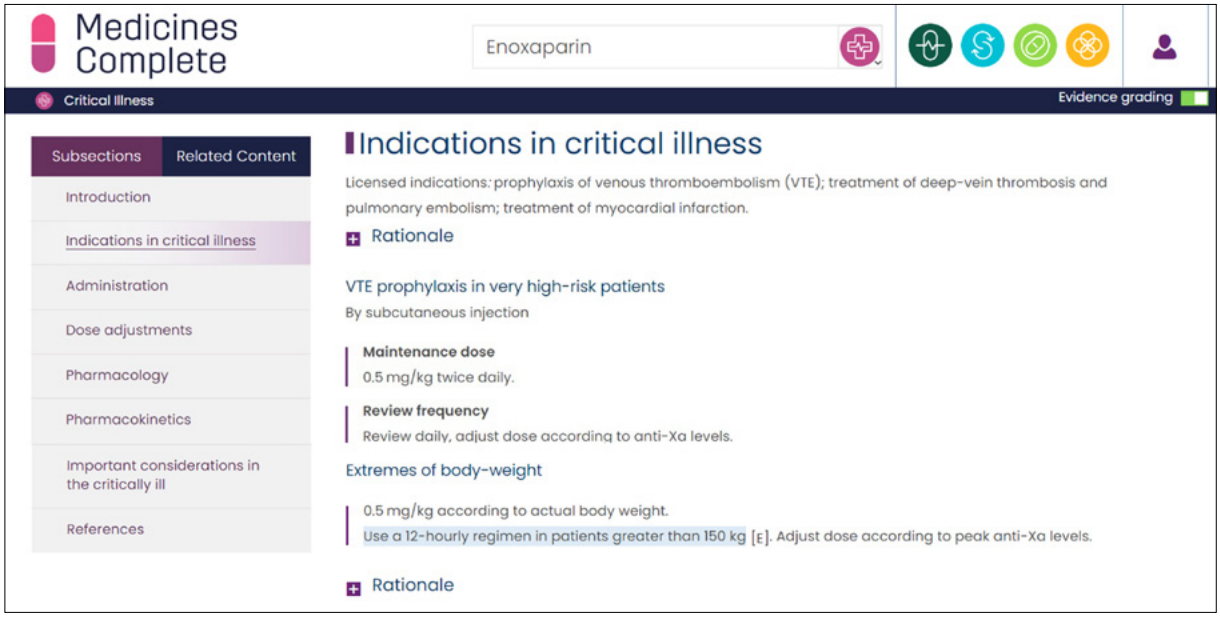
SCCM guidelines suggest that non benzodiazepine sedatives (either propofol or dexmedetomidine) are preferable to benzodiazepine sedatives in critically ill ventilated adults.[5,7]

Thiamine and Alcohol Withdrawal/Dependence

Thiamine depletion is common in alcohol dependence. This is because in addition to poor nutrition and oral absorption, alcohol prevents the phosphorylation of thiamine to its active form, thiamine di-phosphate (TDP). Thiamine is an essential cofactor in for a number of enzymes systems in the brain including, transketolase, alphaketoglutarate and pyruvate dehydrogenase.[40] Typically, in the UK, thiamine is administered as Pabrinex (B vitamins, including thiamine 250 mg, with ascorbic acid (vitamin C)).

SECTION 4: THROMBOPROPHYLAXIS

JD is at a very high risk for venous thromboembolism due to his weight of 150 kg, BMI of 52kg/m^2 and immobility. Low molecular weight heparin (LMWH) is recommended over unfractionated heparin (UH) for thromboprophylaxis in critically ill patients.[41]



JD is prescribed enoxaparin 70 mg SC twice daily (actual dose is 75 mg SC twice daily but rounded down for ease of administration).

Practice point

Twice daily enoxaparin in patients ≥ 150 kg or BMI ≥ 40 kg/m^2. Monitor Anti-Xa levels.

SECTION 5: HEAD ANGLE OF BED ELEVATED or HYDRATION

Maintaining the head above the bed at 30 degrees has been shown to reduce ventilator associated pneumonia.[42]

Fluid replacement is vitally important in sepsis and septic shock. The surviving sepsis guidelines 2021 recommend[43]:

For patients with sepsis-induced hypoperfusion or septic shock, we suggest that at least 30 mL/kg of IV crystalloid fluid be given within the first 3 hours of resuscitation.

Quality of evidence: Low

For JD this would result in 4500 mL, which would be excessive. In clinical practice a moderated initial fluid resuscitation would take place, of say 2500 to 3000 mL over 3 hours (or less). Although the volume and rate of replacement is patient dependent.

SECTION 6: ULCER PROPHYLAXIS (Stress ulcer prophylaxis (SUP))

Gastric acid suppression may be recommended for many patient groups in intensive care. The Stress Ulcer Prophylaxis in the Intensive Care Unit (SUP-ICU) trial of pantoprazole versus placebo in critically ill patients with one risk factor for gastrointestinal (GI) bleeding raised discussion about the widespread use of stress ulcer prophylaxis in this population. Recommendations from this trial were:

"On average, 4% of critically ill patients develop gastrointestinal bleeding. One cause is physiologic stress leading to stress ulcers in the oesophagus, stomach, or duodenum, but critical illness is also associated with other forms of upper gastrointestinal bleeding".[44]

1. Use acid suppression prophylaxis for people with higher risk of gastrointestinal bleeding (4% or higher).

Suggested bleeding risk categorisation (adapted from Ye, 2020.)	
Highest Risk 8 – 10%	Mechanical ventilation without enteral nutrition Chronic liver disease
High Risk 4 – 8%	Concerning coagulopathy 2 or more factors from the 2 – 4% category
Threshold for offering prophylaxis *for patients near the threshold individual values and preferences must be considered	
Moderate Risk 2 – 4%	Mechanical ventilation with enteral nutrition Acute kidney injury Sepsis Shock
Low Risk	Critically ill patients without any risk factors Acute hepatic failure Use of steroids or immunosuppression Use of anticoagulants Cancer Male

2. Where prophylaxis is recommended; a proton pump inhibitor (PPI) can be used either enterally or parenterally. A histamine-2 receptor antagonist is also a reasonable choice, although ranitidine is no longer available. Sucralfate is not a recommended option because of its aluminium content, and because of reports of bezoar formation, which can impede both enteral feeding and drug administration via the enteral route.[45]

Is there a risk of pneumonia with SUP?

The SUP trial indicates that there may not be a difference in the risk of pneumonia between the PPI and the placebo groups.[46] A meta-analysis performed by Huang *et al*. suggest that in critically ill patients receiving enteral feeding, SUP is not beneficial, and the risk of pneumonia may be increased.[47]

Practice point

Standard practice is to discontinue stress ulcer prophylaxis once enteral feeding has been established, except in higher-risk groups (see table above).

JD is mechanically ventilated and therefore in the moderate risk category; it would be reasonable to start a PPI but discontinue it once he is established on enteral feeds.

SECTION 7: GLUCOSE CONTROL

Intensive care related dysglycaemia or reduced glucose stability (hyper- and hypo-glycaemia) has been reported to increase ICU mortality.[48] No benefit is reported from intensive glucose control as recommended by Leuven trial published in 2001.[49] The NICE-SUGAR trial demonstrated an increase in mortality and severe hypoglycaemia associated with blood glucose level of 4.6-6 mmol/L.[50]

The management of glucose control in critically ill patients requires standardisation, and blood glucose levels should be closely monitored, and even moderate hypoglycaemia should be avoided. Treatment with insulin should be commenced if the blood glucose continuously exceeds 10 mmol/L.[51,52]

Practice point

Practice Point: Commence insulin therapy if the blood glucose continuously exceeds 10mmol/L. Avoid hypoglycaemia (blood glucose <5 mmol/L).

SECTION 8: SPONTANEOUS BREATHING TRIAL

Spontaneous breathing trials are techniques used to identify patients who are either likely or unlikely to be successfully liberated from mechanical ventilation. The team will manage JD's sedation and analgesia to allow spontaneous breathing trials to be performed.

SECTION 9: BOWEL CARE AND GASTROINTESTINAL MOTILITY

Constipation is associated with multiple adverse outcomes in critical care, including an increase in mortality and morbidity. Immobility, hypotension, vasopressors, and use of opioid drugs have all been identified as risk factors.

Early introduction of aperients or laxatives is standard practice in ICU. A combination of stimulant (e.g. senna) and softener (e.g. sodium docusate) is routinely prescribed.[43]

SECTION 10: ANTIMICROBIALS

JD was diagnosed with severe LRTI and after a multidisciplinary discussion led by the consultant microbiologist, JD is prescribed and administered a loading dose of meropenem, ideally within the first hour followed by empirical treatment. Meropenem is not typically used as first line antimicrobial therapy in the ICU. However, JD required an antimicrobial agent with dosing strategies in obesity and coverage of resistant Gram-negative organisms.

The majority of ICU's have an antimicrobial policy devised by microbiology, pharmacy, and critical care as a team.

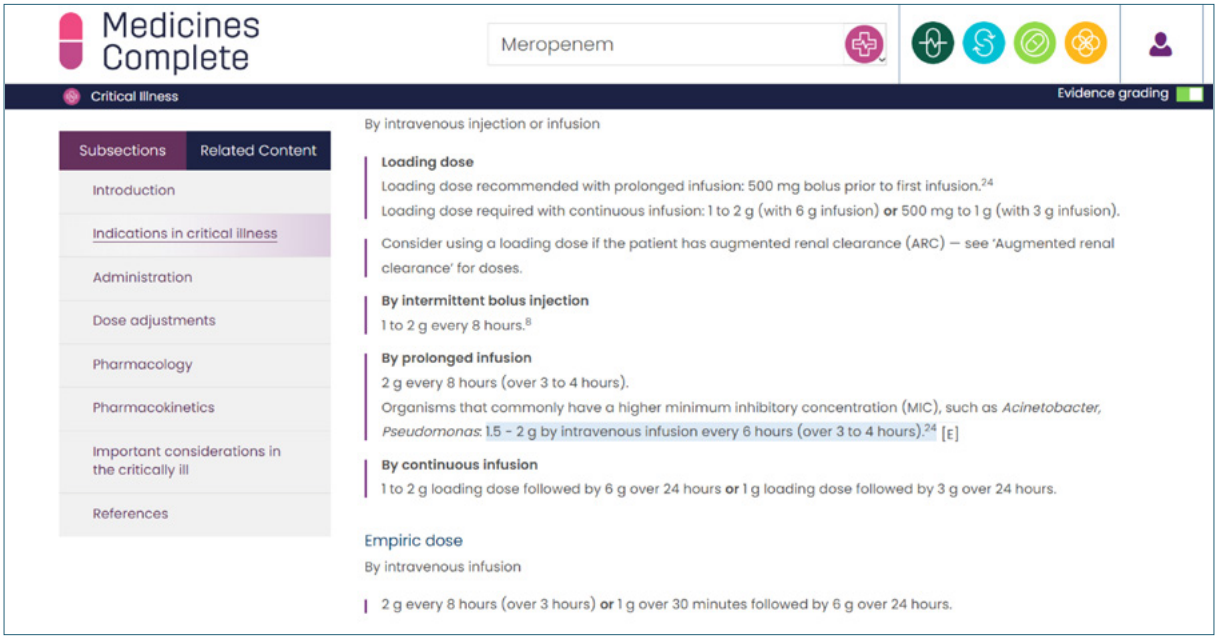
Meropenem is a carbapenem antibiotic important for treatment of serious infections in critically unwell patients. In the ICU patients have variable pharmacokinetics, with contributing factors such as organ function and clinical condition variation, and an increased likelihood of infection with resistant bacteria, especially resistant Gram-negative bacteria. Large inter-patient variability in meropenem concentrations after standard doses in critically ill patients have led to inadequate concentrations in critically ill patients.[53,54,55]

The PK/PD index associated with optimal beta-lactam activity is 40 – 70% fT>MIC. The Defining Antimicrobials Levels in Intensive Care Units (DALI) study demonstrated an association between a favourable clinical outcome and 100% fT>MIC in critically ill patients. Approximately 20% of the DALI cohort failed to achieve even the most conservative PK/PD target (50% fT>MIC) with standard beta-lactam dosing, and 32% of these were more likely to demonstrate negative outcomes.[55]

Individualised dosing strategies should be employed, where feasible, to ensure optimal outcomes.[43,56,57] Avoid using a one dose fits all strategy to avoid clinical failure, emergence of antimicrobial resistance, and drug toxicity. As reported in DALI, many patients fall below even conservative PK/PD targets. Dosing accuracy will be optimised when patients' physiology (fluid status, albumin), organ function, and presence of extracorporeal circuits (RRT) are considered alongside the pathogen susceptibility (MIC).[58] Strategies to improve attainment of target levels include increasing the dose and dose interval, individualising the dose, or the use of prolonged or continuous infusions. Tools such as the MeroRisk can be used to identify patients at risk of underdosing and to guide dosing.[33,54,59]

JD is to start meropenem. Consider the following to ensure an appropriate dose:

1. Micro-organism and severity of illness



The loading dose is ideally given within the first hour of presentation.[43,60]

Two sets of blood cultures should be taken before antimicrobial administration.[33,61] Once bacteria have been identified and reported, the dose can be adjusted according to the MIC required.

2. Renal function and presence of augmented renal clearance

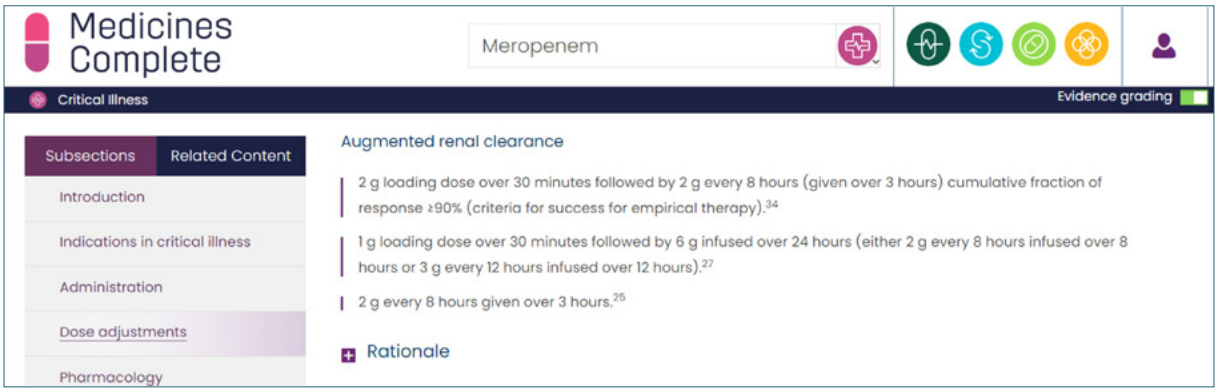
Renal function

Renal function has been reported as a major contributing cause of variability in meropenem exposure,[53,54,62,63,64,65] and effects PK/PD targets or the ability to attain (100% fT>MIC).[54,58,64]

Augmented renal clearance

> "Augmented renal clearance (ARC) is a phenomenon in critically ill patients characterized by increased creatinine clearance and elimination of renally eliminated medications. Patients with severe neurologic injury, sepsis, septic shock, trauma, and burns have been consistently identified as at risk of ARC, with mean creatinine clearances ranging from 170 mL/minute to more than 300 mL/minute".[66] There are also reports of ARC in Covid-19 infections.[67]

Patients with augmented renal clearance are unlikely to achieve the desired pharmacokinetic/pharmacodynamic target at a meropenem dose of 1 g every 8 hours and are therefore at risk of treatment failure without dose up-titration.[68] Critical illness advises a 2 g loading dose of meropenem followed by 2 g every 8 hours (given by prolonged infusion over 3 hours), or a 1 g loading dose followed by 6 g infused over 24 hours.



JD has augmented renal clearance (>130 mL/minute/1.73m^2) and therefore the meropenem dose is adjusted to 2 g IV every 8 hours. As meropenem is not stable for 24 hours, this will need to be administered as 2 g in 50 – 100 mL sodium chloride 0.9% over 8 hours.

3. Obesity

The challenge currently in the ICU is the extent of patients with a very high BMI (in excess of 50 kg/m^2) in the UK and US where antimicrobial dosing has to be optimised, and on a daily basis.[69]

Body mass index has a modest effect on PK/PD parameters of meropenem; Alobaid *et al.* demonstrated that 2 g every 8 hours, as a prolonged infusion, covered 90% of *P. aeruginosa* and susceptible *A. baumanii*.[65] This dose did not achieve coverage in obese and morbidly obese patients when the creatinine clearance was greater than 150 mL/minute/1.73m^2. They concluded that dose adjustment is not necessary if target MIC < 2 mg/L (unless enhanced renal function), but if MIC is unknown and *A. baumannii* or *Pseudomonas* is targeted, then higher doses or prolonged infusions should be used.

JD is obese with a BMI of 52 kg/m^2; a meropenem dose of 2 g IV every 8 hours has been recommended due to his ARC, no further dose adjustments are required.

4. Prolonged infusions versus intermittent bolus

In the study by Alobaid *et al.*, the use of a 3-hour infusion improved the PK/PD target in obese and morbidly obese patients.[65] The approach of using higher meropenem doses of 2 g IV every 8 hours over 3 – 4 hours in patients with life threatening infections has been confirmed by other studies.[62,63,64,70,71,72,73,74]

CNS penetration of meropenem is poor; Lu and colleagues recommend 2 g IV every 8 hours given over 4 hours for patients with meningitis.[75] Feher *et al.* found a 4-hour infusion had better clinical outcomes for the treatment of febrile neutropenia than an intermittent bolus.[76] Monitor for toxicity including seizures.

Practice point

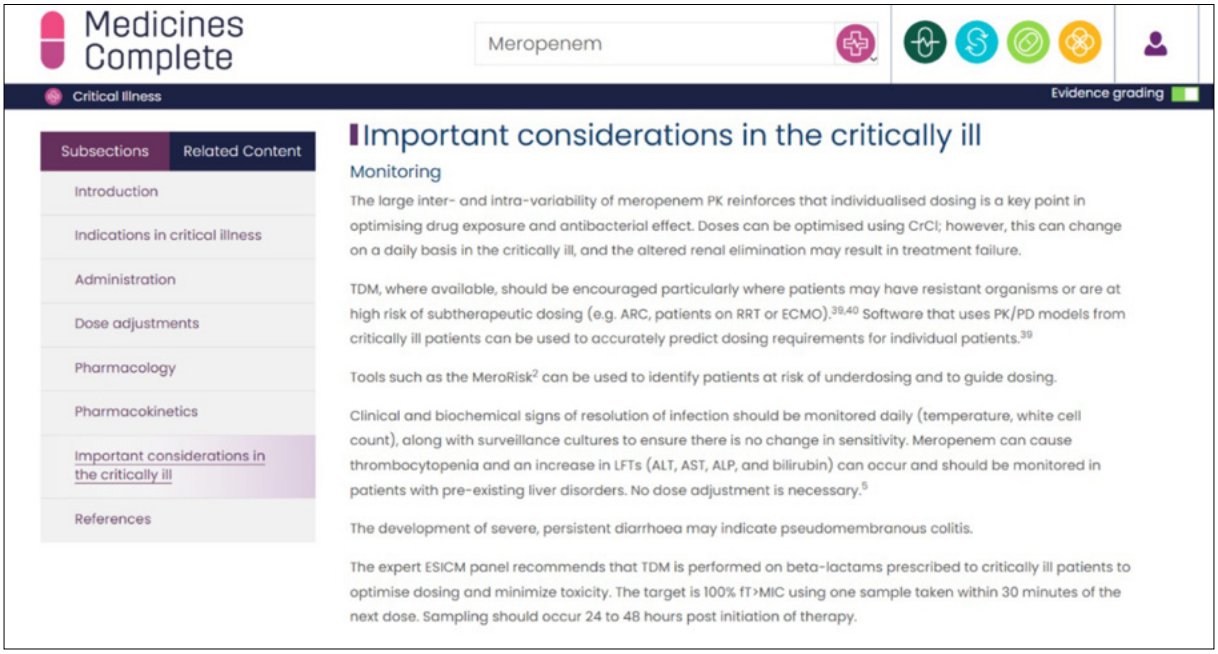
Current guidelines suggest that prolonged infusions could improve the PK/PD target in critically ill patients.[43]

Practice point

Critical Illness through MedicinesComplete supports dynamic prescribing practices; doses may need to be adjusted daily.

5. Monitoring

JD is morbidly obese and has augmented renal clearance (ARC); close attention should be paid to his clinical response to meropenem. TDM is a valuable tool, enabling optimisation of his dose supports therapeutic success.



There is a paucity of TDM services for critical care.

An initial loading dose followed by continuous or extended infusion maximises PK/PD target attainment and is likely to improve clinical outcomes in critically ill patients.[77]

Practice point

Use TDM to optimise doses of beta-lactams in critically ill patients if it is available.

As already outlined, the recommended dose of meropenem for JD is 2 g every 8 hours as a prolonged infusion over 3 – 4 hours. Monitoring of beta-lactam serum levels is recommended, however this is not available in many institutions.

References

1. Vincent JL. Give your patient a fast hug (at least) once a day. Crit Care Med. 2005; 33(6): 1225-1229.
2. Vincent WR 3rd, Hatton KW. Critically ill patients need "FAST HUGS BID" (an updated mnemonic). Crit Care Med. 2009; 37(7) :2326-2327; Author reply 2327.
3. Mabasa VH et al. A standardized, structured approach to identifying drug-related problems in the intensive care unit: FASTHUG-MAIDENS. Can J Hosp Pharm. 2011; 64(5) :366-369.
4. Payen JF et al. Current practices in sedation and analgesia for mechanically ventilated critically ill patients: a prospective multicenter patient-based study. Anesthesiology. 2007; 106(4): 687-892.
5. Barr J et al. Clinical practice guidelines for the management of pain, agitation, and delirium in adult patients in the intensive care unit. Crit Care Med 2013; 41: 263.
6. Kemp HI et al. Chronic pain in critical care survivors: A narrative review. Br J Anaesth. 2019; 123(2): e372-e384.
7. Devlin JW, et al. Clinical practice guidelines for the prevention and management of pain, agitation/sedation, delirium, immobility, and sleep disruption in adult patients in the ICU. Crit Care Med. 2018; 46(9): e825-e873.
8. Payden J-F et al. Assessing pain in critically ill sedated patients by using abehavioral pain scale. Crit Care Med 2001; 29(12): 2258-2263.
9. Gélinas C et al. Validation of the critical-care pain observation tool in adult patients. Am J Crit Care. 2006; 15(4): 420-427.
10. Wang PP et al. Opioid-associated iatrogenic withdrawal in critically ill adult patients: A multicenter prospective observational study. Ann Intensive Care. 2017; 7(1): 88.
11. Martyn J et al. Opioid tolerance in critical illness. N Engl J Med. 2019; 380(4): 365–378.
12. Cammarano WB et al. Acute withdrawal syndrome related to the administration of analgesic and sedative medications in adult intensive care unit patients. 1998; 26(4): 676–684.
13. Lee M et al. A comprehensive review of opioid-induced hyperalgesia. Pain Physician. 2011; 14(2): 145-161.
14. Duprey MS et al. Opioid use increases the risk of delirium in critically ill adults independently of pain. Am J Respir Crit Care Med. 2021. 204(5): 566-572.
15. Murray BP, Newsome AS. Opioids for sedation: Has the pendulum swung too far? Am J Respir Crit Care Med. 2021; 204(5): 611.
16. Erstad BL. Implications of the opioid epidemic for critical care practice. J Am Coll Clin Pharm. 2019; 2: 161-166.
17. Yassin SM et al. A web-based survey of United Kingdom sedation practice in the intensive care unit. J Crit Care. 2015; 30(2): 436
18. Choi L et al. Population pharmacokinetics of fentanyl in the critically ill. Crit Care Med 2016; 44(1): 64-72.
19. Baldwin F et al. Safe prognostication following cardiac arrest: The role of the pharmacokinetics of fentanyl in patients treated with targeted temperature management. Resuscitation. 2020; 149: 10-16.
20. Devlin JW, Roberts RJ. Pharmacology of commonly used analgesics and sedatives in the ICU: Benzodiazepines, propofol, and opioids. Crit Care Clin. 2009; 25(3): 431-449.
21. Erstad BL et al. Pain management principles in the critically ill. Chest. 2009; 135(4): 1075-1086.
22. Narayanan M et al. Analgesia in intensive care: Part 1. BJA Education. 2016; 16(2): 72–78.
23. Hanks F et al. How critical illness impacts drug pharmacokinetics and pharmacodynamics. The Pharmaceutical Journal, PJ. February 2022; 308:7958.
24. Wampole CR, Smith KE. Beyond opioids for pain management in adult critically ill patients. J Pharm Pract. 2019; 32(3): 256-270.
25. Hanks F, McKenzie C. Paracetamol in intensive care – intravenous, oral or not at all? 2016; 71: 1136–1140.
26. Pun BT et al. Caring for critically ill patients with the ABCDEF Bundle: Results of the ICU liberation collaborative in over 15,000 adults. Crit Care Med. 2019; 47(1): 3-14.
27. Ely WE. The ABCDEF Bundle: Science and philosophy of how ICU liberation serves patients and families. Crit Care Med. 2017; 45(2): 321-330.
28. Devlin JW et al. Strategies to optimize ICU liberation (A to F) bundle performance in critically ill adults with coronavirus disease. 2019. Crit Care Explor 2020; 2(6): e0139.
29. Ely EW et al. Monitoring sedation status over time in ICU patients: reliability and validity of the Richmond Agitation-Sedation Scale (RASS). JAMA. 2003; 289(22): 2983–2991.
30. Marra A et al. The ABCDEF Bundle in Critical Care. Crit Care Clin. 2017; 33(2): 225-243.
31. Aitken LM et al. Inconsistent relationship between depth of sedation and intensive care outcome: Systematic review and meta-analysis. Thorax. 2021; 76(11): 1089-1098. DOI: 10.1136/thoraxjnl-2020-216098. PMID: 33859048.
32. Hemphill S et al. Propofol infusion syndrome: A structured literature review and analysis of published case reports. Br J Anaesth. 2019; 122(4): 448-459.
33. Philips B, Mckenzie C, Barton G (eds). Critical Illness [online] London: Pharmaceutical Press https://www.medicinescomplete.com/ (accessed on 20 April 2023).
34. Shehabi Y, Howe BD, Bellomo R, et al. Early sedation with dexmedetomidine in critically ill patients. N Engl J Med 2019; 380(26): 2506-2517.
35. Ankravs MJ et al. Precision-based approaches to delirium in critical illness: A narrative review. Pharmacotherapy 2023. [Epub].
36. Reade MC, Eastwood GM, Bellomo R, et al. Effect of Dexmedetomidine Added to Standard Care on Ventilator-Free Time in Patients With Agitated Delirium: A Randomized Clinical Trial [published correction appears in JAMA. 2016 Aug 16;316(7):775]. JAMA. 2016;315(14):1460-1468.
37. Ng KT et al. The effect of dexmedetomidine on delirium and agitation in patients in intensive care: systematic review and meta-analysis with trial sequential analysis. Anaesthesia. 2019; 74(3): 380-392.

38. Eadie R et al. Clinical pharmacist's views on the role of alpha-2- agonists in practice and research for the management of agitation, sedation, and delirium (ASD). J Intensive Care Soc. 2022; 23(1 Suppl): 1–210.

39. Pun BT et al. Prevalence and risk factors for delirium in critically ill patients with COVID-19 (COVID-D): a multicentre cohort study. Lancet Respir Med 2021; 9(3):239-250.

40. Lonsdale D. (2006). A review of the biochemistry, metabolism and clinical benefits of thiamin(e) and its derivatives. Evid Based Complement Alternat Med. 2006; 3(1): 49-59.

41. Fernando SM et al. VTE prophylaxis in critically ill adults: A systematic review and network meta-analysis. Chest. 2022; 161(2): 418-428.

42. Wang L. Semi-recumbent position versus supine position for the prevention of ventilator-associated pneumonia in adults requiring mechanical ventilation. Cochrane Database Syst Rev. 2016; 2016(1): CD009946.

43. Evans L et al. Surviving sepsis campaign: international guidelines for management of sepsis and septic shock 2021. Intensive Care Med. 2021; 47: 1181–1247.

44. Ye Z et al. Gastrointestinal bleeding prophylaxis for critically ill patients: A clinical practice guideline. BMJ. 2020; 368: l6722.

45. Joint Formulary Committee. British National Formulary (online). London: BMJ Group and Pharmaceutical Press. Available at: https://www.medicinescomplete.com [accessed on 11/05/23].

46. Krag M et al. SUP-ICU trial group. Pantoprazole in patients at risk for gastrointestinal bleeding in the ICU. N Engl J Med. 2018; 379(23): 2199-2208.

47. Huang, Hui-Bin et al. Stress ulcer prophylaxis in intensive care unit patients receiving enteral nutrition: a systematic review and meta-analysis. Crit Care. 2018; 22(1): 20.

48. Badawi O et al. Association between intensive care unit-acquired dysglycemia and in-hospital mortality. Crit Care Med. 2012; 40(12): 3180-3188.

49. Van den Berghe G et al. Intensive insulin therapy in critically ill patients. N Engl J Med. 2001; 345(19): 1359-1367.

50. NICE-SUGAR Study Investigators, Finfer S, Chittock DR, et al. Intensive versus conventional glucose control in critically ill patients. N Engl J Med. 2009;360(13):1283-1297.

51. Finfer S et al. Clinical review: Consensus recommendations on measurement of blood glucose and reporting glycemic control in critically ill adults. Crit Care. 2013; 17(3): 229..

52. Flower O, Finfer S. Glucose control in critically ill patients. Intern Med J. 2012; 42(1): 4-6.

53. Tsai D et al. Optimising meropenem dosing in critically ill Australian indigenous patients with severe sepsis. Int J Antimicrob Agents. 2016; 48: 542-546.

54. Ehmann L et al. Role of renal function in risk assessment after standard dosing of meropenem in critically ill patients—a prospective observational study. Crit Care. 2017; 21(1): 263.

55. Roberts J et al. DALI: Defining antibiotic levels in intensive care unit patients—are beta-lactam doses sufficient for critically ill patients. Clin Infect Dis. 2014b; 58(8): 1072–1083.

56. Weinelt FA et al. Evaluation of a meropenem and piperacillin monitoring program in Intensive Care Unit patients calls for the regular assessment of empirical targets and easy-to-use dosing decision tools. Antibiotics (Basel). 2022; 11(6): 758.

57. Hagel S, Bach F, Brenner T, et al. Effect of therapeutic drug monitoring-based dose optimization of piperacillin/tazobactam on sepsis-related organ dysfunction in patients with sepsis: a randomized controlled trial [published correction appears in Intensive Care Med. 2022 May;48(5):646-647]. Intensive Care Med. 2022;48(3):311-321.

58. Roberts J et al. Challenges and potential solutions: individualised antibiotic dosing at the bedside for critically ill patients—A structured review. Lancet Infect Dis. 2014a; 14(6): 498–509.

59. Liebchen U et al. Evaluation of the MeroRisk calculator, a user-friendly tool to predict the risk of meropenem target non-attainment in critically ill patients. Antibiotics (Basel). 2021; 10(4): 468.

60. Kumar A et al. Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock. Crit Care Med. 2006; 34(6): 1589-1596.

61. Kumar A et al. Early combination antibiotic therapy yields improved survival compared with monotherapy in septic shock: A propensity-matched analysis. Crit Care Med. 2010; 38(9): 1773–1785.

62. Jaruratanasirikul S et al. Population pharmacokinetics and Monte Carlo dosing simulations of meropenem during early phase of severe sepsis and septic shock in critically ill patients in intensive care units. Antimicrob Agents Chemother. 2015: 59: 2995–3001.

63. Roberts JA, Kirkpatrick CMJ, Roberts MS, Robertson TA, Dalley AJ, Lipman J. Meropenem dosing in critically ill patients with sepsis and without renal dysfunction: intermittent bolus versus continuous administration? Monte Carlo dosing simulations and subcutaneous tissue distribution. The Journal of Antimicrobial Chemotherapy. 2009; 64(1): 142-150

64. Isla A et al. Meropenem dosing requirements against Enterobacteriaceae in critically ill patients: influence of renal function, geographical area and presence of extended-spectrum ⊠-lactamases. Eur J Clin Microbiol Infect Dis 2016; 35(3): 511-519.

65. Alobaid A et al. Effect of obesity on the population pharmacokinetics of meropenem in critically ill patients. Antimicrob Agents Chemother. 2016; 60(8): 4577–4583.

66. Cook A.M., Hatton-Kolpek J. Augmented renal clearance. Pharmacotherapy. 2019, 39(3): 346-354.

67. Dhaese S et al. Augmented renal clearance in critically ill COVID-19 patients: Forewarned is forearmed. J Crit Care. 2021; 66: 93-95.

68. Carlier M et al. Meropenem and pip/taz prescribing in critically ill patients does augmented renal clearance effect pharmacokinetic pharmacodynamic target attainment when extended infusions are used? Crit Care. 2013; 17(3): R84.

69. Anderson MR, Shashaty MGS. Impact of obesity in critical illness. Chest. 2021; 160(6): 2135-2145.

70. Crandon JL et al. Optimization of meropenem dosage in the critically ill population based on renal function. Intensive Care Med. 2011; 37(4): 632–638.

71. Lertwattanachai T et al. Clinical outcomes of empirical high-dose meropenem in critically ill patients with sepsis and septic shock: a randomized controlled trial. J Intensive Care. 2020; 8: 26.

72. Kothekar A et al. Response to: 500 mg as bolus followed by an extended infusion of 1500 mg of meropenem every 8 h failed to achieve in one-third of the patients an optimal PK/PD against nonresistant strains of these organisms: is CRRT responsible for this situation? Ann Intensive Care. 2020; 10(1): 164.

73. Sjovall F et al. Maximally effective dosing regimens of meropenem in patients with septic shock. J Antimicrob Chemother. 2018: 73: 191–198.

74. Raphaël Burger et al. Effect of renal clearance and continuous renal replacement therapy on appropriateness of recommended meropenem dosing regimens in critically ill patients with susceptible life-threatening infections. J Antimicrob Chemother. 2018; 73(12): 3413–3422.

75. Lu C et al. Population pharmacokinetics and dosing regimen optimization of meropenem in cerebrospinal fluid and plasma in patients with meningitis after neurosurgery. Antimicrob Agents Chemother. 2016; 60(11): 6619-6625.

76. Feher C et al. Effect of meropenem administration in extended infusion on the clinical outcome of febrile neutropaenia. J Antimicob Chemother. 2014; 69(9): 2556-2562.

77. Abdul-Aziz MH et al. infection section of European society of intensive care medicine (ESICM); pharmacokinetic/pharmacodynamic and critically ill patient study groups of European society of clinical microbiology and infectious diseases (ESCMID); infectious diseases group of international association of therapeutic drug monitoring and clinical toxicology (IATDMCT); infections in the ICU and sepsis working group of international society of antimicrobial chemotherapy (ISAC). antimicrobial therapeutic drug monitoring in critically ill adult patients: A position paper. Intensive Care Med. 2020; 46(6): 1127-1153.