ICU
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INTENSIVE CARE - EMERGENCY MEDICINE - ANAESTHESIOLOGY
VOLUME 18 - ISSUE 4 - WINTER 2018

**SPECIAL SUPPLEMENT**
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# Imaging



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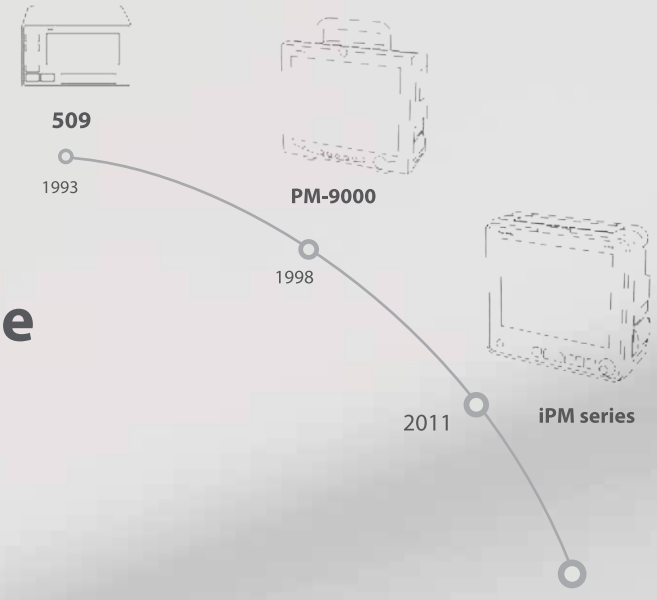


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# Imaging

Our cover story this issue is Imaging. The radiology armamentarium is vast, with many imaging modalities available to aid diagnosis and monitoring of therapy in critically ill patients—both at the bedside (x-ray, ultrasound) and in the radiology department (MRI, CT and PET). Research is underway to image even deeper, such as the PROTEUS collaboration in the UK, which is investigating molecular imaging to detect bacteria deep in the lungs. Hand-held microscopes which can assess the microcirculation at the bedside may come into more widespread use in management of tissue perfusion (Uz et al. 2018).

The days of the daily routine chest x-ray for ICU patients on mechanical ventilation are (mostly) gone. A recent study found that negative sentiment by intensivists in the written notes in the electronic medical record was associated with increased use of imaging (Ghassemi et al. 2018). As with any procedure or treatment, imaging should be performed for the right patient at the right time. With the advent of point-of-care ultrasound, intensivists, with the right training and experience, can perform many US examinations at the bedside.

Anthony McLean outlines the evolving partnership between intensive care and radiology, with an explanation of advances in functional neuroimaging and cardiac imaging. Clear communication with the Imaging department about the need and potential benefit from an imaging procedure is essential, he emphasises.

Next, André Denault, David Canty, Milène Azzam, Alex Amir and William Beaubien-Souligny describe the current impact of the integration of whole-body ultrasound into clinical care including specific clinical conditions that are common in the ICU. Renske Wiersema, Geert Koster, Iwan C.C. van der Horst explain why whole body ultrasonography for hypotension or shock is needed in the ICU. They argue that a mono-organ focus in unravelling disease states results in less clear understanding of the pathophysiologic state in critically ill patients.

Ultrasound can be used to diagnose and prevent ventilator-induced diaphragm dysfunction. Tom Schepens and Ewan C. Goligher explain its use to assess the diaphragm structure and function and its potential to improve outcome by optimising ventilator management.

Collaboration with the radiology department is vital, and radiologist Marcelo Sánchez gives some tips next.

The secrets of the abdomen as revealed by POCUS are discussed by Jonathan Wilkinson, Adrian Wong, Angel Augusto Perez-Calatayud and Manu L.N.G. Malbrain, who describe the potential diagnoses and findings common to the critical care patient population.

Isabel González and David Santamarta report on secondary complications arising from insertion of a multimodal monitoring sensor using a dual lumen introducer kit in patients with subarachnoid haemorrhage, head injury or intracranial haemorrhage. CT scans showed bone fragments in some of the patients studied.

Information useful when considering purchase of ultrasound systems is provided by ECRI Institute - minimum requirements, preferred features, and other advantageous features for ultrasound systems for common exam types.

Mehdi Mezidi, Jean-Christophe Richard highlight the advances in capnography and the benefit of using it to monitor expired $CO_2$ in the ICU. They encourage intensivists to use and study this technology.

Around half the world's population is at risk from dengue and severe dengue. In our Matrix section, Sameer Jog, Payal Kalyani, Anuja Kulkarni explain how to diagnose and treat severe dengue infection. Andrea Cortegiani and Matteo Bassetti describe best practice in antifungal treatment, and advise on the clinical approach.

On Management, Andreas Xyrichis asks if interprofessional teamwork in the ICU is a panacea or an illusion, with reflections on research insights and suggestions for how to improve. ■

As always, if you would like to get in touch, please email JLVincent@icu-management.org.

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# COVER STORY: IMAGING



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# Sedation practices in the ICU

Report of a symposium presented at LIVES 2018: 31st congress of the European Society of Intensive Care Medicine, Paris, France

*Chairs:* **Michael Sander**, *Germany*
& **Jean-Daniel Chiche**, *France*

***Safety first: insights from clinical pharmacists***
**Rob Shulman** *(London, UK)*

***What a difference a drug makes?***
**Jean-Daniel Chiche** *(Paris, France)*

***Good past—better future?***
**Marc Leone** *(Marseille, France)*

Knowledge and practice in sedation and analgesia in the ICU have advanced greatly in recent years. The risks of delirium and of over-sedation and effect on outcomes are well-known. Simple measures such as protocols and sedation strategies can improve outcomes for patients. Technical advances have enabled the use of new techniques in the operating theatre and promise to improve sedation practice in the ICU.

This symposium discussed sedation and analgesia from expert angles, including medication safety in sedation and analgesia, prescribing and using sedation and analgesia, and concluded with a look to the future of sedation and analgesia in the ICU.

Supplement in collaboration with Aspen Pharma

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# Safety first: insights from clinical pharmacists

A critical care pharmacist's perspective and advice on medication safety around sedative and analgesic therapy in the ICU.

Medication errors occur at every stage of the drug therapy process. A recent report on medicines processes in English hospitals identified notably high error rates in prescribing (8.8%) and preparation and administration (78.6%) (Elliott et al. 2018).

## Medication errors in ICU

ICU patients are at particular risk of errors around preparation and administration of intravenous therapies due to the high number of infused drugs. Furthermore, the nature of the ICU environment with the nurses often being interrupted at the bedside and the need for drug concentration calculations contributes to this risk. A multinational observational study found an error rate in parenteral drug administration of around 7% (Valentin et al. 2009). A similar ratio was highlighted in a single-centre observational study of ICU nurses, who knew they were being observed, and the author found an administration error rate of 6.6% (Tissot et al. 1999). A study in which nurses did not know they were being observed had an error rate of administration of 33%, excluding errors of wrong time (van den Bemt et al. 2002).

The 2009 24-hour observational study included 113 ICUs in 27 countries (Valentin et al. 2009). From 1328 patients and 12,000 medicines administrations 861 errors affecting 441 patients were reported. One-third of patients received one or more medication error, of which 19% had one error, and 14% had one or more error. Although most errors did not affect patient status, in 28% of cases medication errors led to temporary change in the patient status. Also, seven patients experienced permanent harm and five died. Looking at the involved drug categories, it appeared that 9% of administrations of sedatives and analgesics were associated with errors (181/2136); resulting in one death and one incident of permanent harm (Valentin et al. 2009). Another study, called the PROTECTED-UK study, analysed data from 21 ICUs from a 2-week period where pharmacists identified all their contributions to care, including noting errors, optimisations and consultations. Out of 20,517 prescriptions, 1 in 6 had such a contribution, and 1 in 15 prescriptions had an error (Shulman et al. 2015; Rudall et al. 2017). The data showed that 5.5% of all errors identified were around sedation and analgesia. Of contributions to care relating to sedation and analgesia (384/3294) 50% were errors, 45% optimisations and 5% consults (Shulman R, pers. comm.).

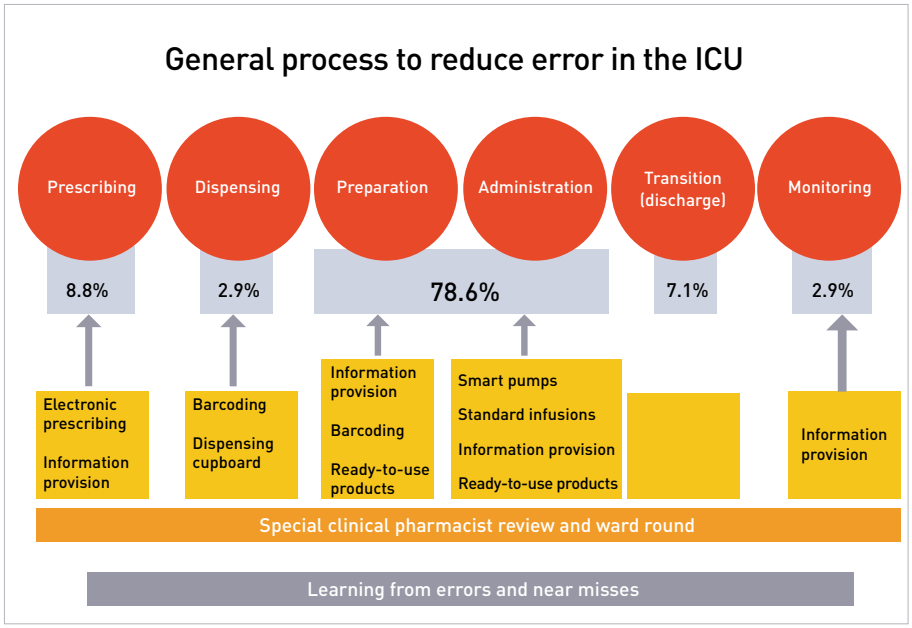


**Figure 1.** General processes to reduce medication error in the ICU

Data source: Elliott et al. 2018

## What can go wrong with sedation and analgesia in the ICU?

Potential errors include selecting the wrong drug, wrong dose, incorrect preparation, contamination in preparation of the product, administration at the wrong rate and compatibility issues. There may be inadequate monitoring of sedation and/or delirium, over- or under-sedation, and errors related to unlicensed use of medications. Commonly used drugs that are not licensed include clonidine (sedation) and haloperidol (delirium) and lidocaine for analgesia.

**Table 1.** Risk assessment of injectable medicines: example of noradrenaline and milrinone

| Risk factors | Noradrenaline 4mg, 8mg, 16mg in 50mL infusion | | Milrinone 20mg in 50mL infusion | |
|---|---|---|---|---|
| | Current status | Ready-to-use syringes | Current status | Ready-to-use syringes |
| Therapeutic risk | Yes | Yes | Yes | Yes |
| Use of a concentrate | Yes | No | Yes | No |
| Complex calculation | Yes | Yes | Yes | Yes |
| Complex method | Yes | No | Yes | No |
| Reconstitution of powder in a vial | No | No | No | No |
| Use of a part vial or ampoule, or use of more than one vial or ampoule | Yes | No | Yes | No |
| Use of a pump or syringe driver | Yes | Yes | Yes | Yes |
| Use of non-standard giving set/device required | Yes | No | No | No |
| Total number of product risk factors | **Six** | **Three** | **Six** | **Three** |

**Six or more risk factors** = high-risk product (Red). Risk reduction strategies are required to minimise these risks.
**Three to five risk factors** = moderate-risk product (Amber). Risk reduction strategies are recommended.
**One or two risk factors** = lower-risk product (Green). Risk reduction strategies should be considered.
Source: National Patient Safety Agency (2007)

## How to prevent medication errors in the ICU?

Several interventions at the different phases of drug therapy can help to mitigate errors (**Figure 1**).

### *Prescribing*

Electronic prescribing is widely used in critical care. A 2005 study that analysed errors before and after introduction of electronic prescribing found that error rates went down, but that the types of errors were potentially more harmful than with handwritten prescribing (Shulman et al. 2005). Nevertheless, both electronic prescribing and information provision at the point of prescription can reduce errors. Electronic systems can include preset standards of infusions, such as the UK Intensive Care Society's standard concentrations for infusions used in critical care (Intensive Care Society 2017).

> "having pharmacists knowledgeable about intensive care can make a big difference"

### *Dispensing*

Solutions to reduce selection errors include robotic dispensing, barcode readers and dispensing cupboards that are barcoded.

### *Preparation*

Most ICUs prepare intravenous (IV) infusions at the bedside. Ready-to-use products reduce handling and preparation complexity. The case for pre-filled syringes is strong. It is generally accepted that 10% too high or too low dose is acceptable (Wheeler et al. (2008). Ferner et al. (2001) studied concentrations in discarded bags of N-acetylcysteine (NAC) administered to 66 patients. Of these 63% were outside of 10% of the intended dose, 39% outside of 20% and 9% outside of 50%. Parshuram et al. (2003) randomly sampled 232 opioid infusions in a Paediatric Intensive Care Unit and found that 65% were outside of 10% of the intended dose and 6% had two-fold errors or greater. In 2008, the same author tested a scenario of 464 morphine calculations and preparation and found that 35% were outside of 10% of the intended dose, and 8% had two-fold errors or greater (Parshuram et al. 2008).

The UK National Patient Safety Agency produced a risk assessment tool for preparation and administration of injectable medicines in clinical areas (NPSA 2007). **Table 1** shows risk assessment for noradrenaline and milrinone; using pre-filled syringes halved the number of risk factors.

Purchasing pre-filled syringes or ready-to-use infusion vials reduces the number of manipulations of the product and improves safety.

### *Contaminated propofol*

Propofol has been associated with healthcare-associated infections; a review of 58 studies identified 103/1405 (7.3%) incidents of contaminated propofol in theatres and 36/894 (4%) incidence of contaminated propofol in ICUs (Zorrilla-Vaca et al. 2016). Not all propofol formulations contain disodium edetate or EDTA, which reduces microbial growth; Fukada and Ozaki (2007) studied microbial growth in propofol preparations and found that propofol with disodium edetate suppressed bacterial growth more than propofol without. Taking a purchasing for safety approach to propofol, ICUs should consider using prefilled syringes and formulations that contain EDTA.

**Figure 2** shows microbial growth in commercially available formulations; Fukada and Ozaki (2007) found that propofol with EDTA suppressed the growth of MSSA, MRSA, *E. coli*, and *K. pneumoniae* to a greater extent than propofol without EDTA.

### *Clinical pharmacist role*

Having clinical pharmacists review and attend ward rounds has been shown to reduce errors.

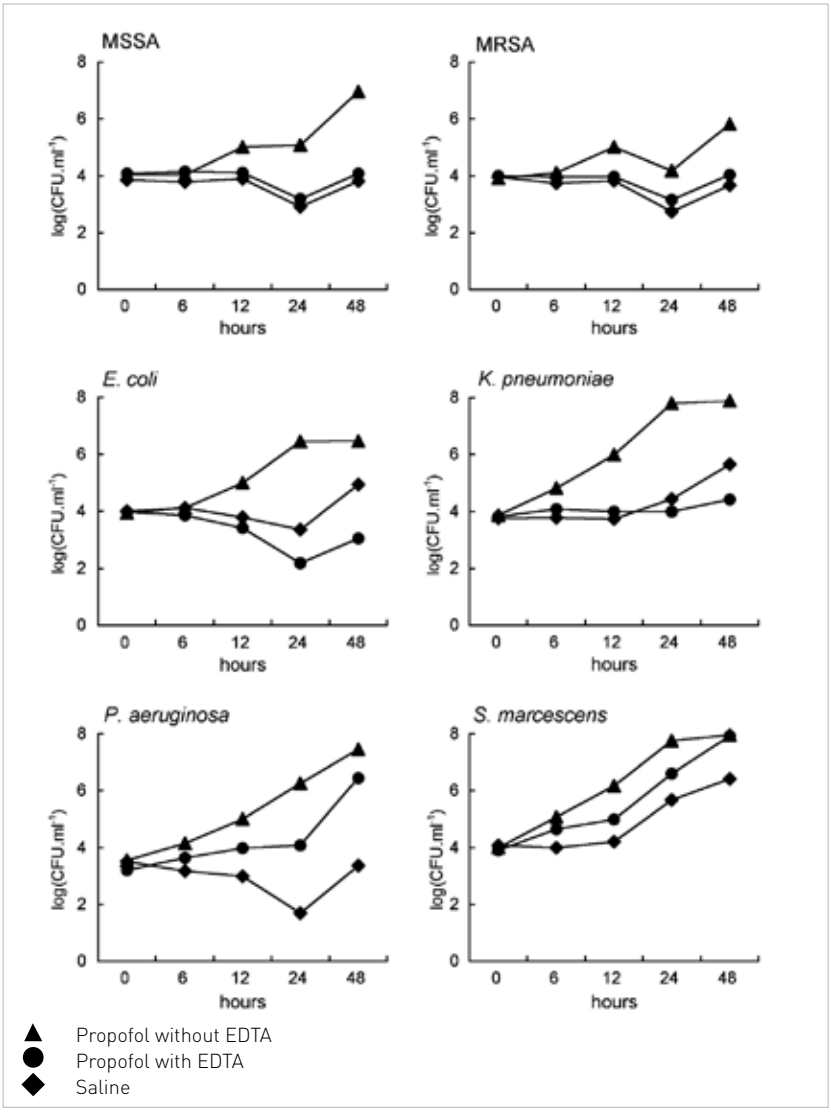


**Figure 2.** Microbial growth in propofol formulations with disodium edetate

Source: Fukada T, Ozaki M (2007) Microbial growth in propofol formulations with disodium edetate and the influence of venous access system dead space. Anaesthesia, 62(6):575-80.



Meaningful reviews of critical incidents and near miss events, and disseminating solutions to colleagues can all help reduce errors (Shulman et al. 2015; Leape et al. 1999; MacLaren and Bond 2009).

## Conclusion

There are many initiatives which ICUs can take to mitigate against error at every stage of the drug therapy process, and ensure patient safety. These include minimising interruptions during preparation, including a specialist clinical pharmacist in the multidisciplinary team, using electronic prescribing systems with guidelines and pre-prepared products. ■

## Key Points

- Medication errors are likely to occur at the preparation and administration stages particularly in Intensive Care Units
- Consider pre-filled syringes to decrease the risks related to drug preparation
- Prefer formulations of propofol that include a microbial growth retardant (e.g. EDTA)
- A clinical pharmacist in the ICU can improve medication safety
- Barcoding solutions with ready-to-use products can improve patient safety

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# What a difference a drug makes?

Asking why the patient needs to be sedated is as important as the choice of drug for sedation.

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## Why use sedation?

Intensivists should ask why they use sedation every time they order it. Sedation is used to reduce the burden and stress of critical illness. Sedative agents mixed with analgesic agents reduce pain and keep the patient calm, especially at night. Intensivists need to look for the cause of agitation and use an algorithm to eliminate the most common causes of agitation e.g. urinary retention, pain.

## How much and what sedation?

Less is better in sedation. Side effects of sedation include prolonged mechanical ventilation, increased risk of infection, longer hospital and ICU length of stay and risk of mortality.

The ideal ICU sedation drug has a good ability to provide analgesia, is rapid onset and easy to titrate. Drugs for sedation should allow the possibility to communicate haemodynamic instability and not be associated with delirium.

The concept of titrating the drug to its effect is good. Intensivists should define the target of sedation so that the more drug used the closer to the target is achieved. Sedation is very time-sensitive. Sedating the patient with shock and high agitation so that they can be intubated is essential and they need a high dose for some hours.

The 2018 guidelines for management of pain, agitation/sedation, delirium and immobility and sleep disruption recommend propofol or dexmedetomidine over benzodiazepines for sedation in critically ill, mechanically ventilated adults who are not undergoing cardiac surgery [conditional recommendation, low quality of evidence] (Devlin et al. 2018). A 2013 meta-analysis of benzodiazepine vs non-benzodiazepine-based sedation for mechanically ventilated critically ill patients found that benzodiazepine-based regimens were associated with more ICU days and longer duration of mechanical ventilation, and probably more delirium (Fraser et al. 2013). Lonardo et al. (2014) compared midazolam and lorazepam in adult ICU patients in a retrospective, multicentre study for single ICU admissions with a single ventilation event (>48h) who were treated with continuously infused sedation. There were 2,250 propofol-midazolam and 1,054 propofol-lorazepam matched patients. Patients treated with propofol had a reduced risk of mortality, increased likelihood of earlier ICU discharge and earlier discontinuation of mechanical ventilation.

## How to use sedation?

A recent paper outlines assessment tools and advice on sedation (Mehta et al. 2018).

### *Daily sedation stops*

Daily interruption of sedations was shown in a randomised controlled trial (RCT) to reduce duration of mechanical ventilation, facilitate weaning and shorten duration of ICU stay (Kress et al. 2000).

### *Paired sedation and weaning protocols*

Sedation stops can be combined with spontaneous breathing trials (SBT); Girard et al. (2008) showed this reduced duration of mechanical ventilation, ICU stay and mortality. Computerised provider order entry (CPOE) systems can place sedation stops and SBT on the nurses' task list.

## Tailor the drug to the patient status

The Sedation Practice in Intensive Care Evaluation (SPICE) study compared deeply sedated with lightly sedated (RASS score [-2 to +1]) patients. Patients who had light sedation within the first 4 hours had reduced time to extubation and improved probability of survival (Shehabi et al. 2012). Other studies demonstrated the same results with shorter time to extubation and better survival in patients with light sedation during the first hours (Shehabi et al. 2013; 2018); the probability of 180-day survival increased with how efficiently sedation was decreased (Shehabi et al. 2018). Importantly, the results did not depend on the drug used but did depend on how they used the drugs.

WHAT' S NEW IN INTENSIVE CARE

### Ten tips for ICU sedation

1. **Prioritize pain assessment & management**
2. **Target an awake, interactive patient shortly after intubation**
3. **Multimodality symptom-based management**
4. **When deep sedation is indicated, de-escalate ASAP**
5. **For patients receiving opioids/sedatives, use validated tools and explicit targets**
6. **Use non-pharmacologic interventions for patient comfort & engagement**
7. **Avoid benzodiazepines, particularly infusions**
8. **Identify iatrogenic benzodiazepine & opioid withdrawal**
9. **Remove catheters (all) as soon as possible, and avoid physical restraint**
10. **Be attentive about night-time sedation**

Source: Mehta, Sangeeta, Spies, Claudia, Shehabi, Yahya (2018) Ten tips for ICU sedation. Intensive Care Med. 44: 1141-1143.
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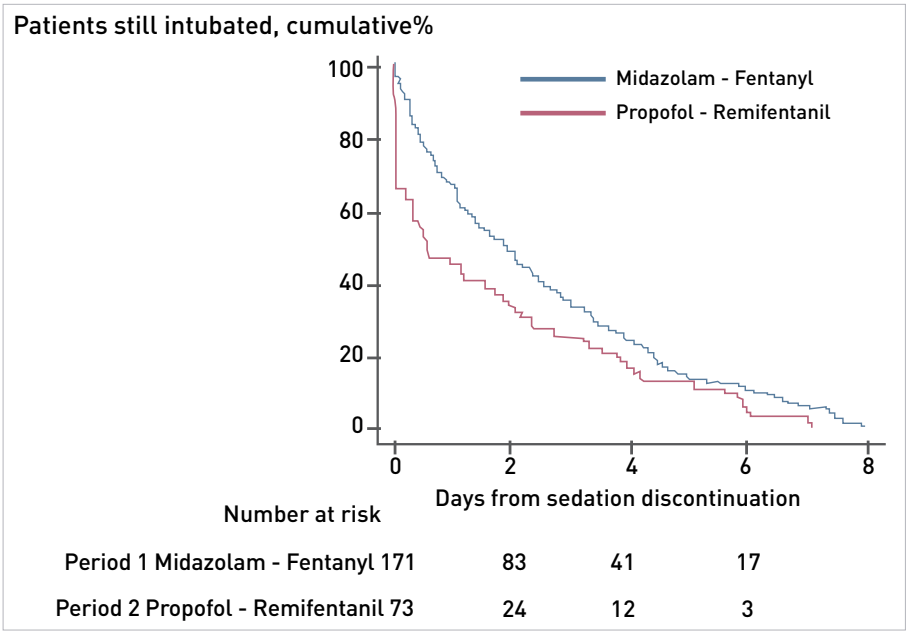


**Figure 1.** Time from discontinuation of sedation to weaning of mechanical ventilation in survivors



Two randomised controlled trials that compared dexmedetomidine to midazolam (MIDEX) or propofol (PRODEX) for sedation in more than 1,000 patients during prolonged mechanical ventilation mandated SBT and RASS-targeted sedation (Jakob et al. 2012). The results showed very little change in duration of mechanical ventilation when comparing dexmedetomidine with midazolam; between dexmedetomidine and propofol there was no difference. Patients were more able to communicate and had similar duration of mechanical ventilation and outcomes when dexmedetomidine was used, compared to midazolam or propofol, in patients who did not require deep sedation (Jakob et al. 2012).

***Delirium assessment***

Some delirium is associated with sedation and is rapidly reversible so it is advised to coordinate delirium assessment with a daily sedation stop (Patel et al. 2014). Delirium is sometimes the result of inflammation and in patients with septic shock there is not significant benefit from dexmedetomidine (Kawazoe et al. 2017).

## Does the choice of drug make no difference in all clinical contexts?

In a study of sedation in patients admitted after out-of-hospital cardiac arrest two periods were compared: propofol-remifentanil, period P2, vs midazolam-fentanyl, period P1 (Paul et al. 2018). Time to awakening and the proportion of comatose patients decreased with the propofol-remifentanil regimen. The propofol-remifentanil regimen was also associated with reduction in mechanical ventilation duration and reduction in incidence of delayed awakening (**Figure 1**).

## How long to sedate?

Intensivists need to consider length of sedation. When strict protocols to target a specific RASS score are implemented, it is possible to reduce sedation, and the proportion of patients on sedation after five days goes down dramatically.

## Conclusion

Always ask why the patient needs sedating. Protocols to target the level of sedation are extremely helpful and will reduce the proportion of patients who are sedated for a long period. The less sedation the better—for duration of mechanical ventilation and survival. ■

## Key Points

- Prescribe sedation in response to pain, anxiety, agitation, sleeplessness
- Non-benzodiazepine-based sedation vs benzodiazepine is associated with less mortality, less ICU days and earlier discontinuation of mechanical ventilation
- Track compliance with protocols for stopping sedation
- The less sedation the better the likelihood of survival and the shorter the time to extubation

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# Good past—better future?

From massive sedation in the past, through current sedation practice relying on cooperation between patients and care providers, the future may further improve sedation in the ICU.

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The concepts for good sedation include defining the range of sedation, the need for agents with rapid response that can be easily and rapidly varied in restless and confused patients, various modes of ventilation, continuous supervision and adequate monitoring.

The benzodiazepines era brought diazepam, lorazepam, midazolam, but they are associated with delirium, whatever the drug or dose (Ely et al. 2001; Pandharipande et al. 2007). Propofol has a better pharmacokinetic profile, but in most RCTs there was difference in time to extubation, and no difference in ICU discharge (Ely et al. 2001; Pandharipande et al. 2007). Propofol infusion syndrome limits the use of propofol as the main agent for sedation in the ICU for more than two days or at a dose of more than 4mg/kg/h (Bray 1998).

## Current practice

### *Use boluses*

When boluses are used sedation can be titrated. Kollef et al. compared continuous and intermittent intravenous (IV) sedation, and showed that intermittent boluses of IV sedatives can be titrated more easily and that duration of mechanical ventilation shortened when using an intermittent bolus (Kollef et al. 1998).

### *Build a sedation strategy*

A sedation strategy should include:

- A daily sedation stop, which can reduce duration of mechanical ventilation (Kress et al. 2000).
- Choice of drug. An RCT published in 2006 showed there were more ventilator-free days when propofol was used with daily sedation interruption (Carson et al. 2006).
- Monitoring (De Jonghe et al. 2005).
- Progress towards no sedation. An example is from Strøm et al. (2010).

### *Reduce sedation by titration*

De Jonghe et al. (2005) developed a management protocol based on an algorithm relying on monitoring by a nurse, and a target based on a score. The nurse is in charge of the flow of the sedation agent to keep the patient in a predefined target. Cooperation between the nurse and the patient is important (Reade et al. 2016; Flükiger et al. 2018).

Strategies are required for deep and light/comfort sedation (**Figure 1**). Deep sedation is required for patients with acute respiratory distress syndrome (ARDS) and who require intracranial pressure monitoring. Deep sedation targets a RASS score of -4 or -5. For light sedation a RASS score of 0 ensures that the patient is awake, not agitated and can cooperate with the nurses. There is no middle approach.

## The future of sedation

### *Target-controlled infusion (TCI)*

TCI rapidly loads plasmatic compartment up to the peak effect. This approach enables to reach the desired concentration effect very quickly. If continuous infusion is used, there is a long time to reach the target. Anyway, without a close titration, there is a risk of exceeding the target and of over-sedation (**Figure 2**).

TCI is based on predictive models (Struys et al. 2016). The target is set to also include patient features such as body mass index (BMI), gender and age. In future creatinine clearance or liver function could be included. The TCI system could have a pharmacokinetic parameter set in an infusion device and a user interface in a single smart pump. The concentration target can be set according to stimulation provided to the patient. For example, in the ICU, during nursing care, increase the target, when no nursing care is taking place, or at night, decrease the target.

There are few publications on using TCI in the ICU for sedation. Sufentanil and ketamine, compared in a RCT using a TCI system, found the model was quite predictive for sufentanil but unpredictive for ketamine and midazolam (Bourgoin et al. 2005). The study showed that the increase in sufentanil or ketamine plasma concentrations using TCI was not associated with adverse effects on cerebral haemodynamics in patients with severe brain injury. A more recent paper used a TCI propofol Marsh model system for general anaesthesia and sedation in neurosurgical patients and found a bias of -34.7% and precision of 36% (Cortegiani et al. 2018). More data for specific pharmacokinetic models are needed for TCI to be used in ICU patients.

### *Closed-loop systems*

A closed-loop system requires a relevant target

| Deep sedation | Comfort sedation |
|---|---|
| **Midazolam**<br>Propofol<br>Sevoflurane<br>+<br>Opioids<br>± Muscle relaxants | **Dexmedetomidine**<br>Propofol<br>+<br>**Non-opioid analgesics**<br>±<br>Opioids (if VAS > 30) |

**Figure 1.** Strategies for sedation

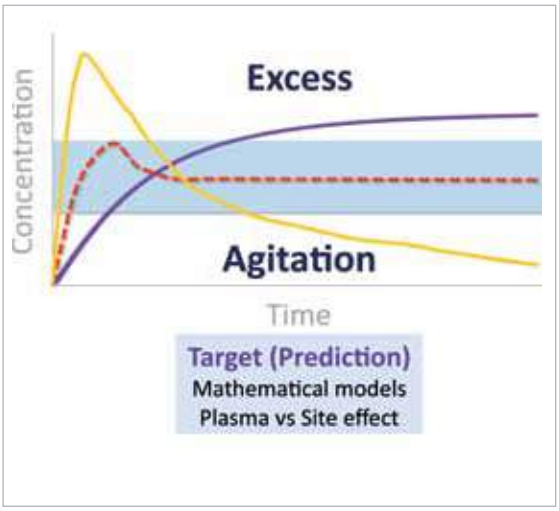


**Figure 2.** Target-controlled infusion in the operating room

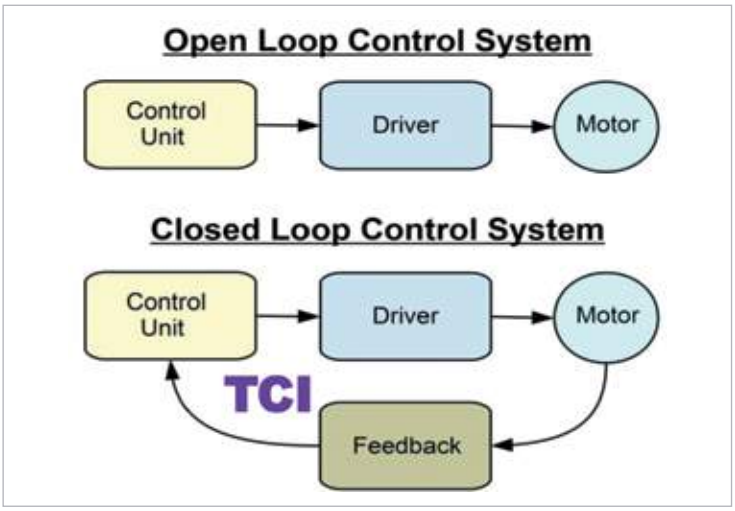


**Figure 3.** Closed-loop system

value (setpoint), strong monitoring that is not influenced by artefacts, a drug with a short delay and short half-life and an adaptive control algorithm with a dynamic learning strategy or fuzzy logic system (Le Guen et al. 2016). Closed-loop systems have been used in the operating room (**Figure 3**). A trial that compared dexmedetomidine to saline as a placebo using a bispectral index-guided closed-loop system found that dexmedetomidine significantly reduced propofol and remifentanil consumption during anaesthetic induction and reduced propofol use during maintenance of anaesthesia (Le Guen et al. 2014).

The most commonly used target for ICU patients is bispectral index, and can include respiratory rate (RR) or blood pressure (BP) if it is important that the patient was not hypotensive (Haddad et al. 2009). Alternatively drug plasma concentration can be targeted directly. A future composite index might include cerebral activity, sedation score, RR, BP and blood plasma concentration.

### *Use fewer opioids*

In the ICU up to 90% of patients receive opioids (Arroliga et al. 2005; Payen et al. 2007; Wøien et al. 2012), and these are associated with morbidity and mortality (Kamdar et al. 2017). Dexmedetomidine, ketamine, ketoprofen, paracetamol and lidocaine could be used as alternatives. It is important to monitor the patient first, and to consider other ways to provide analgesia apart from opioids.

## Conclusion

In the past sedation patients received massive sedation. Now sedation relies on good cooperation between patients, nurses and intensivists. The future will bring target-controlled infusion in a closed-loop system, reduced use of opioids and a multimodal approach to sedation. ■

## Key Points

- Include in the protocol a daily interruption of sedation
- Cooperation between patients, nurses and intensivists is vital in sedation
- In future, target-controlled infusions in a closed-loop system may be used in the ICU

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# Imaging and intensive care medicine

## An evolving partnership

A major evolution is underway involving critical care and imaging.

The intensive care patient population is changing. Increasingly intensive care units (ICUs) are treating older patients, with more comorbidities, and variable prognosis, at a time when family expectations are different and often with higher expectations of recovery. Life support technology is increasingly sophisticated, surgery is minimally invasive in many cases and nonsurgical interventions such as interventional radiology have come to play a greater role in patient care.

The intensive care unit has benefited greatly from advances in imaging—from diagnosis to planning and monitoring treatment. The radiology-ICU partnership is still evolving, building on recent advances in functional imaging.

Medical specialties by their very nature can work in semi-isolation. While both radiology/imaging and intensive care medicine have become more specialised, they both have more horizontal cross-collaborative practices. Communication is more challenging because of increasing complexity, e.g. determining the significance of T2 weighting on a brain magnetic resonance imaging (MRI) scan, or an unstable patient with invasive haemodynamic monitoring in situ requiring cerebral angiography. The acute nature of work is more accentuated, e.g. uncontrollable gastrointestinal (GI) bleed, the need for a computed tomography (CT) scan of the brain prior to thrombolytic therapy, and deciding where the patient goes to after the procedure.

Challenges for the intensive care doctor include keeping up-to-date with advances in all modes of imaging (CT, angiography, MRI, positron emission tomography [PET], ultrasound). Clear communication with the Imaging department about the need and potential benefit from an imaging procedure is essential, as is knowing when and where to apply a particular imaging technique to an individual patient. The financial perspective should always be recognised by the intensivist requesting an imaging procedure. Point-of-care ultrasound enables many examinations to be done at the bedside. Logistical challenges remain when transporting mechanically ventilated patients to the Imaging department. Translation of findings into everyday clinical practice can also be challenging.

Medical imaging provides structural information, functional imaging and real-time imaging of tissue metabolic activity (**Figure 1**).

### Neuroimaging

#### Magnetic resonance imaging

MRI has great value in the ICU for prognostication. A recent systematic review and meta-analysis of studies evaluating the predictive value of acute MRI lesion patterns for discriminating clinical outcome in traumatic brain injury confirmed that MRI following traumatic brain injury yields

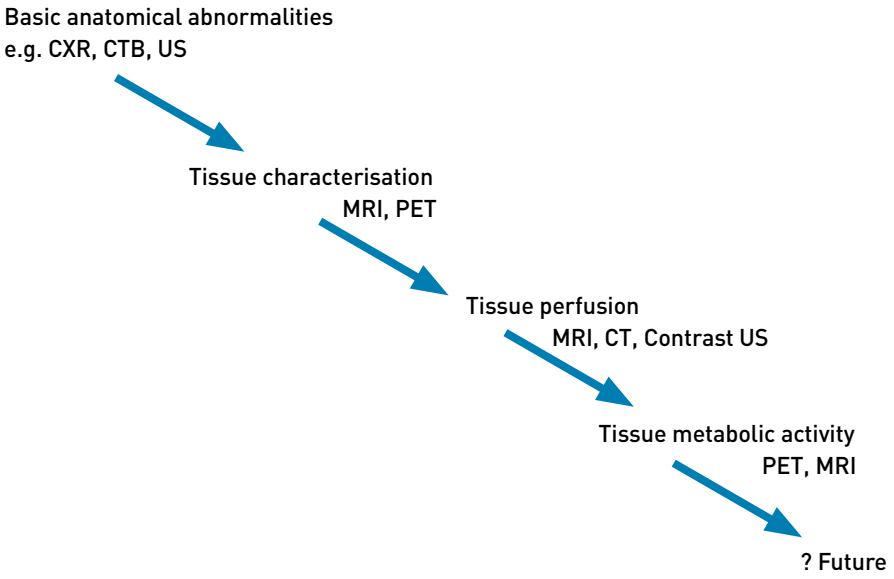


**Figure 1.**
CXR chest x-ray CT computed tomography CTB computed tomography brain MRI magnetic resonance imaging PET positron emission tomography US ultrasound

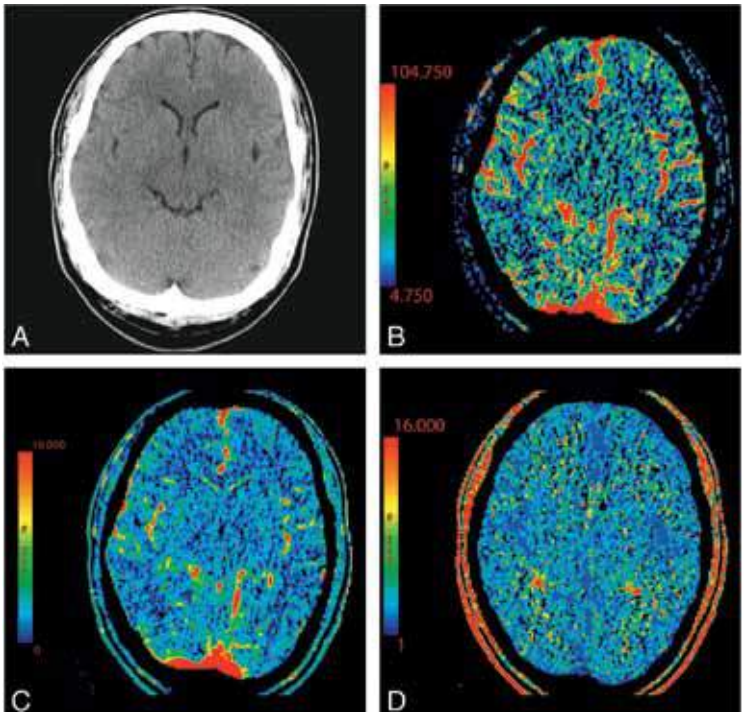


**Figure 2.** NCCT (A) and CTP parametric maps, CBF (B), CBV (C), and MTT (D), demonstrate normal symmetric brain perfusion. By convention, all colour maps are coded red for higher values and blue for lower values.

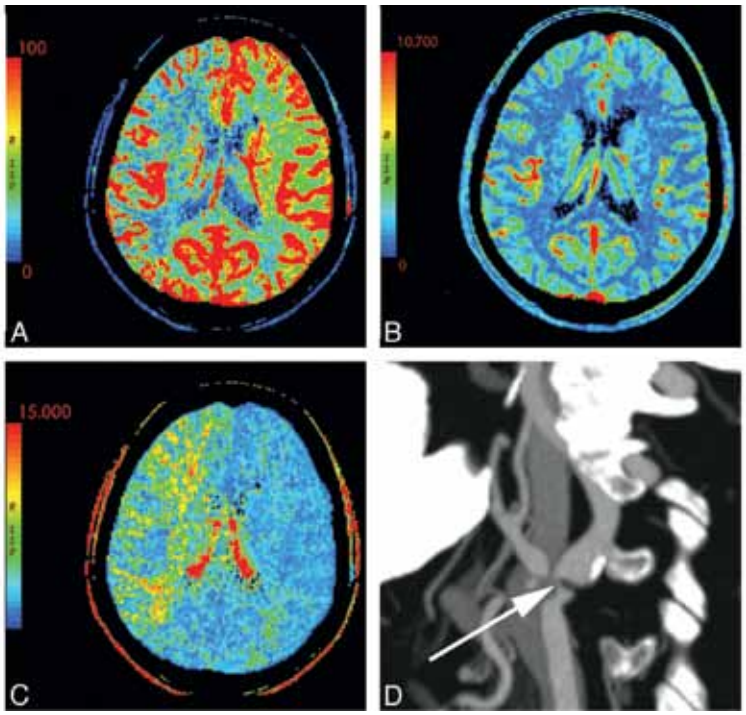


**Figure 3.** A 76-year-old man with change in mental status.
NCCT findings (not shown) were normal. A–C, There is decreased CBF (A) and prolonged MTT (C) in the right MCA and ACA territories with preserved CBV (B). D, CTA reveals severe right ICA stenosis at its origin (arrow).

ACA anterior cerebral artery CBF cerebral blood flow CBV cerebral blood volume ICA internal carotid artery MCA middle cerebral artery MTT mean transit time NCCT non contrast CT

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important prognostic information (Haghbayan et al. 2017). Already, functional MRI can compare activation patterns in the brain with task functional MRI (fMRI) mapping with subjects performing a simple 'hand task' (Ugurbil 2016).

### CT scanning

CT brain scanning is usually readily available for the critically ill patient due to organisational preferences in imaging departments. CT scanning has developed to provide advanced structural and functional tissue characterisation. Increasingly used to triage stroke patients, CT perfusion imaging distinguishes normal from abnormal perfusion. It can identify an ischaemic penumbra for example. It is more sensitive for detecting cerebral contusions. Perfusion neuroimaging techniques include CT bolus perfusion,

**CT brain scanning is usually readily available for the critically ill patient**

MR imaging bolus perfusion, MR arterial spin labeling perfusion and xenon CT, as recently explained by Douglas et al. (2018).

In acute traumatic brain injury, contrast-enhanced perfusion CT, as illustrated by Lui et al. (2010), can be used to differentiate salvageable tissue from unsalvageable tissue (**Figure 2, Figure 3**).

### Functional brain scanning

The brain represents 2% body weight, and uses 15% cardiac output, 20% total body $O_2$ consumption and 25% total body glucose consumption (Villien et al. 2014). MRI and PET are suitable for structural brain imaging, but not yet suitable for functional brain scanning, as explained below.

The radiotracer 18 F-fluorodeoxyglucose (FDG) has been used to study brain glucose metabolism by PET for the past 40 years. However the "snapshot" takes 20-40 minutes post bolus and it is difficult to obtain temporal resolution compared to fMRI. A recent

**Table 1.** Time related parameters in MRI scanning

**T1 pulse sequence**
T1- Time taken for correction to underlying magnetic plane following administration of a radiofrequency (RF) pulse. (e.g. 180°)

**T1 faster- Fe, fat**
Normal
High/longer – fibrosis/inflammation/oedema

**T2 pulse sequence**
T2 is the time taken to return to normal following RF pulse causing rotational move, i.e. precision factor normally T2< T1

**T2 high/longer - inflammation oedema**
i.e. if only T1 is high/longer then there is likely to be underlying fibrosis

technique (fPET-FDG) that uses constant infusion FDG appears promising (Villien et al. 2014).

fMRI has good temporal resolution, which is obtained in one pass. Blood oxygen-level dependant (BOLD) is widely employed for brain mapping. However, it is not quantitative in the absolute sense.

## Cardiac imaging

### Cardiac MRI and myocardial injury

Cardiac MRI can show myocardial tissue structure in detail using the contrast agent gadolinium. Gadolinium differentially accumulates in regional segregated tissue such as a post-infarction scar, thus known as late gadolinium enhancement (LGE) (Puntmann et al. 2016). However, it is not so helpful where diffuse disease is present, as a continuum of disease is present with no reference in the imaging plane. Gadolinium shortens T1 time and the difference

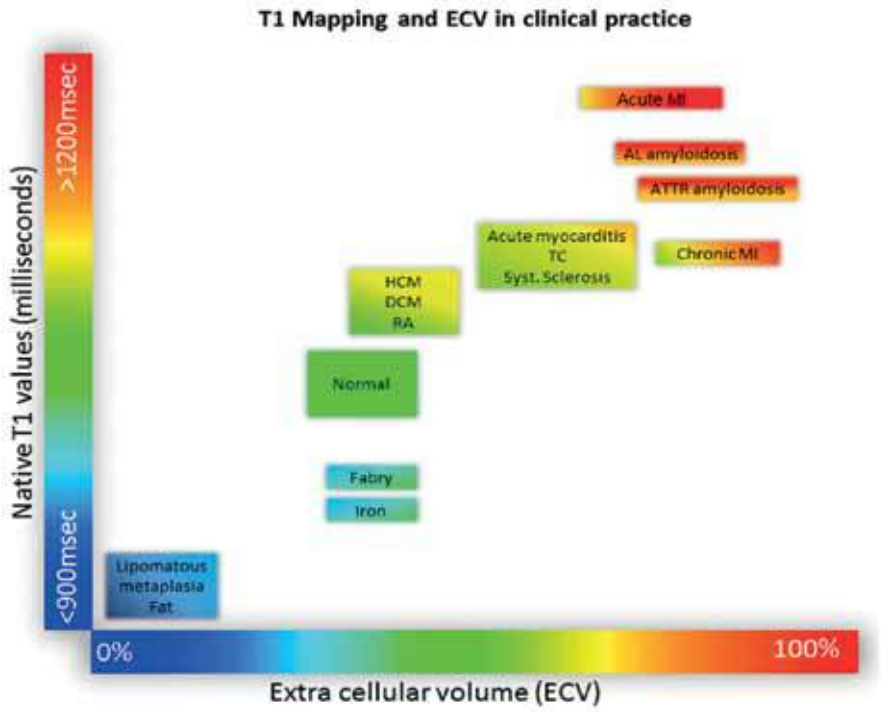


**Figure 4.** T1 mapping and ECV in clinical practice

Source: Haaf et al. (2016) Reproduced under CC BY 4.0 (creativecommons.org/licenses/by/4.0)
Tissue characterisation using native T1 and extracellular volume fraction (ECV). Absolute values for native T1 depend greatly on field strength (1.5 T or 3 T), pulse sequence (MOLLI or ShMOLLI), scanner manufacturer and rules of measurements. For the purpose of comparability, only studies using 1.5 T scanners were considered in this figure.

$$ECV = (1-haematocrit)\frac{\frac{1}{post\ contrast\ T1\ myo} - \frac{1}{native\ T1\ myo}}{\frac{1}{post\ contrast\ T1\ blood} - \frac{1}{native\ T1\ blood}}$$

**Figure 5**

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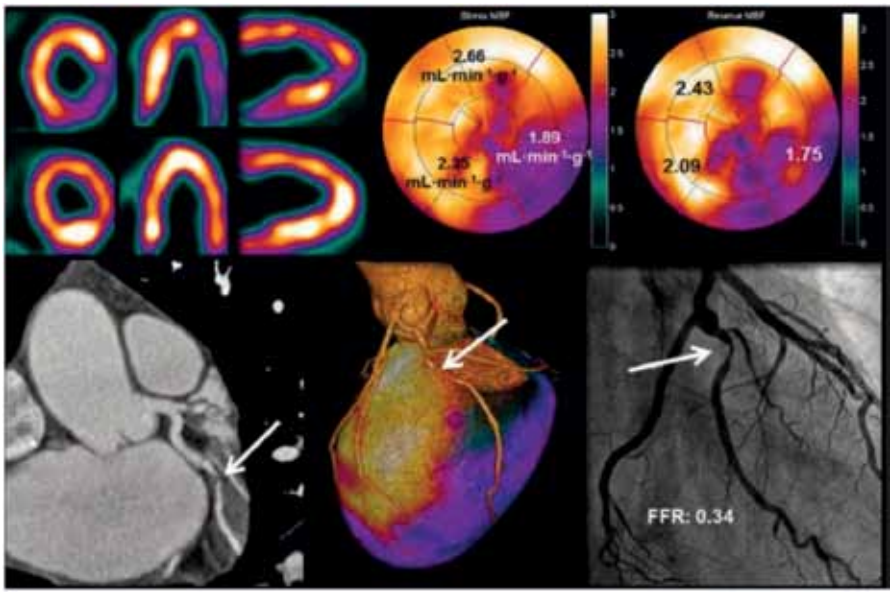


**Figure 6.**

Source: Driessen et al. (2017) Reproduced under CC BY 4.0 (creativecommons.org/licenses/by/4.0)

between T1 native and T1 gadolinium gives an idea of how much gadolinium is in the extracellular myocardium providing a guide to extracellular volume.

Diffuse myocardial processes can be shown with cardiac MRI, including inflammation, oedema, extravascular volume expansion, infiltrative disease, microvascular ischaemia and fibrosis.

**Myocardial oedema**

Laine and Allen in 1991 demonstrated in a study of dogs implanted with porous polyethylene capsules that measured end-diastolic interstitial fluid pressure in the left ventricle, that acute myocardial oedema compromises cardiac function and that chronic right heart pressure elevation and chronic arterial hypertension produce left ventricular myocardial oedema (Laine and Allen 1991).

Now pulsing MRI techniques can be used to assess myocardial oedema. On MRI it shows as increased global left ventricular T2 values that decrease with successful decongestion (Verbrugge et al. 2017).

**Native T1 (T1 imaging without contrast)**

T1 time measures the time taken to recover longitudinal magnetisation. It is moderately water sensitive and elevated in diffuse myocardial fibrosis, inflammation and oedema (Taylor et al. 2016).

**Imaging extracellular volume fraction (ECV)**

MRI can be used to image myocardial extracellular volume fraction (**Figure 4**). The process first obtains T1 in myocardium and blood precontrast, then after administration of gadolinium obtains T1 in the myocardium and blood. ECV is elevated in expansion of extracellular space such as amyloid and myocardial oedema. Imaging can quantify ECV and confirm expansion of extracellular space. The measures are pre- and post-contrast T1 relaxation times of blood and myocardium with correction for blood volume of distribution via the haematocrit (**Figure 5**).

For ICU patients native T1 MRI imaging can be used to assess inflammation, myocardial oedema and expansion of extracellular volume fraction as well as microvascular dysfunction/microvascular ischaemia.

> intensivists need to be proactive: find out what technology is available in their institution

**Myocardial perfusion using PET**

Hybrid PET/CT scanners can provide anatomical and functional information, as shown in **Figure 6**. This shows a 46-year-old male with typical anginal chest pain. The PET scan shows an inferolateral perfusion defect with a myocardial flow reserve 1.75. Coronary computed tomography angiography (CCTA) showed an obtuse marginal defect. Fused PET and CCTA showed a downstream perfusion defect. Invasive coronary angiography showed marked luminal obstruction with a fractional flow reserve (FFR) of 0.34.

## Conclusion

Intensivists need to be proactive: find out what technology is available in their institution, identify which patients could have treatment enhanced, and be prepared to move beyond traditional imaging practices. Diagnostic and interventional procedures in radiology are used regularly in everyday critical care practice. Functional imaging is possible in multiple imaging modalities, some for clinical use, but many still at the research stage. Functional brain and cardiac imaging is the next frontier in the ICU. As logistical considerations are still a challenge, bedside imaging techniques should be a major objective. ■

## Case studies

Two illustrative case studies are on the next pages.

**Conflict of interest**

Anthony McLean declares that he has no conflict of interest.

**Abbreviations**

ACA anterior cerebral artery
CBV cerebral blood volume
CT computed tomography
CTB computed tomography brain
ECV extracellular volume
ICA internal carotid artery
ICU intensive care unit
MCA middle cerebral artery
MTT mean transit time
PCA posterior cerebral artery
PET positron emission tomography

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# Case 1

26-year-old woman, G2 P1 in her 2nd uncomplicated pregnancy
Presented at 34 weeks –hypertension, headache, visual changes
Reflexes not increased
Urinary protein +++
Prescribed Magnesium sulfate (MgSO4), hydralazine
Fetal distress, went for caesarean section
Admitted to ICU post delivery (late afternoon)
Blood pressure (BP) well controlled, comfortable
Nil headache or visual changes
Brisk reflexes, ankle – 1 beat of clonus
Stat dose clonidine given overnight BP 150/83

0600 next morning unresponsive, incomprehensible noises
Normal reflexes, BP 171/99
No focal neurological defects on examination

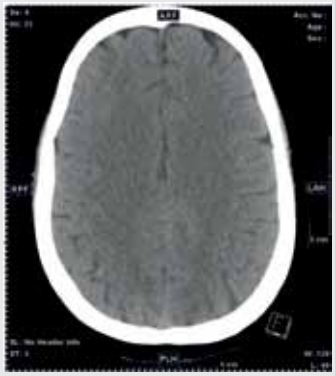
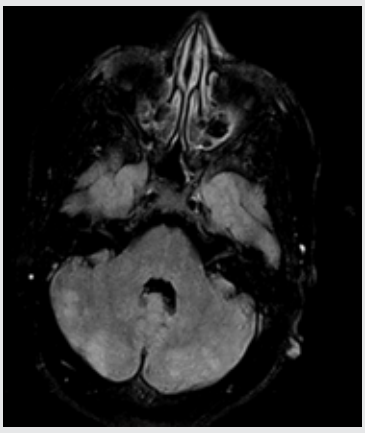


**Image 1**
The CT scan of the brain showed no dural vein thrombosis.



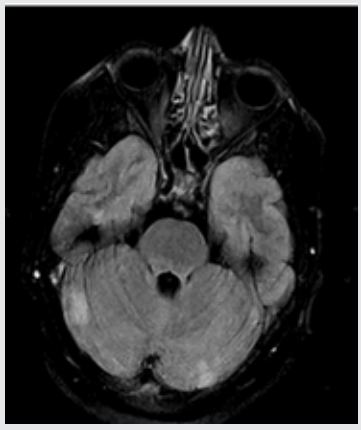


**Image 2** shows early ischaemic change in both cerebellar hemispheres on fluid-attenuated inversion recovery (FLAIR) MRI (no concurrent diffusion change)

**Image 3** shows extensive restricted diffusion within grey and white matter consistent with ischaemia in the frontal lobes, left parietal lobe, and to a lesser extent in the right parietal lobe.

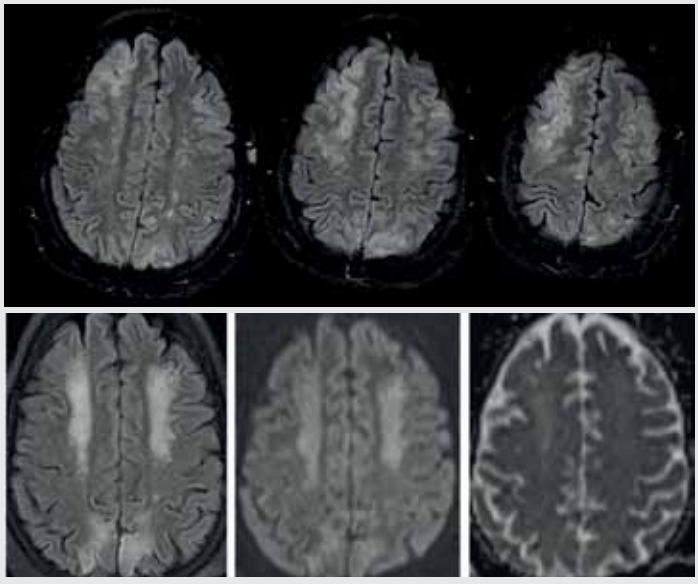
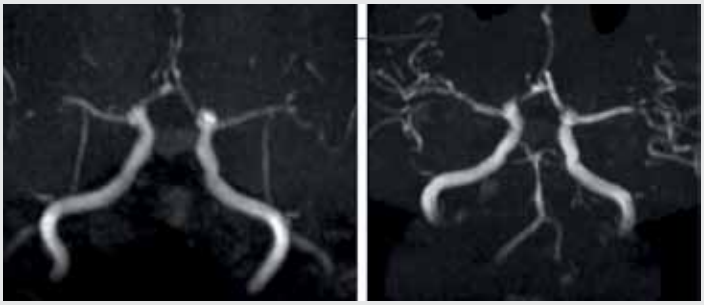


**Image 4** is the 3D time-of-flight imaging, which shows a smooth tapered narrowing of basilar artery and generalised narrowing of anterior circulation arteries bilaterally, suggestive of vasospasm.



The pathophysiology in this case suggested differential diagnosis of eclampsia- induced vasospasm, eclampsia-associated Posterior Reversible Encephalopathy Syndrome (PRES), eclampsia-associated Reversible Cerebral Vasoconstriction Syndrome (RCVS) or eclampsia-associated RCVS-PRES overlap.
The final diagnosis was eclampsia-associated RCVS-PRES overlap.

## Case 2

41-year-old woman, history of hypertension/diabetes II
Argument with brother – loud and angry, followed by sudden collapse
No striking of head, no obvious seizure
Stopped breathing for 2 minutes
CPR by family 10 -15 minutes
Ambulance arrived- patient had underlying cardiac rhythm, applied automated external defibrillator (AED)
ED - decerebrate posturing, intubated, urgent CTB
CTB (**Image 5**)– no bleed, subtle hypodensity in right basal ganglia and anterior temporal lobe associated with mild effacement of overlying sulci.
Diagnosis: possible early infarction

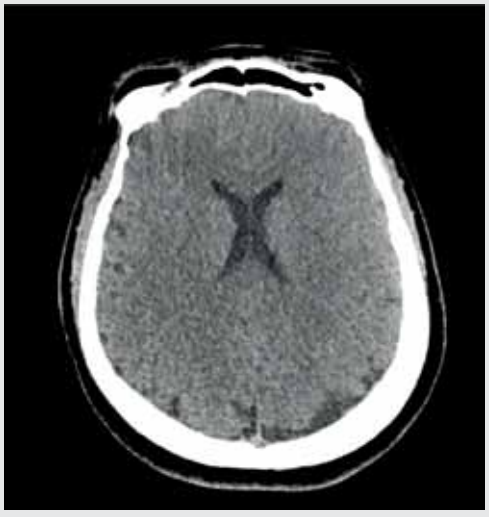


**Image 5**

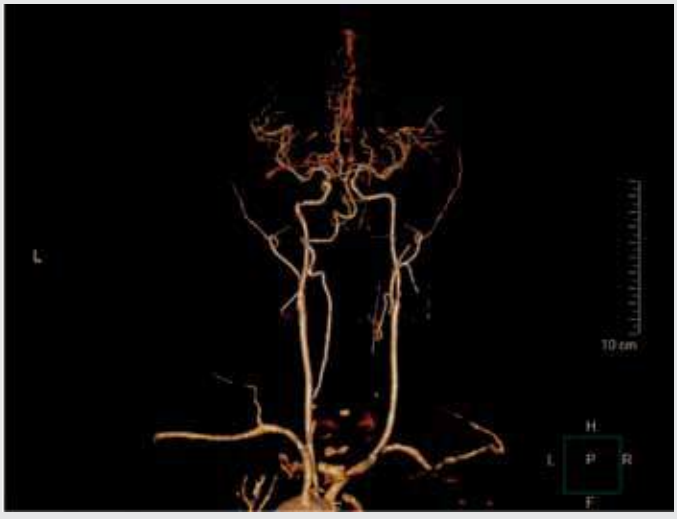


**Image 6**

CT angiography (image 7)– no filling defect to suggest acute thrombus
Bilateral ACA/ MCA/ PCA normal
Large left PCA/ absent right PCA
Basilar artery supplied by large left vertebral artery
Right vertebral artery small vessel which directly supplies the posterior inferior cerebellar artery

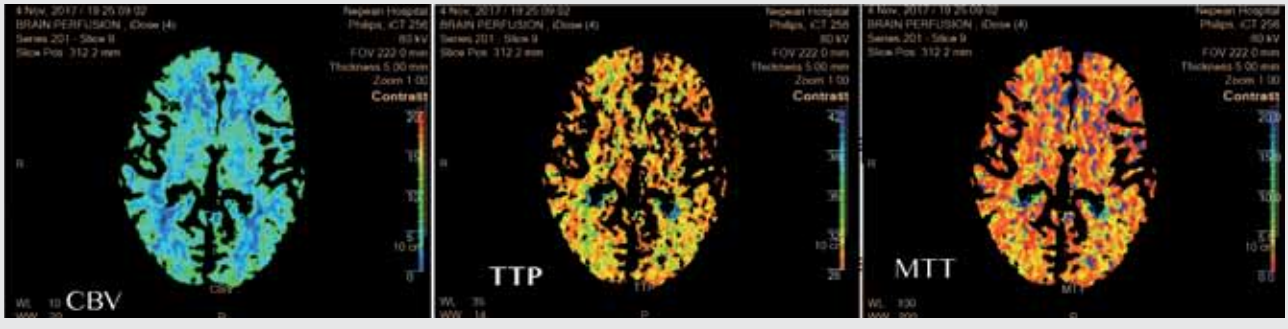



**Image 7** Cerebral CT perfusion scan totally normal
CBV cerebral brain volume MTT mean transit time TTP time to peak

Patient outcome: no neurological deficits, 'normal on discharge'

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# Whole-body ultrasound in the intensive care unit

## Bedside ultrasound of the whole body

Whole-body ultrasound can be used in the evaluation of many critical conditions including encephalopathy where brain and ocular ultrasound combined with transcranial Doppler can identify elevated intracranial pressure. Hypoxaemia is mostly related to pulmonary disease and lung ultrasound can rapidly identify the aetiology. Cardiac, lung and abdominal ultrasound will be useful to identify both the mechanism and aetiology of haemodynamic instability. Finally, in any oligo-anuric patient, renal ultrasound should be performed. The use of ultrasound is further supported by several prospective and randomised trials.

Bedside ultrasound, also known as point-of-care ultrasound (POCUS), has been considered the new fifth pillar of physical examination (Narula et al. 2018) and is poised to replace the stethoscope. Based on its Greek etymology, the term "stethoscope" composed of stetho (breast) and scope (look into) may better suit miniaturised handheld ultrasound devices rather the tool invented by Laënnec in 1819 for auscultation. However, portable ultrasound devices have the ability to look beyond the chest. Therefore, the term "bodyscope" or whole-body ultrasound (WHOBUS) would more appropriately describe the potential of bedside ultrasound (Karabinis et al. 2010). It does not imply that the whole body should be examined every time, but rather that ultrasound can be used to complement clinical evaluation where indicated. Applications of ultrasound in the intensive care unit (ICU) are numerous, enabling simultaneous assessment of multiple organs. Two-dimensional (2D) or three-dimensional (3D) ultrasound offers a window into the anatomy of the patient, while haemodynamic physiology can be assessed using Doppler. In this article we describe current impact of the integration of WHOBUS into clinical care including specific clinical conditions that are common in the ICU and how WHOBUS can be used to identify the mechanism.

### WHOBUS and the encephalopathic patient

Altered mental status in a critically ill patient requires consideration of a broad differential diagnosis, including various causes of intracranial hypertension, metabolic derangements and drug intoxication. The diagnostic approach requires careful history, physical examination, and complementary diagnostic investigations. Point-of-care neurologic ultrasound in the encephalopathic patient enables the critical care physician to rapidly detect life-threatening conditions including (but not restricted to) the presence of raised intracranial pressure (ICP) (Maissan et al. 2015; Lau and Arntfield 2017; Denault et al. 2018), midline shift from a space occupying lesion such as traumatic brain injury or stroke (Denault et al. 2018), and cerebral vasospasm following subarachnoid haemorrhage (Denault et al. 2018). Furthermore, it can be used to confirm brain death (Ducrocq et al. 1998).

Examples of situations where point-of-care ultrasound may be useful in detection of intracranial hypertension include when invasive ICP monitoring is contraindicated (such as coagulopathy), or when a patient is too unstable to be transported for diagnostic imaging. Bedside intracranial pressure measurement with ultrasound is performed by placing a high frequency linear probe on the orbit to identify the optic nerve sheath diameter (ONSD) (**Figure 1**). An ONSD > 5.0 mm predicts the presence of ICP > 20 mmHg with a sensitivity of 94% and specificity of 98% (Maissan et al. 2015), representing excellent diagnostic performance (area under the curve [AUC] of 0.99) (Maissan et al. 2015) (**Figure 1**). Serial ONSD measurements can be done to follow the progression of ICP. Intracranial

hypertension may also be detected with ultrasound by measurement of blood flow velocity of the middle cerebral artery with spectral Doppler, known as transcranial colour-coded sonography (TCCS) (Lau and Arntfield 2017) (**Figure 2**). The pulsatility index (PI) is a Doppler-derived measure of the resistance to blood flow and is calculated as the difference between the peak systolic flow velocity and end-diastolic flow velocity, divided by the mean velocity. An elevated PI correlates with increased ICP, regardless of the nature of the intracranial pathology (Bellner et al. 2004). Typically a PI > 2.3 (normal PI value < 1.2) correlates with an ICP > 22 mmHg (Lau and Arntfield 2017). Presence of a midline shift of the cerebrum, a condition associated with ipsilateral intracranial hypertension, can also be detected by two-dimensional transcranial ultrasound. A transtemporal view of the third ventricle (**Figure 3**), a midline structure, is obtained and the distance to the middle of the third ventricle from the ipsilateral and contralateral edges of the cranium are measured; a discrepancy between the measured distances indicates presence of a midline shift (Denault et al. 2018).

An important caveat is that transcranial ultrasound requires an experienced operator, and even then is very difficult or impossible in up to 10% of patients (Denault et al. 2018). Detailed description of this technique is beyond the scope of this article but is well described elsewhere (Lau and Arntfield 2017; Denault et al. 2018).

Finally, it is important to perform a systematic evaluation of the encephalopathic patient, as extra-cranial causes of altered mental status are numerous, such as cerebral congestion secondary to right heart dysfunction or volume overload (**Figure 4**), or cerebral hypoperfusion due to various causes of shock. WHOBUS can help identify the presence of these contributing pathologic states as we will describe in the following sections.

## WHOBUS in the hypoxaemic patient

The approach to the hypoxaemic critically ill patient can be greatly simplified and enhanced with the use of point-of-care ultrasound (Piette et al. 2013). Lung and pleural ultrasound, as an adjunct to the clinical exam, can readily identify important causes of hypoxia

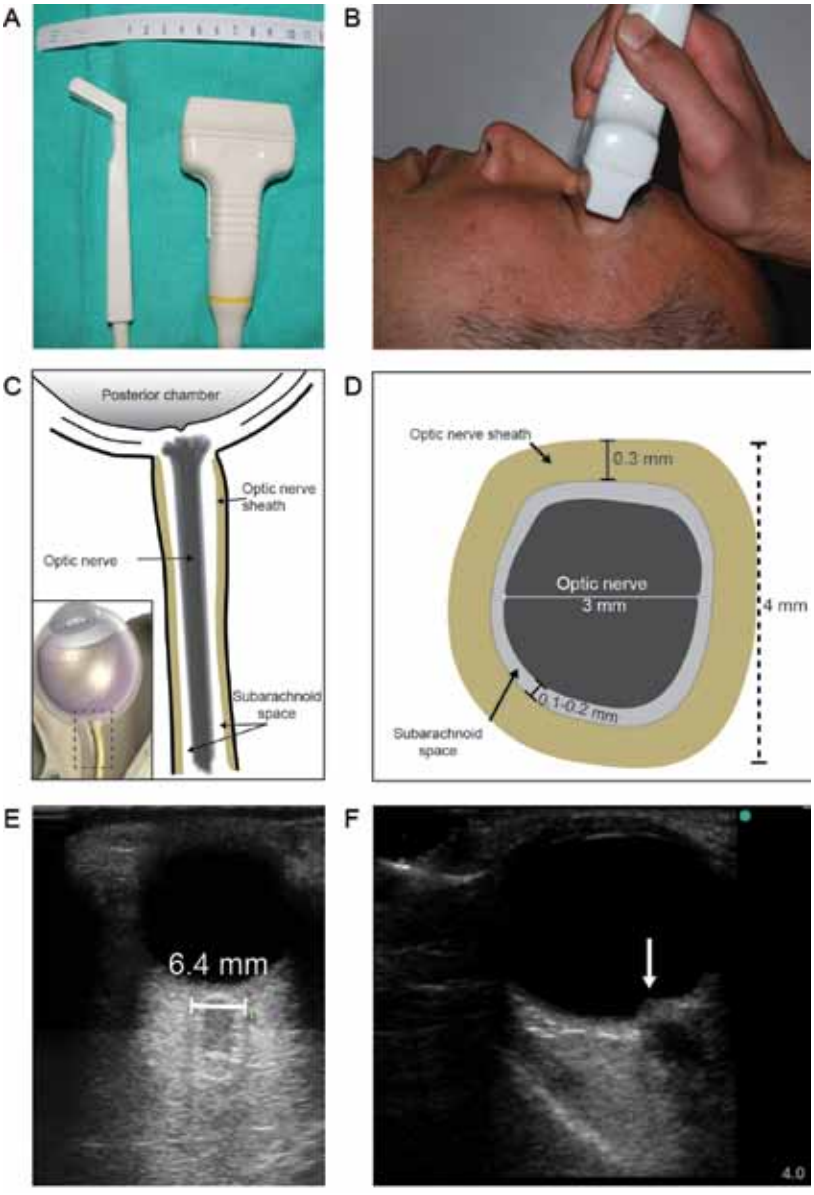


**Figure 1.** (A) Photo of high-frequency ultrasound (US) probes which can be (B) gently positioned over the eyelid of a closed eye. (C) Aspect of the eye and optic nerve sheath for which the measurement is taken at 3mm from the retina. (D) Cross sectional view of the optic nerve. (E) Dilated optic nerve and (F) papilloedema. (Adapted from Denault at al. 2018 and Soldatos et al. 2009).

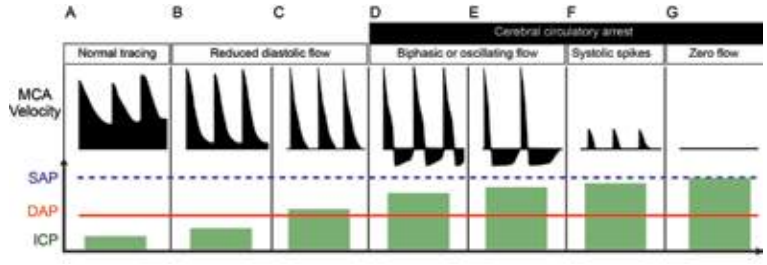


**Figure 2.** Intracranial hypertension and circulatory arrest. Transcranial Doppler changes in middle cerebral artery (MCA) mean flow with progressive increase in intracranial pressure (ICP) are shown compared with (A) normal MCA flow trace and normal ICP. (B,C) The initial stage has a normal pattern of systolic peaks with progressive (abnormal) reduction in diastolic velocities. (D-G)The three patterns that correspond to culmination in intracranial circulatory arrest are shown: biphasic oscillating flow, systolic spike flow and zero flow.

DAP diastolic arterial pressure SAP systolic arterial pressure

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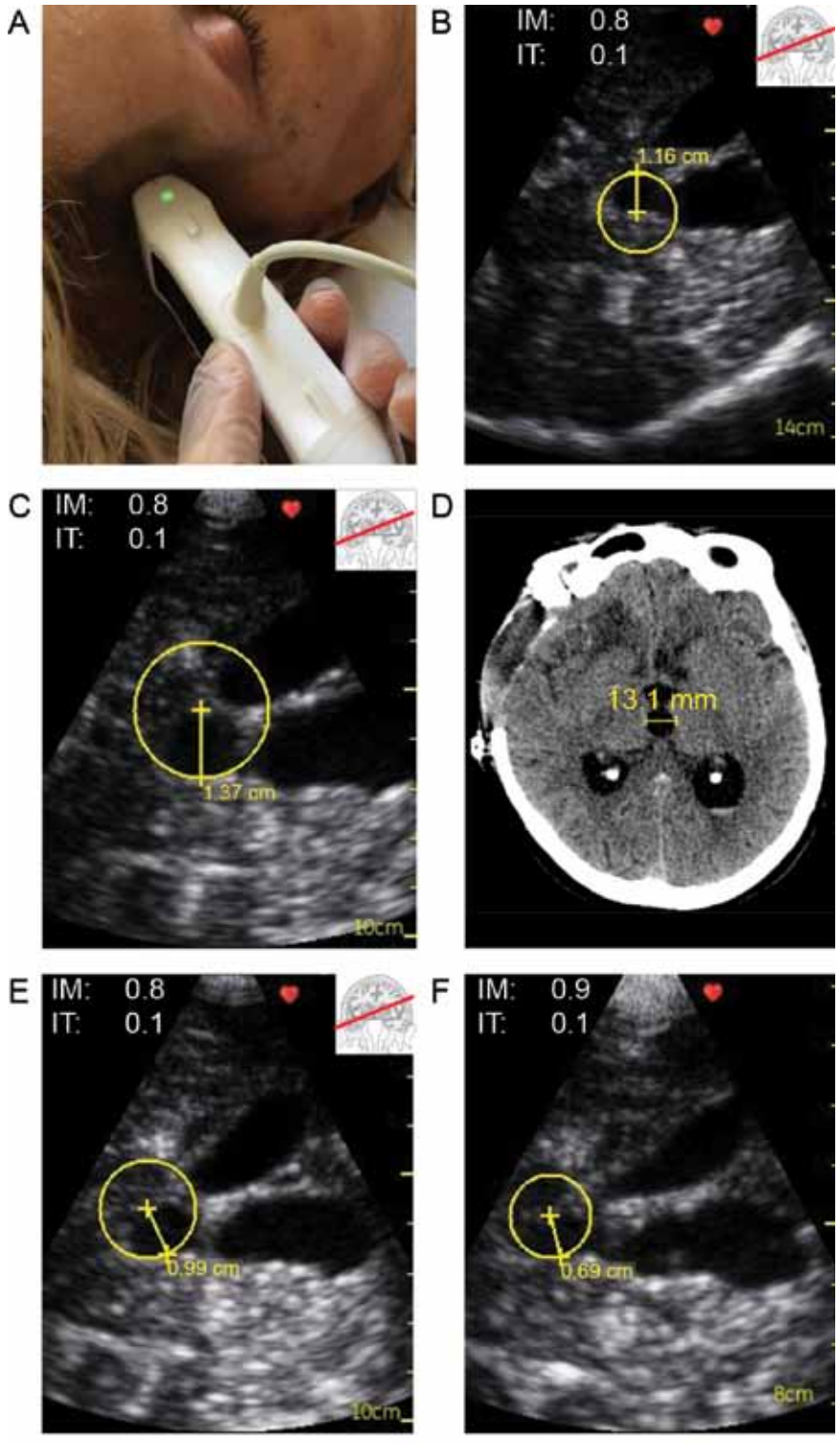


**Figure 3.** (A) Transcranial sonography (TCS) using a hand-held pocket ultrasound device (GE Vingmed Ultrasound AS, Horten, Norway) on a patient with craniectomy. (B) Prior to external ventricular drain (EVD) clamping, TCS showed a measurement of the 3rd ventricle at approximately 1.16cm. (C) On the third day, TCS showed a dilated 3rd ventricle measuring 1.37cm. (D) Computed tomography scan confirmed those sonographic findings showing a dilated 3rd ventricle measuring 1.31 cm (13.1mm). (E) One day after reopening the EVD, the size of the 3rd ventricle decreased to 0.99cm as measured by TCS. (F) The following day, it went down to 0.69 cm.

IM mechanical index IT thermal index
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and respiratory distress such as pulmonary oedema, acute respiratory distress syndrome, pneumothoraxes, pneumonia and pulmonary embolus.

The systematic, complete bilateral assessment of the chest allows the identification of key artefacts that are the result of the interplay between air, physiologic and pathologic tissue, pleura and fluid. When performed and interpreted correctly, the user can reach an accurate diagnosis, perhaps even obviating the need for other investigations such as chest radiography or computed tomography (Zanobetti et al. 2011; Volpicelli et al. 2008).

Numerous algorithms exist to direct users in the evaluation of the hypoxaemic patient (**Figure 5**), of which the BLUE protocol is probably the most well-known (Lichtenstein and Mezière 2008). The assessment begins with an examination of the anterior chest. The presence of lung sliding below the probe rules out a pneumothorax in that location. The absence of lung sliding does not enable a definitive diagnosis; however, a pneumothorax can still be ruled out by identifying a lung pulse in the pleura (fine oscillatory lung sliding from cardiac activity) or B lines, vertically projected pleural artefacts. Conclusive evidence of a pneumothorax can be identified by lung ultrasound by identification of a junction where areas of normal lung sliding and absent lung sliding meet the lung point (Zhang et al. 2006). Alveolar interstitial syndrome is identified if more than two B lines are seen in one intercostal space. Bilateral anterior B lines that have increased density in the dependent portions of the lung are characteristic of pulmonary oedema, where focal or skipped areas are more pathognomonic of pneumonitis or chronic interstitial disease respectively. A peripherally located focal lung consolidation could be a pulmonary embolus (Comert et al. 2013), which could be confirmed by detection of a deep venous thrombosis with ultrasound (Denault et al. 2018). Pleural effusion (**Figure 4**), consolidation and atelectasis (Lichtenstein et al. 2004) are usually found in the dependent lung regions. The volume of effusion can be estimated (Froudarakis 2008).

This modality is not without limitations, including the need for appropriate training, difficult imaging in obese patients or lung pathology that is very central with unaf-

fected pleural boundaries (Mayo et al. 2009; Denault et al. 2018). In such a situation, a transoesophageal approach can be considered (Cavayas et al. 2016). However, in conjunction with WHOBUS of other relevant organ systems as well as conventional clinical tools, the diagnostic yield remains high and will likely grow in conjunction with user expertise (Denault et al. 2018). Lung ultrasound has surpassed the popularity of transthoracic echocardiography in many centres (Yang et al. 2016). In 5 to 10% of the time, hypoxaemia will be associated with normal lung ultrasound. In those conditions, a cardiac aetiology such as intracardiac shunt (**Figure 6**), obstructive pulmonary diseases or acute pulmonary embolism should be suspected.

## WHOBUS in the haemodynamically unstable patient

A reported method of using WHOBUS to assist in management in haemodynamic instability involves a two-step approach (Vegas et al. 2014; Denault et al. 2014b). The first is to identify the mechanism of haemodynamic instability (distributive, haemorrhagic, cardiogenic or resistive), using a combination of inferior vena cava (IVC) and hepatic venous flow (HVF) interrogation (**Figure 7**). The second step is to identify the aetiology.

The initial step of identification of the mechanism of shock can be determined using the concept of venous return, which was popularised by Guyton et al. (1957). Haemorrhagic and distributive shock are typically associated with reduced systemic venous pressure. Cardiogenic shock is associated with an increase in right atrial pressure. Resistance to venous return can result from an infra-diaphragmatic obstruction such as abdominal compartment syndrome or a supra-diaphragmatic obstruction such as cardiac tamponade or tension pneumothorax. The IVC will be small in compartment syndrome (**Figure 8A-C**) and distended in tamponade. Rarely, IVC stenosis can occur after certain procedures such as liver transplantation (**Figure 8D**) and will be associated with a distended IVC with reduced ventricular cavities (Hulin et al. 2016). The hepatic venous flow will remain normal in shock states associated with preserved cardiac function (**Figure 7, pattern 1**) but will be abnormal when right ventricular dysfunction is present (**Figure 7 pattern 3**). However, in cases of resistance to venous return, absent or monophasic will be observed (**Figure 7 pattern 2&3**) (Beaubien-Souligny et al. 2018c).

A major advantage of WHOBUS over pres-

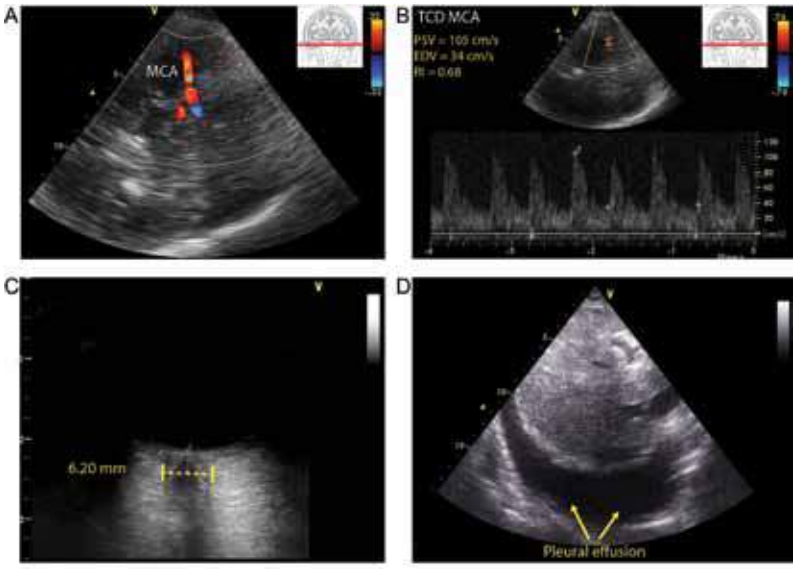


**Figure 4.** A 75-year-old man admitted to the intensive care unit for pneumonia and hypercapnic encephalopathy with right ventricular dysfunction from pulmonary hypertension. (A) Transcranial Doppler (TCD) of the right middle cerebral artery (MCA) showed a normal (B) resistance index (RI) of 0.68. (C) The optic nerve sheath diameter was 6.2mm and (D) using a left subcostal view, a pleural effusion was diagnosed. This imply that the dilated optic nerve sheath was not related to acute increase in intracranial hypertension but possibly secondary to an edematous state associated with right ventricular dysfunction.

EDV end-diastolic velocity PSV peak systolic velocity RI resistance index
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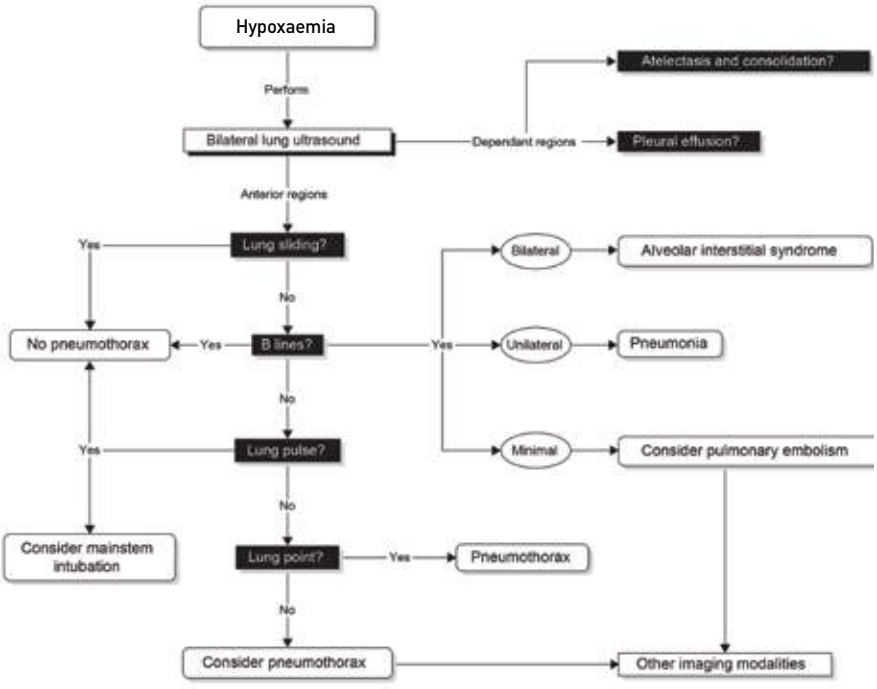


**Figure 5.** Lung ultrasound algorithm. Simple algorithm incorporating the notions presented in this chapter to assess the lung with ultrasound

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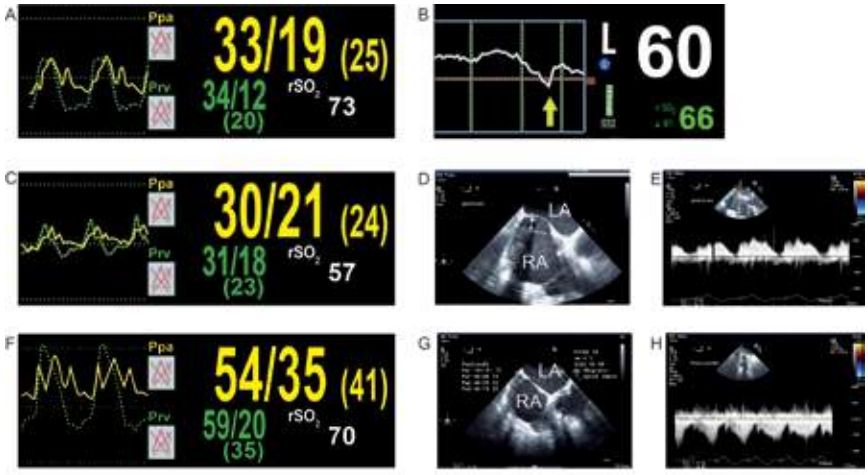


**Figure 6.** Acute right ventricular failure in a 70-year-old man undergoing aortic valve replacement. (A) His baseline pulmonary artery pressure (Ppa) and right ventricular pressure (Prv) waveform are shown. (B) Following separation from cardiopulmonary bypass (CPB) significant brain desaturation occurred (arrow on B) associated with haemodynamic instability. (C) The aspect of the Prv changed with diastolic pressure equalisation with the Ppa. (D) This was associated with right ventricular dysfunction and an atrial septal shift from the right atrium (RA) to the left atrium (LA). (E) This led to a right-to-left shunt across an atrial septal defect (ASD) with consequent hypoxaemia. (F) The patient returned on CPB and upon the second weaning attempt with the use of inhaled agents, adrenaline and increase in heart rate, the Prv increased and the diastolic pressure equalisation disappeared. (G) At the same time, the interatrial septum returned to a normal position and (H) the ASD shunt became left-to-right. This was associated with an increase in brain saturation ($rSO_2$) (B). The patient was extubated 2 hours later in the intensive care unit and had an uneventful post-op course.

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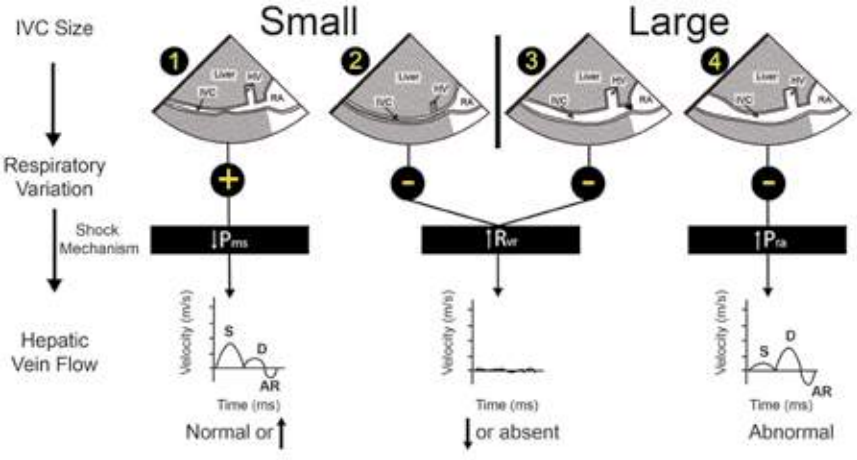


Projet 124 Figure 07

**Figure 7.** Shock mechanism. Algorithm to determine shock mechanism by using inferior vena cava (IVC) size, respiratory variation during spontaneous ventilation and hepatic venous flow (HVF) is shown. In patients with reduced mean systemic venous pressure (Pms) the IVC is small with respiratory variation (1) and the HVF is typically normal or increased due to the reduced dimension of the hepatic vein (HV). In patients with increased resistance to venous return (Rvr), the IVC can be collapsed from an abdominal compartment syndrome (2) or distended from a mechanical obstruction in the right atrial to IVC junction (3). In both situations, the HVF signal is significantly reduced, monophasic or absent. In a situation where the right atrial pressure (Pra) is increased, the IVC is dilated without respiratory variation (4) and the HFV will be abnormal with reduced systolic to diastolic velocity ratio.

AR atrial reversal velocity of the HVF D diastolic HVF velocity HV, hepatic vein IVC inferior vena cava Pms, mean systemic venous pressure RA, right atrium S systolic HVF velocity

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sure and flow-based monitors is the ability of WHOBUS to be used to identify the aetiology of shock. Reduced venous systemic pressure from blood loss into the pleural and peritoneal spaces is readily detected with WHOBUS, but gastrointestinal bleeding and retroperitoneal bleeding are more difficult to detect. Septic shock will reduce venous systemic venous pressure through an increase in venous compliance. Many infective causes are detectable with WHOBUS, such as pneumonia, empyema, cholecystitis, pyelonephritis, bacterial peritonitis in cirrhosis and endocarditis. Echocardiography is the gold standard for diagnosis of the aetiology of cardiogenic shock.

An important caveat is that two or more co-existing causes of haemodynamic instability may be present (Costachescu et al. 2002). In subarachnoid haemorrhage, myocardial depression can occur but also left ventricular outflow tract obstruction from the use of milrinone **(Figure 9)**. In septic shock both left and right-sided myocardial depression can be present (Kimchi et al. 1984; Romero-Bermejo et al. 2011; Turner et al. 2011; Vallabhajosyula et al. 2017), which if missed, may result in excessive fluid overload (Andrews et al. 2017). As mentioned, pulmonary oedema is readily detected with WHOBUS (Beaubien-Souligny et al. 2017). Portal pulsatility (**Figure 10**) predicts both portal hypertension and complications after cardiac surgery (Eljaiek et al. 2018 In press), including renal failure (Beaubien-Souligny et al. 2018a).

## WHOBUS in the oligo-anuric patient

The approach to the critically ill patient with an acute reduction of urine output involves multiple aspects. These include the rapid recognition of reversible causes and the accurate identification of patients who will progress to severe acute kidney injury (AKI). A blind approach consisting of administration of fluids in an attempt to increase urine output is often ill-advised as renal fluid responsiveness is absent in 50% of oliguric critically ill patients and resulting fluid overload may lead to complications (Prowle et al. 2010). Urinary sodium measurements are ineffective in identifying responders (Legrand et al. 2016).

WHOBUS may be used as an adjunct to enhance the evaluation of the oligoanuric patient. A proposed approach is presented in **Figure 11**. WHOBUS can not only be used to identify both presence and level of renal obstruction and urine formation, fluid responsiveness but can also be used to determine renal hypoperfusion and extra-renal haemodynamic factors contributing to renal hypoperfusion. These concepts are beyond the scope of this short article.

Kidney and bladder ultrasound are enabling clinicians to rapidly screen for the possibility

of lower or higher urinary tract obstruction. Lower urinary tract obstruction can occur frequently in critically ill patients because of urinary catheter dysfunction. Hydronephrosis may occur in the setting of urologic or other types of abdominal surgery (Narita et al. 2017) as well as retroperitoneal bleeding (Yumoto et al. 2018). After excluding urinary obstruction, Doppler ultrasound can be used to assess intra-renal blood flow velocities. Colour Doppler showing no signals in the renal parenchyma after adequate scale adjustments may offer a simple way to identify kidney hypoperfusion (Schnell and Darmon 2012; Barozzi et al. 2007; Schnell et al. 2014). The use of pulse-wave Doppler may have two applications. Arterial Doppler of the interlobar artery can identify patients with a highly abnormal resistive index (RI > 0.70). While this parameter is modified by numerous factors, a high RI has been demonstrated to be predictive of subsequent AKI or progression to severe AKI in critically ill patients and thus may be useful to identify which oliguric patients are the most concerning (Ninet et al. 2015). Venous Doppler at the level of the interlobar veins can assess whether alterations in intra-renal venous flow (periods of interrupted flow) are present (Iida et al. 2016; Nijst et al. 2017). The presence of severe alterations (venous flow present only in diastole) may suggest that venous hypertension is present and have a deleterious effect on kidney function, as it has been associated with AKI after cardiac surgery (Beaubien-Souligny et al. 2018b; 2018a).

## The impact of WHOBUS

In order to explore the impact of WHOBUS, we performed a search based on a systematic review reported by Heiberg et al. (2016) with the aim of identifying the impact on diagnosis, management and outcome of POCUS in the emergency room, intensive care unit and the operating room. PubMed, MEDLINE and EMBASE electronic databases were searched using the following search terms: ("Echocardiography" OR "Ultrasonography") OR "Heart Diseases/Ultrasonography" AND ("Perioperative Care" OR "Intensive Care" OR "Emergency Department") AND ("Humans"). The references of each publication were searched for eligible publications. The search was restricted to peer-reviewed, original research, including prospective, retrospective cohort, case–control and cross-sectional studies, but excluded systematic reviews, case reports, non-English language publications, studies published before 1 January 1995 or publications without the full text being available. Participants were

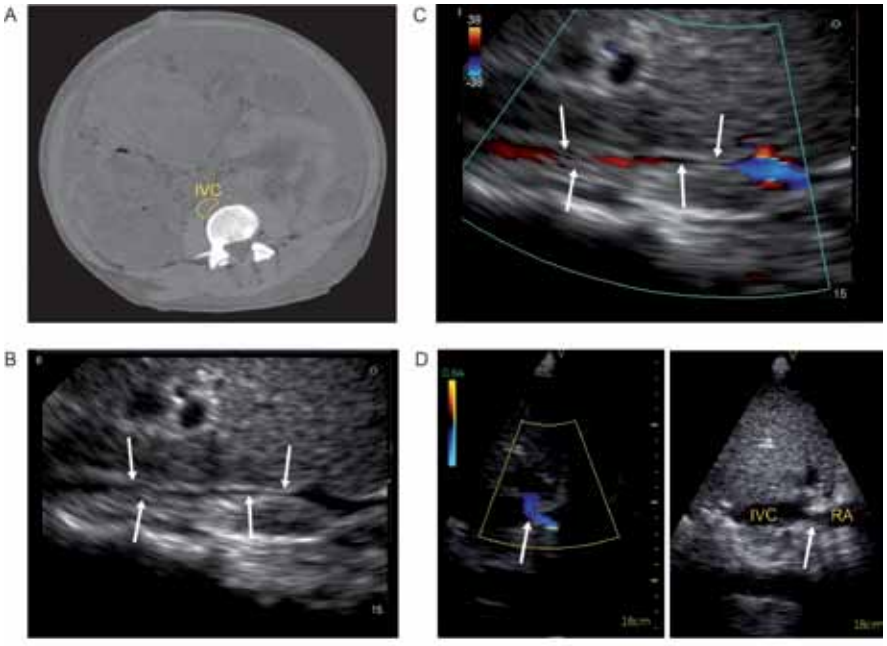


**Figure 8.** (A) Computed tomography of a patient with abdominal compartment syndrome. (B) Zoomed subxiphoid longitudinal view of the inferior vena cava (IVC) using bedside ultrasound shows a reduced diameter of the IVC (arrows). (C) In some patients, the compressed IVC can only be identified using colour Doppler (arrows). (D) Longitudinal subxiphoid view by ultrasound of a mechanical stenosis of the IVC (arrow) in a haemodynamically unstable patient after liver transplantation. Note the colour flow acceleration (arrow) at the level of the IVC stenosis.

RA right atrium

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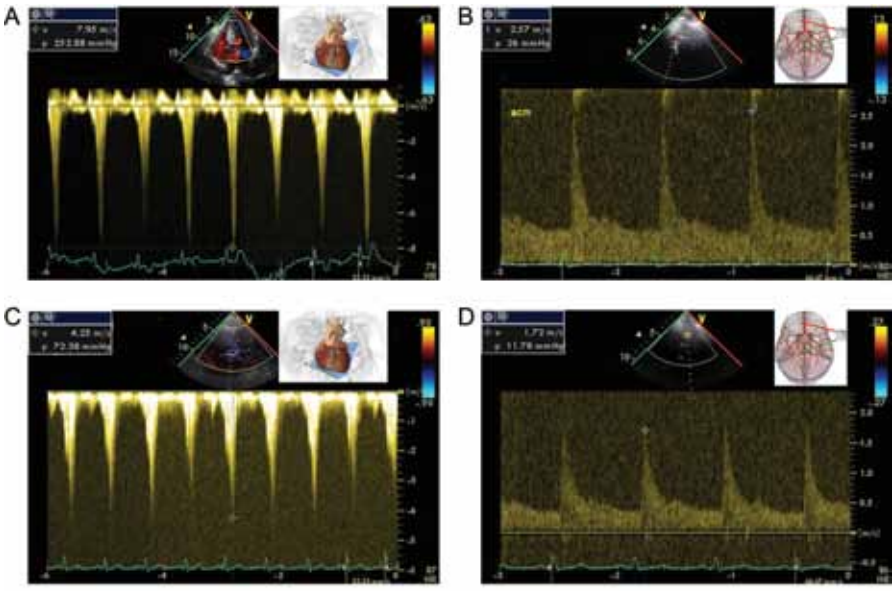


**Figure 9.** Left ventricular outflow tract (LVOT) obstruction. A 31-year-old man with subarachnoid haemorrhage receiving intravenous milrinone develops LVOT obstruction. (A) Note the significant pressure gradient (252 mmHg) and velocities (7.9 m/s) across the LVOT obtained using an apical five-chamber view. (B) The associated transcranial Doppler velocities of the right middle cerebral artery (MCA) were 2.57 m/s. (C,D) Following a bolus of 500mL of crystalloid, (C) the LVOT gradient drops to 72 mmHg and (D) the right MCA velocity decreases to 1.72 m/s.

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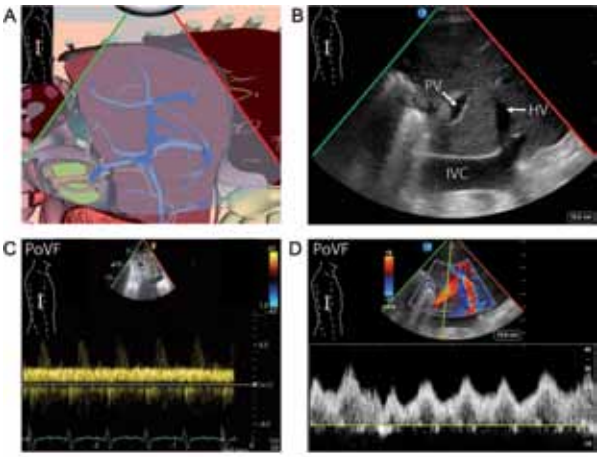


**Figure 10.** Portal venous flow. (A) Portal venous flow (PoVF) assessment from a posterior axillary line coronal view. (B) Using the same view, the inferior vena cava (IVC), portal vein (PV) and hepatic vein (HV) can be seen. Note the increased echogenicity of the PV wall. (C) Normal portal vein pulsed-wave Doppler has a monophasic signal indicating that blood is directed toward the transducer. Note the background pulsatile higher velocity of the hepatic artery, which is in the same direction. (D) Abnormal pulsatile portal flow with a pulsatility fraction of more than 50%. This finding indicates portal hypertension which, in right heart dysfunction, is associated with increased risk of complications.

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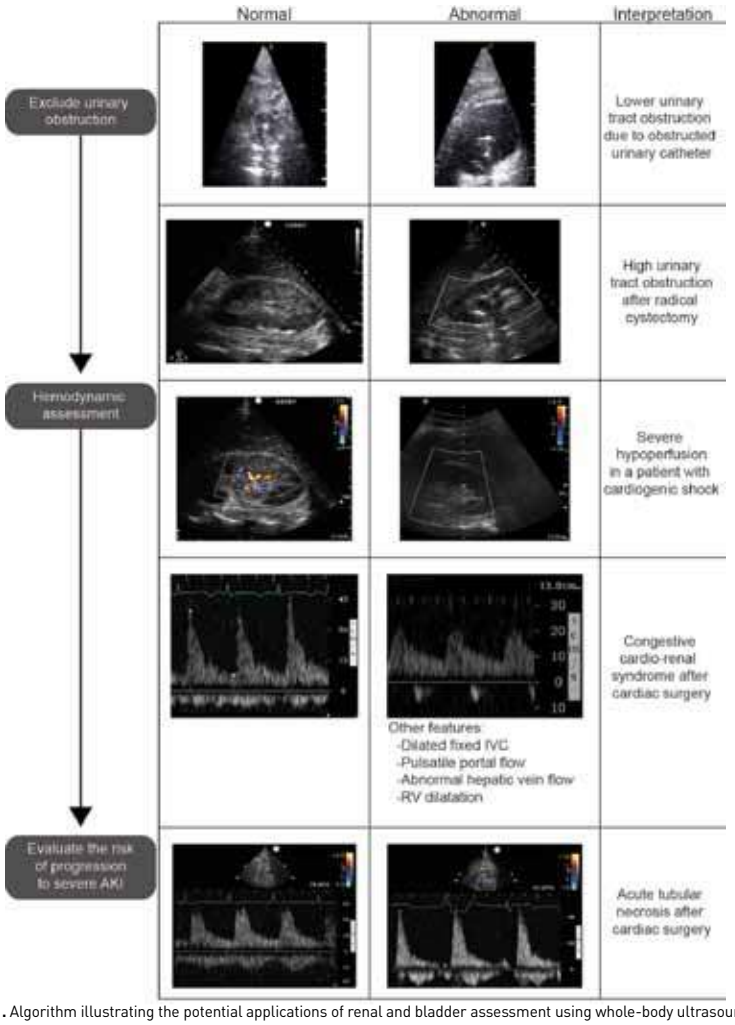


**Figure 11.** Algorithm illustrating the potential applications of renal and bladder assessment using whole-body ultrasound at the bedside of critically ill patients.

AKI acute kidney injury IVC, inferior vena cava RV right ventricle

humans aged at least 18 years. The intervention was focused echocardiography, lung ultrasound, abdominal ultrasound or deep venous thrombosis ultrasound performed either before, during or after non-cardiac surgery or in a critical care or emergency medicine setting. Outcomes included changes in clinical diagnosis, management, cardiac complications and death. For each individual publication, an outcome-level assessment of bias was performed that included the following parameters: patient selection, sonographer expertise, indication for surgery and indication for ultrasound. This bias assessment was considered in the synthesis of the result, but no scoring system was used. The impact on diagnosis, management and outcome of ultrasound of 2,020 patients are summarised in **Table 1**. Most studies were observational studies with few, randomised controlled trials. Changes in management and diagnosis range from 8% to 78%. Many of these studies have limited the use of ultrasound to the chest or the abdomen. There is a paucity of studies investigating whether an approach guided by ultrasound improves clinical outcomes. Consequently, there is an unmet need to design pragmatic trials to address these questions.

## Conclusion

The clinical uses of ultrasound in critical care are increasing. Whole-body ultrasound is becoming a routine and useful tool for the critical care physician and is becoming incorporated into critical care training (Diaz-Gomez et al. 2017). ■

### Conflict of interest

André Denault is on Speakers Bureau for CAE Healthcare and Masimo.

### Abbreviations

AKI acute kidney injury
HVF hepatic venous flow
ICP intracranial pressure
ICU intensive care unit
IVC inferior vena cava
ONSD optic nerve sheath diameter
PI pulsatility index
POCUS point-of-care ultrasound
TCCS transcranial colour-coded sonography
WHOBUS whole-body ultrasound

## References

**For full references, please email editorial@icu-management.org or visit https://iii.hm/qp2**

**Table 1.** Impact of point-of-care focus cardiac ultrasound (FCU) on diagnosis, management and outcome of patients in the anaesthesia and intensive care setting

| First author, year | Methodology | Ultrasound operator | Cohort | Summary |
|---|---|---|---|---|
| **Impact of FCU on diagnosis and management** | | | | |
| **Emergency department and pre-hospital setting** | | | | |
| Breitkreutz 2010 | Randomised controlled trial | Emergency physicians | 204 patients undergoing cardiopulmonary resuscitation (100) or in shock (104) | In 35% of those with an electrocardiographic (ECG) diagnosis of asystole, and 58% of those with pulseless electrical activity, coordinated cardiac motion was detected, and associated with increased survival. Echocardiographic findings altered management in 78% of cases. |
| Chardoli 2012 | Randomised controlled trial | Emergency physician residents | 100 patients with out-of-hospital cardiac arrest requiring cardiopulmonary resuscitation with initial diagnosis of pulseless electrical activity. 50 randomised to FCU and 50 controls | FCU identified mechanical ventricular activity in 78% (i.e. not pulseless electrical activity but shock) in whom FCU identified pericardial effusion in 14% and hypovolaemia in 22%. Return of spontaneous circulation occurred in 43% of patients where mechanical ventricular activity was identified with FCU. No patients had return of spontaneous circulation where FCU identified no mechanical ventricular activity.<br>Among patients who did not receive FCU, no reversible aetiology was detected. However, there was no significant difference in resuscitation results between groups (p =0.52). |
| Levitt 2002 | Prospective non-comparative observational study | Cardiac sonographers | 83 patients admitted with either chest pain (45) or dyspnea (38) with clinical suspicion of cardiovascular pathology by a senior emergency physician | There was a change in diagnosis in 45%, a change in management in 30%, and a change in disposition in 13% of patients. |
| Jones 2004 | Randomised controlled trial | Attending emergency physicians | 184 patients with nontraumatic hypotension and symptoms of shock (e.g. syncope, dyspnea, unresponsiveness, fatigue) of whom 88 received FCU on admission and 96 received FCU 15-30 minutes after admission | Early FCU increased the likelihood of detecting the correct diagnosis of hypotension from 50% to 80%. |
| **Anaesthesia setting** | | | | |
| Canty 2009 | Prospective non-comparative observational | Anaesthesiologists | 87 patients undergoing non-cardiac surgery (preoperative, intraoperative and postoperative) received FCU when transthoracic echocardiography (TTE) was requested by the attending aneasthesiologist | FCU changed medical management in 34% (haemodynamic management, anaesthetic technique, and postoperative care) and surgical management in 7% (surgery altered in 2% and deferred in 5%). |
| Cowie 2011 | Prospective non-comparative observational | Anaesthesiologists | 170 patients scheduled for elective or non-elective surgery with either haemodynamic instability, undifferentiated murmur / valve disease, suspected ventricular dysfunction, dyspnea or hypoxaemia, poor functional capacity, suspected pulmonary hypertension or dysrhythmia | FCU changed management in 82% of patients (same changes as above). |
| Canty 2012a | Prospective non-comparative observational | Anaesthesiologists | 100 patients scheduled for elective non-cardiac, non-minor surgery who were referred for preoperative assessment by an anaesthesiologist in the preoperative clinic where the anaesthesiologist suspected significant cardiac disease or patient age>65 years | FCU changed management in 54% including changed surgery in 2%. Changes included a step up in treatment in 36% (delay surgery for cardiology assessment, intraoperative invasive monitoring and vasopressor infusion, postoperative intensive care unit (ICU)) and a step down in treatment in 8% (circumvented the need for invasive monitoring, vasopressor infusion, postoperative ICU admission). |
| Canty 2012c | Prospective non-comparative observational | Anaesthesiologists | 99 patients scheduled for urgent (non-elective surgery) where the attending anaesthesiologist suspected significant cardiac disease or patient age>65 years | FCU changed diagnosis in 67% and changed management in 44% including changed surgery in 2%. Changes included a step up in treatment in 20% and a step down in treatment in 34% (same changes as above). |
| Botker 2014 | Prospective non-comparative observational | Anaesthesiologist | 112 patients scheduled for urgent (non-elective) non-cardiac surgery were screened with FCU before surgery | FCU changed the diagnosis in 17% and changed management in 12%. |
| **Intensive care setting – screening** | | | | |
| Manasia 2005 | Prospective non-comparative observational | Intensivists who received brief training and FCU checked by cardiac sonographers | 90 patients admitted to intensive care after non-cardiac surgery and cardiac surgery | FCU changed diagnosis in 84% and changed management in 37%. FCU imaging was diagnostic in 94% and interpreted correctly in 84%. |
| Stanko 2005 | Prospective non-comparative observational | Cardiac sonographers | 90 patients admitted to intensive care after non-cardiac surgery and cardiac surgery | FCU led to changed management in 41% of patients. Major changes occurred in 8% (surgery changes or other new active treatment) and minor changes in 92% (medication changes or referral). |
| Marcelino 2008 | Prospective non-comparative observational | Intensivists | 704 patients admitted to intensive care received FCU | FCU revealed abnormal findings in 33%, of which 7.5% were severe. |
| Christiansen 2013 | Prospective non-comparative observational | Intensivists | 80 patients received FCU and lung ultrasound 1 day after open aortic valve replacement | FCU and lung ultrasound changed the diagnosis of pericardial and pleural effusion in 51% of patients. |
| **Intensive care setting – FCU indicated** | | | | |
| Joseph 2004 | Prospective non-comparative observational | Cardiac sonographers | 100 patients admitted to intensive care with shock (systolic blood pressure < 100mmHg or fall in systolic blood pressure of ≥25% and inotrope use or evidence of low output or pulmonary/venous congestion) received FCU | Cardiac cause of shock was identified by FCU in 63%. FCU resulted in a change in management in 51%, including 29% medical therapy changes and 22% procedural changes (surgery 12%, pericardiocentesis 4%, intra-aortic balloon pump 4%, thrombolysis 2%, angioplasty 1%). |
| Orme 2009 | Prospective non-comparative observational | Intensivists | 187 patients admitted to intensive care after non-cardiac surgery. Indications included LV and RV assessment, infective endocarditis, pericardial effusion, and pulmonary oedema. | FCU led to a change in management in 51% of patients and included changes to fluid administration, inotrope or drug therapy, and treatment limitation. The main impact was in haemodynamically unstable patients. Diagnostic images were obtained in 91.3% of spontaneously breathing and 84.2% of mechanically ventilated patients. |
| **Impact of FCU on outcome** | | | | |
| Plummer 1992 | Retrospective comparative cohort study | Emergency physicians | 49 patients admitted to the Emergency Department with penetrating cardiac injury of whom 28 received FCU on arrival and 21 did not | In patients who received FCU there was greater survival (100% vs 57.1%, p=0.01), Glasgow Outcome Score (5.0 vs 4.2, p=0.007) and a shorter time to diagnosis and disposition for surgical intervention (15.5±11.4 vs 42.4±21.7 minutes p < 0.001). |

| | | | | |
|---|---|---|---|---|
| Canty 2012b | Retrospective comparative cohort study | Anaesthesiologists | 130 patients scheduled for hip fracture surgery at two institutions of whom 64 received preoperative FCU and 66 matched controls who did not receive FCU | Preoperative FCU was associated with lower mortality at 30 days (4.7% vs 15.2%, p=0.047, number needed to treat 9.5) and 12 months after surgery (17.1% v 33.3%, p=0.031, number needed to treat 6.2). |
| Ferrada 2014 | Randomised controlled trial | Surgeons, Emergency Department physicians, emergency medicine and surgical residents | 215 patients admitted to the Emergency Department with blunt or penetrating trauma with systolic blood pressure <100mmHg, mean arterial blood pressure <60mmHg or heart rate >120 beats per minute | Patients who received FCU received less fluids (1.5L vs 2.5L, p < 0.0001), less time to surgery (35.6 minutes vs 79.1 minutes, p=0.0006), higher rate of intensive care unit admission (80.4% vs 67.2%, p=0.04) and mortality was lower but not statistically significant (11.0% vs 19.5%, p=0.09). |
| Kanji 2014 | Retrospective comparative cohort study | Intensivists | 110 patients admitted to intensive care with shock (despite vasopressor infusion and intravenous fluid challenge achieving a central venous pressure (CVP) of at least 8mmHg) received FCU compared with 110 matched retrospective controls who did not receive FCU | Patients receiving FCU received less fluids (49 (33-74) vs 66 (42-100) mL/kg, p=0.01), more dobutamine infusions (22% vs 12%, p=0.01). FCU was associated with less mortality at 28-days (34% vs 44%, p=0.04, NNT 9.1), less stage 3 acute kidney injury (20% vs 39%), and more days alive and free of renal support (28 (9.7-28) vs 25 (5-28), p=0.04). |
| Canty 2018 | Pilot randomised controlled trial | Anaesthesiologists | 100 patients scheduled for hip fracture surgery of whom 49 received 49 preoperative FCU and 51 controls who did not receive FCU | FCU altered the management of 35% of participants. The 30-day primary composite outcome of any death, acute kidney injury, non-fatal myocardial infarction, stroke, pulmonary embolism or cardiac arrest within 30 days of surgery occurred in 7 of the FCU group patients and 12 of the control group patients (group separation 39.3%). Number needed to treat (NNT) 10.9. |
| **Impact of lung ultrasound or/and FCU on diagnosis and management** | | | | |
| **Ultrasound screening** | | | | |
| Christiansen 2013 | Prospective non-comparative observational | Intensivists | 80 patients received FCU and lung ultrasound 1 day after open aortic valve replacement | FCU and lung ultrasound (LUS) changed the diagnosis of pericardial and pleural effusion in 51% of patients. |
| Alsaddique 2016 | Prospective non-comparative observational | Cardiac sonographers | 91 patients received FCU and lung ultrasound 1 day after cardiac surgery requiring median sternotomy | FCU and/or LUS changed the diagnosis of important cardiac and/or respiratory disorders in 67% including cardiac dysfunction (42%), pericardial effusion (5%), mitral regurgitation (2%), hypovolaemia (1%), pleural effusion (33%), pneumothorax (4%), alveolar interstitial syndrome (3%) and pneumonia (1%). |
| Ford 2017 | Prospective non-comparative observational study | Medical students with images reviewed by a surgeon | 78 patients undergoing cardiac or thoracic surgery received lung ultrasound and chest radiography either before (42 patients) or after (36 patients) surgery (not in intensive care) | LUS identified lung pathology that was missed by clinical assessment and chest x-ray in 20% of patients. Lung ultrasound detected lung pathology in 10 of 42 (24%) patients before surgery in the preoperative clinic and in 34 of 36 (94%) patients after surgery. |
| Haji 2018 | Prospective non-comparative observational | Intensivists | 93 patients admitted within <24h to intensive care received FCU and lung ultrasound | Haemodynamic diagnosis was altered in 66% of participants, including new (14%) or altered (25%) abnormal haemodynamic states or exclusion of clinically diagnosed abnormal haemodynamic state (27%). Valve pathology of at least moderate severity was diagnosed for mitral regurgitation (7%), aortic stenosis (1%), aortic stenosis and mitral regurgitation (1%), tricuspid regurgitation (3%), and 1 case of mitral regurgitation was excluded. Management changed in 65% of participants including increased (12%) or decreased (23%) fluid therapy, and initiation (10%), changing (6%) or cessation (9%) of inotropic, vasoactive or diuretic drugs. |
| **Ultrasound indicated** | | | | |
| Silva 2013 | Prospective non-comparative observational study | Intensivists | 78 patients admitted to intensive care with acute respiratory failure received FCU, lung and deep venous thrombosis (DVT) ultrasound | Ultrasound was more accurate than standard assessment (83% vs 63%, p=0.02) resulting in a change in diagnosis of 20%. Receiver operating characteristic curve (ROC) analysis showed greater diagnostic performance of ultrasound than standard approach in pneumonia (0.74+-0.12 vs 0.87+-0.14, p=0.02), acute haemodynamic pulmonary oedema (0.79+-0.11 vs 0.93+-0.08, p=0.007), decompensated chronic obstructive pulmonary disease (0.8+-0.09 vs 0.92 +- 0.15, p=0.05), and pulmonary embolism (0.81 +- 0.17 vs 0.65+-0.12, p=0.04). |
| Bataille 2014 | Prospective non-comparative observational study | Intensivists | 136 patients admitted to intensive care with acute respiratory failure received FCU and lung ultrasound | The diagnostic accuracy of combined FCU and lung ultrasound was greater than lung ultrasound alone (p=0.05). Comparisons between ROC curves showed that combined FCU and lung ultrasound improves the diagnosis of acute haemodynamic pulmonary oedema (p=0.001), pneumonia (p=0.001), and pulmonary embolism (p=0.001). |
| Xirouchaki 2014 | Prospective non-comparative observational study | Intensivists | 253 patients admitted to the intensive care unit (108 in patients with unexplained hypoxaemia and 145 with suspected lung pathology) received lung ultrasound | LUS changed the diagnosis in 86% and changed the management in 47%, consisting of invasive interventions (chest tube, bronchoscopy, diagnostic thoracentesis/fluid drainage, continuous venous–venous haemofiltration, abdominal decompression and tracheotomy) in 32% and noninvasive interventions (positive end-expiratory or PEEP change/titration, recruitment manoeuvre, diuretics, physiotherapy, change in bed position, antibiotics initiation/change) in 15%. |
| Zanobetti 2017 | Prospective non-comparative observational study | Emergency physicians | 2,683 patients admitted to the Emergency Department with dyspnea received FCU and lung ultrasound | Average time to diagnosis was lower in patients who received ultrasound compared to those who received standard evaluation without ultrasound (24+-10 min vs 186+-72 min, p=0.025). The diagnostic accuracy was similar for acute coronary syndrome, pneumonia, pleural effusion, pericardial effusion, pneumothorax, and dyspnea from other causes. Ultrasound was more accurate in diagnosis of heart failure and standard evaluation was more accurate in the diagnosis of chronic obstructive pulmonary disease/asthma and pulmonary embolism. |
| **Impact of lung ultrasound or/and FCU on outcome** | | | | |
| Laursen 2014 | Randomised controlled trial | Respiratory physician | 317 patients admitted to the Emergency Department with respiratory rate of more than 20 breaths per minute, oxygen saturation of less than 95%, requiring oxygen therapy, dyspnea, FCU, lung and DVT ultrasound, cough, or chest pain. 158 received ultrasound on admission and 157 did not. | Patients receiving ultrasound had a higher proportion of correct presumptive diagnosis at 4 hours after admission (88.0% [82.8–93.1] vs 63.7% [56.1–71.3], p<0·0001). No differences were found in hospital length of stay or in-hospital mortality. |
| Atkinson 2018 | Randomised controlled trial | Emergency physicians | 270 selected patients admitted to the Emergency Department with persistent hypotension in whom 136 received point-of-care ultrasound (FCU, lung and abdomen) and 134 controls who did not receive point-of-care ultrasound | Follow-up was completed for 270 of 273 patients. The most common diagnosis in more than half the patients was occult sepsis. There was no difference between groups for the primary outcome of 30-day survival (point-of-care ultrasonography group 104 of 136 patients versus standard care 102 of 134 patients; difference 0.35%; 95% binomial confidence interval [CI] −10.2% to 11.0%), survival in North America (point-of-care ultrasonography group 76 of 89 patients versus standard care 72 of 88 patients; difference 3.6%; CI −8.1% to 15.3%), and survival in South Africa (point-of-care ultrasonography group 28 of 47 patients versus standard care 30 of 46 patients; difference 5.6%; CI−15.2% to 26.0%). There were no important differences in rates of computed tomography (CT) scanning, inotrope or intravenous fluid use, and ICU or total length of stay. |

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# Clinical assessment of critically ill patients by whole-body ultrasonography

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In this article we focus on the evidence of whole-body ultrasonography used for hypotension or shock. We first highlight individual ultrasound components in association to hypotension and shock. Second, we provide an outline of current literature on whole-body ultrasonography, its effect on outcome, and try to integrate the previous observations.

Critical care ultrasonography (CCUS) is increasingly advocated and used, and is defined as point-of-care image acquisition, interpretation and clinical application, all performed by the critical care clinician, and directed to inform on specific clinical questions (Narasimhan et al. 2016). Recently, Zaidi and Koenig (2018) splendidly described the use of ultrasonography in critical care in this journal, where they advocate using methods of CCUS appropriate for each patient-specific problem. One of the frequent problems in critically ill patients is how to guide diagnostics and treatment in patients with hypotension or shock. In these patients diagnostic challenges focus on unravelling the underlying cause(s), and treatment challenges focus on the need and titration of fluids, vasopressors and inotropes. Hypotension can result from various underlying causes, such as cardiac failure, cardiac tamponade, tension pneumothorax, sepsis due to pneumonia, liver and spleen rupture due to blunt trauma and ruptured aortic aneurysm. To capture the entire scope of the problem or provide necessary clues for unravelling the underlying causes, whole-body ultrasonography has been advocated to be more valuable than single organ CCUS (Narasimhan et al 2016; Lichtenstein and Axler 1993).

> recent innovations enable assessments of organs in more detail

## Individual component ultrasonography

The individual components of whole-body ultrasonography have been extensively described (Frankel et al. 2015). Volpicelli et al. presented in their study on undifferentiated hypotension in the emergency department a protocol that summarises the views of the heart, lungs, inferior vena cava, (minimal) abdomen and peripheral veins with a focus on diagnosis (Volpicelli et al. 2013). Mok advocated the SIMPLE approach to manage patients with shock (Mok 2016). Balmert et al. made a systematic overview on ultrasonography in the acute setting (Balmert et al. 2018). They highlighted all the potential indications for ultrasonography and described recent innovations that enable assessment of organs in more detail, for example by strain imaging of the heart or measuring perfusion of the kidneys and liver. Our description of each organ focuses on the potential of ultrasonography to unravel underlying causes in patients with hypotension or shock as well as the potential to guide treatment.

### Cardiac ultrasonography

The heart is one of the most important ultrasonography sites for identifying potential causes of hypotension. Different types of shock can be discriminated based on the information acquired from CCUS. The most striking example is a pericardial effusion in the presence of obstructive shock. Ultrasonography of the heart or echocardiography is often summarised, and numerous protocols have been developed (RACE [rapid assessment by cardiac echo]/ RUSH [rapid ultrasound in shock]/FATE [focused assessed transthoracic echocardiography]) (Volpicelli et al. 2013; Perera et al. 2010; McLean and Huang 2012; Jensen et al. 2004; McLean 2016). The ultrasound signs are evaluated using basic level two-dimensional (2D) and M-mode ultrasonography. Underlying major cardiac pathology can be visualised using the orthodox parasternal, apical 4 - and 5 chamber and subcostal 4 chamber views identifying pericardial effusions, severely depressed contractility of the left (LV) and/or right ventricle (RV), (severe) dilatation of the LV and/or RV, or clues to intravascular volume status (e.g. "kissing ventricle") (McLean and Huang 2012). Assessment of LV contractility can be done by measuring fractional shortening using M-mode (FS) and LV ejection fraction (LVEF) using eyeballing or the modified Simpson biplane method; eyeballing is the preferred method, but it requires training.

Studies have shown that non-cardiologists could achieve good agreement on the visual estimation of LV ejection fraction with cardiologists (Unlüer et al. 2014; Randazzo et al. 2003; Bustam et al. 2014). Assessment of right ventricular function is challenging; the measurement of the Tricuspid Annular Plane Systolic Excursion (TAPSE) is often used to get a global estimation of right ventricular function, together with an impression of the presence or absence of right ventricular dilatation. More advanced techniques such as colour Doppler, tissue Doppler imaging and speckle tracking allow identification of (major) valve defects, LV diastolic dysfunction and more subtle analyses of cardiac dysfunction (i.e. Strain, RV S'). Measuring strain is a promising tool for early diagnosis of cardiac injuries that are non-detectable with conventional measurements (Boissier et al. 2017; Sanfilippo et al. 2017; Clancy et al. 2017; De Geer et al. 2015). Despite suboptimal positioning and hampered image quality in the critically ill, several studies have shown that these advanced techniques/measurements are viable in the critical care setting (Boissier et al. 2017; Sanfilippo et al. 2017; Clancy et al. 2017; De Geer et al. 2015).

The presence or absence of cardiac dysfunction may inform the clinician about the type of ([non-]cardiogenic) origin of the shock. However, in critically ill patients, diagnostic clues are not so straightforward and frequently patients present with a combination of types of shock. The cardiac ultrasonography findings ultimately have to be integrated into the overall assessment of the patient.

Besides diagnostic information, CCUS of the heart can also give more information on the haemodynamic profile at hand and guide treatment. For instance, an advanced measurement such as ultrasound-derived cardiac output can evaluate fluid responsiveness or the effects of inotropes. Kanji et al. (2014) suggested that echocardiography in patients with undifferentiated shock in the ICU guided towards treatment with less fluids and more dobutamine, which was associated with improved 28-day mortality and improved renal function. However, these results were obtained by a retrospective cohort without echocardiography and a prospective cohort with echocardiography.

**Lung ultrasonography**

Lung ultrasonography relies mainly on the detection of ultrasonography artefacts (Lichtenstein 2015). In the intercostal space the pleural line is seen as the hyperechoic line that moves upward and downward with ventilation, which is called lung sliding: the movement of the visceral with the parietal pleura (Goffi et al. 2018). The A-lines are hyperechoic horizontal lines and they are reverberation artefacts generated from the strong reflectivity of the pleural line. Along with lung sliding, they make up the normal view of lung tissue in ultrasonography (Miller 2016; Lichtenstein 2014). When the lung tissue increases in density, due to increased lung weight (e.g. accumulation of blood, lipids, pus or proteins, increased extravascular lung water, deposition of collagen and fibrotic tissue) or lung de-aeration (i.e. atelectasis), this is associated with the appearance of B-lines. B-lines are discrete laser-like vertical hyperechoic reverberation artefacts that arise from the pleural line and extend to the bottom of the screen without fading, erasing the A-lines (Volpicelli et al. 2012). It is considered a positive finding when there are three or more B-lines in a longitudinal plane between two ribs, because even two lines may be present in the normal lung. The presence of multiple B-lines is the sonographic sign of lung interstitial syndrome, which can be caused by pulmonary oedema, interstitial pneumonia and diffuse parenchymal lung disease (pulmonary fibrosis) (Covic et al. 2018). Furthermore, a focal (localised) sonographic pattern of interstitial syndrome may be seen in the presence of atelectasis, pulmonary contusion, pulmonary infarction, pleural disease and neoplasia.

**Ultrasonography of the inferior vena cava**

Normally the inferior vena cava (IVC) has a diameter with an average of around 20 mm and it will collapse slightly at inspiration and dilate again at expiration. Ferrada et al. (2012) found in 108 acutely admitted critically ill patients that guiding fluid treatment based on a IVC of 20 mm or smaller was associated with a decrease in lactate levels. By measuring the minimal and maximal diameter of the IVC, the Inferior Vena Cava–Collapsibility Index (IVC–CI) can be calculated (Brennan et al. 2007). A small IVC–CI would imply venous congestion, for there is too much intravascular fluid and the IVC can no longer collapse normally. A normal collapsibility is arbitrarily set at 40 to 50%, although the diagnostic accuracy is not perfect (Brennan et al. 2007; Lang et al. 2015). In mechanically ventilated patients the IVC–CI may not be as reliable, since intrathoracic pressure is mechanically increased (Ilyas et al. 2017). Citilcioglu et al. (2014) investigated the association between the IVC measured by bedside ultrasonography and CVP measured by a central venous catheter. In 45 patients the IVC diameter at both expiration and inspiration was associated with CVP in spontaneous breathing patients. In mechanically ventilated patients this association was not seen. Stawicki et al. (2009) showed similar results.

**Liver and spleen ultrasonography**

Liver Doppler ultrasonography may show signs of abnormalities in haemodynamic function (McNaughton et al. 2011). The splenic arterial and venous flow indices have similarly mostly been investigated in patients with liver disease (Baik 2010; Piscaglia et al. 2002), and no association with systemic haemodynamic function was found. One study by Bolognesi et al. (2012) evaluated the use of splenic ultrasonography in heart failure patients and found that splenic pulsatility index was associated with right arterial pressure and right ventricle end-diastolic pressure, suggesting that this measurement reflects congestion of the spleen. Characteristics of arterial and venous flow in the liver and spleen have been used mostly in specific disease, but could add to our understanding of venous congestion or shock in a more general population of critically ill patients.

**Renal and bladder ultrasonography**

Renal ultrasonography includes focused renal ultrasonography for evaluation of renal, pre- or post-renal pathology. The Renal Resistive Index (RRI) and Venous Impedance Index (VII) have been used in a variety of clinical settings. Doppler imaging identifies changes in blood flow at the microvascular level (Kelahan et al. 2018). Evaluation of changes in blood flow at different sites of the renal

**Table 1.** Examples of studies on whole-body ultrasonography focusing on diagnosis and outcome

| First author, year | No. of centres | Pt* | Study type | Population | Measurement and timing | Organs assessed | Ultrasonographers | Results |
|---|---|---|---|---|---|---|---|---|
| **Intensive Care Unit** | | | | | | | | |
| Manno 2012 | 1 | 125 | Prospective | ICU patients | One-time assessment within 12h of admission | Heart, lung, abdomen, large veins | Attending physician, independent of treatment | Modified admitting diagnosis in 26%, led to changes in therapy in 18% |
| Wang 2014 | 1 | 128 | Prospective | ICU patients with pulmonary oedema | Organ function/ signs of oedema on admission | Heart, lung, IVC | Independent attending intensivist, not involved in patient care, no validation | Faster and better clinical decision making, shortened time of diagnosis, decreased fluid use |
| Zieleskiewicz 2015 | 142 | 709 | Snapshot prospective | ICU patients | As deemed necessary, 87% to assess diagnosis and 13% procedural guidance | Heart (51%), lung (17%), brain 16%, abdomen (< 10%) | No validation | Diagnosis confirmed in 63% and changed in 21% |
| Brunauer 2016 | 1 | 30 | Prospective | Septic shock patients | Pulsatility indices at day 1, 2 and 3 | Liver, spleen, kidney, intestines | 1 of 2 investigators, no info about validation of images | Peripheral perfusion (CRT/mottling) may be related to pulsatility index of visceral organs in early septic shock |
| Bernier-Jean 2017 | 3 | 968 | Retrospective | ICU patients | - | Heart, lung, IVC, abdomen | Physicians working on the ICU, independent evaluation random sample <10% | Ultrasound findings led to a change in diagnosis in 25% and to a change in management in 40% |
| Yin 2017 | 1 | 451 | Retrospective | ICU patients | One-time assessment within 12h of admission | Heart, lung, IVC | Experienced and trained physician, double checked by senior physicians | Ultrasound findings predict possible prognosis and aids caregivers in understanding haemodynamic characteristics |
| Lanspa 2018 | 1 | 30 | RCT | Septic shock patients | Following RCT algorithm, median time to randomisation 3.1 hrs | Heart, lung, IVC | Diagnostic cardiac sonographer or an echocardiographer-physician | No difference between patients in EDGT arm vs ECHO arm, likely due to resuscitation at ED |
| **Emergency department** | | | | | | | | |
| Jones 2004 | 1 | 184 | RCT | Non-traumatic hypotension | Immediate vs. late goal-directed ultrasound | Heart, IVC, abdomen | Third-year resident or attending physician of emergency medicine, all supervised if necessary | Number of differential diagnoses at 15 min 4 vs. 9 and at 30 min 4 vs. 3 in the immediate versus late group (p < 0.0001). In-hospital mortality 17% vs. 15% |
| Volpicelli 2013 | 1 | 108 | Prospective | Non-traumatic hypotension | Assessment on arrival | Heart, lung, IVC, abdomen, leg veins | Independent qualified emergency physician | Concordance final clinical diagnosis was 89% (Cohen's k = 0.71, p < 0.0001) |
| Laursen 2014 | 1 | 320 | RCT | Respiratory distress or chest pain | One-time assessment within 1h after primary clinical assessment | Heart, lung | One independent qualified physician | Percentage of patients with a correct presumptive diagnosis within 4h after admission to the emergency department, with audit diagnoses used as the gold standard |
| Shokoohi 2015 | 1 | 118 | Prospective | Undifferentiated hypotension | One-time assessment after admission | Heart, lung, IVC, abdomen | One independent qualified physician | Diagnostic uncertainty 28% decrease after CCUS. Concordance with final diagnosis (Cohen's k=0.80) |
| Ahn 2017 | 1 | 308 | Prospective | Emergent cardiopulmonary symptoms | Sequential two-step approach | Heart, lung, IVC, abdomen, suprasternal | Two residents or one attending physician of emergency medicine | Number of differential diagnoses was significantly reduced from 2.5 to 1.4. Concordance with the criterion standard was 89% (Cohen's k = 0.87, p < 0.001) |
| Sasmaz 2017 | 1 | 180 | Prospective | Non-traumatic hypotension | After initial assessment | Heart, lung, IVC, abdomen, leg veins | Emergency physician | Concordance with definite diagnosis from 61% before CCUS to 85% after CCUS (Cohen's k = 0.82, p < 0.001) |
| Atkinson 2018 | 6 | 273 | RCT | Non-traumatic undifferentiated hypotension | After initial assessment and consent | Heart, lung, IVC, abdomen, pelvis | Resident (supervised) or attending physician of emergency medicine | Mortality at 30 days 32/136 patients vs. 32/134 patients |

Pt patients * total number of included patients or patients included out of evaluated patients IVC inferior vena cava RCT randomised controlled trial

parenchyma could provide useful diagnostic and prognostic information for critically ill patients. An increase in RRI may be an early sensitive sign of haemodynamic deterioration, even in stable patients. Ninet et al. (2015) showed in a meta-analysis that an elevated RRI may be a predictor of persistent acute kidney injury in critically ill patients. The VII has only been evaluated in specific patient populations such as diabetic and heart failure patients (Jeong et al. 2011; Nijst et al. 2017). Potential limitations of these methods are whether RRI and VII can be obtained in such a manner that measures can be reproduced and whether it is feasible to measure VII in unstable, critically ill patients. To establish a more definite role for Doppler imaging of the kidney it should first be investigated in a large unselected group of critically ill patients. When imaging the bladder free fluid in the pelvis could be detected.

### Ultrasonography of the aorta

The abdominal aorta can be investigated along the midline of the abdomen. The normal size of the abdominal aorta should be less than 30 mm. A larger abdominal aorta is suggestive of an aneurysm. Rupture of the abdominal aorta might be identified as the cause of hypotension or shock. The diagnostic accuracy of CCUS is very high for acute aneurysm.

## Whole-body ultrasonography

The benefit of whole-body ultrasonography has been highlighted by cases presented in the literature (Schmidt et al. 2016; Mosier 2014). In these cases, a stepwise approach is most often used to unravel the underlying cause of hypotension or shock. The simplest benefit of whole-body ultrasonography over single organ ultrasonography results for instance from measuring the cardiac output and investigating the presence or absence of alveolar oedema in one patient, which may narrow down the differential diagnosis of shock significantly (Cecconi et al. 2014). A stepwise approach of many organs in one examination may result in a standard protocol such as RACE for echocardiography, as noted previously. Many protocols have been created to evaluate multiple organs using ultrasonography, including ACES (abdominal and cardiac evaluation with sonography in shock), FATE (focused assessed transthoracic echocardiography), SIMPLE, RUSH (rapid ultrasound in shock) and SEARCH 8Es (Sonographic Evaluation of Aetiology for Respiratory difficulty, Chest pain, and/or Hypotension) (Mok 2016; Perera et al. 2010; Ahn et al. 2017; Atkinson et al. 2008; Skrzypek et al. 2018). Each of these protocols contains more or less the same core ultrasound components. The SIMPLE protocol additionally focuses on intramural mass and intimate flap. The most important difference between these protocols is the order of procedure priority and the specific focus.

The first study published on whole-body ultrasound in the ICU came from Lichtenstein and Axler (1993). In 150 consecutive patients they visualised the abdomen, pleural space, peritoneal cavities, great vessels, bile ducts, urinary and gastrointestinal tract and femoral veins. In 33 (22%) patients ultrasonic positive findings contributed to the immediate management. Thereafter, an increasing number of studies, with number of patients ranging from case series to a cohort of up to 1000 patients, focused on the use of multi-organ or whole-body ultrasonography for evaluating hypotension or shock (**Table 1**). Irrespective of the setting whole-body ultrasonography seems to increase the number of patients with a definite diagnosis or to have implications on treatment as compared to patients in whom whole-body ultrasonography is not performed. Other measures were a decrease in diagnostic uncertainty and time to diagnosis. In the emergency department two studies even randomised patients to different strategies (Jones et al. 2004; Laursen et al. 2014). Early ultrasonography seems to result in a right diagnosis at an earlier time. The Sonography in Hypotension and Cardiac Arrest in the Emergency Department (SHoC-ED) trial investigated whether randomisation to whole-body ultrasonography compared to standard work-up without ultrasonography was associated with a better outcome in the emergency room and found equal survival after 30 days (Atkinson et al. 2018). Interestingly, despite the benefit for establishing a diagnosis in a larger number of patients treatment was equal (Atkinson et al. 2018).

### Challenges

The primary challenge concerns technical difficulties of the measurements and the highly operator-dependent method of obtaining the measurements. In the case of whole-body ultrasonography various individual components should be obtained and interpreted. For the purpose of a concise but complete assessment, measurements need to be simple to perform and interpret. Furthermore, the understanding and integration of ultrasonography findings in relation to other patient-derived parameters needs further investigation (Frankel et al. 2015). Another challenge concerns the interpretation of large amounts of data that are generated when repeatedly performing whole-body ultrasonography. There are developments in the areas of machine learning and artificial intelligence that could aid in interpretation and/or analysis of data generated in these exams, but these are not yet fully developed to be used in daily practice. Last, as more and more technical possibilities arise in the ICU it is difficult to evaluate the precise additional value of CCUS in deliberating diagnosis. However, it is fast, noninvasive and supposedly simple, and deserves to be investigated.

### Conclusion

We think that a mono-organ focus in unravelling disease states, such as ultrasonography of only the heart or the kidney, results in less clear understanding of the pathophysiologic state in critically ill patients as compared to a wide, open focus. Multiple protocols of integrated CCUS assessments exist, but improving techniques allow for more and more ultrasonographic possibilities. Interpretation of this integrated assessment may improve with increasing knowledge in this subject and become more universal. As new measurements and approaches continue to be investigated our diagnostic and prognostic accuracy will improve. We consider the whole-body and system focus important.

### Conflict of interest

Renske Wiersema declares that she has no conflict of interest. Geert Koster declares that he has no conflict of interest. Iwan C.C. van der Horst declares that he has no conflict of interest. ■

**Abbreviations**

CCUS critical care ultrasonography
IVC inferior vena cava
IVC–CI Inferior Vena Cava–Collapsibility Index
LV left ventricle
RRI Renal Resistive Index
RV right ventricle
VII Venous Impedance Index

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# Using ultrasound to prevent diaphragm dysfunction

Diaphragm ultrasound is a valuable tool to diagnose and prevent ventilator-induced diaphragm dysfunction. This review focuses on the use of ultrasound to assess diaphragm structure and function in ventilated patients.

The diaphragm is the primary muscle of inspiration. It is a thin dome-shaped muscle that inserts into the lower ribs, xiphoid process, and lumbar vertebrae. It runs parallel to the rib cage in the zone of apposition before curving along the inferior pleural surface (Mead 1979). Shortening of the diaphragm muscle fibres during inspiration results in a piston-like action, drawing the lungs downward and forcing the lower chest wall outward (de Troyer and Loring 2011; Gauthier et al. 1994). Downward excursion of the diaphragm varies from about 1 cm during normal tidal breathing to over 1-2 cm during deep inspiration. Diaphragm function is a crucial determinant of respiratory capacity in respiratory failure; injury to the diaphragm in the intensive care unit (ICU) has a substantial impact on patient outcome (Dres et al. 2017; Goligher et al. 2018). Recent advances in ultrasound imaging enable clinicians to more feasibly assess diaphragm function and potentially protect the diaphragm during mechanical ventilation.

## Diaphragm ultrasound techniques

Two techniques to image the diaphragm using ultrasound have been described. First, a low-frequency phased array transducer can be used to quantify downward excursion of the diaphragm in M-mode. The probe is positioned subcostally at the mid-clavicular line and angled upward, so that the ultrasound beam projects perpendicular to the dome of the diaphragm—the probe may be angled slightly medially if needed. **Figure 1** shows an example of the images obtained with this approach. Normal values of diaphragm excursion during various inspiratory manoeuvres have been reported and the technique has excellent reproducibility (Boussuges et al. 2009). This evaluation is only valid in the absence of ventilatory support, as thoracic insufflation by applied positive pressure will also lead to downward diaphragm excursion.

> "widespread implementation of diaphragm ultrasound in clinical practice has the potential to improve outcome"

The second approach measures diaphragm cross-sectional thickness in the zone of apposition. A high-frequency linear array transducer can be employed to measure the cross-sectional thickness of the diaphragm (B-mode) and the percentage change in thickness from expiration to inspiration, referred to as the thickening fraction (TF) (M-mode) (**Figure 2**) (Sarwal et al. 2013; Matamis et al. 2013). This technique has been described extensively and is well validated (Cohn et al. 1997). The probe is positioned in the 8th or 9th intercostal space between the mid- and anterior axillary lines in the zone of apposition. The diaphragm is visualised as the space intervening between the pleural and peritoneal lines. Both thickness and thickening fraction measurements show excellent reproducibility in ventilated patients (Goligher, Laghi et al. 2015).

## Application: monitoring diaphragm function

Both measurements can help to diagnose diaphragm dysfunction. Reduced excursion during various inspiratory manoeuvres is an established diagnostic criterion for dysfunction (Lerolle et al. 2009). Serial measurements of diaphragm thickness can reveal acute decreases in diaphragm thickness, indicative of rapid muscle atrophy. As the thickening fraction is related to the degree of diaphragmatic shortening during inspiration, it correlates with the changes in lung volume (Wait and Johnson 1997; Wait et al. 1989), inspiratory pressure development (Ueki et al. 1995; Dubé et al. 2017) and work of breathing (Vivier et al. 2012; Umbrello et al. 2015). As a result, a reduced maximal thickening fraction is a marker for diaphragm weakness. The validity of this technique to diagnose diaphragm weakness is crucially dependent on obtaining maximal volitional inspiratory effort. Using ultrasound to diagnose diaphragm weakness may help to guide the management of patients with difficult weaning from mechanical ventilation (Vorona et al. 2018; Heunks et al. 2015).

The thickening fraction measured during a spontaneous breathing trial (SBT) predicts the weaning outcome (DiNino et al. 2014; Zambon et al. 2016). In contrast to commonly used parameters like the rapid shallow breathing index (RSBI), the thickening fraction specifically reflects diaphragmatic action. This

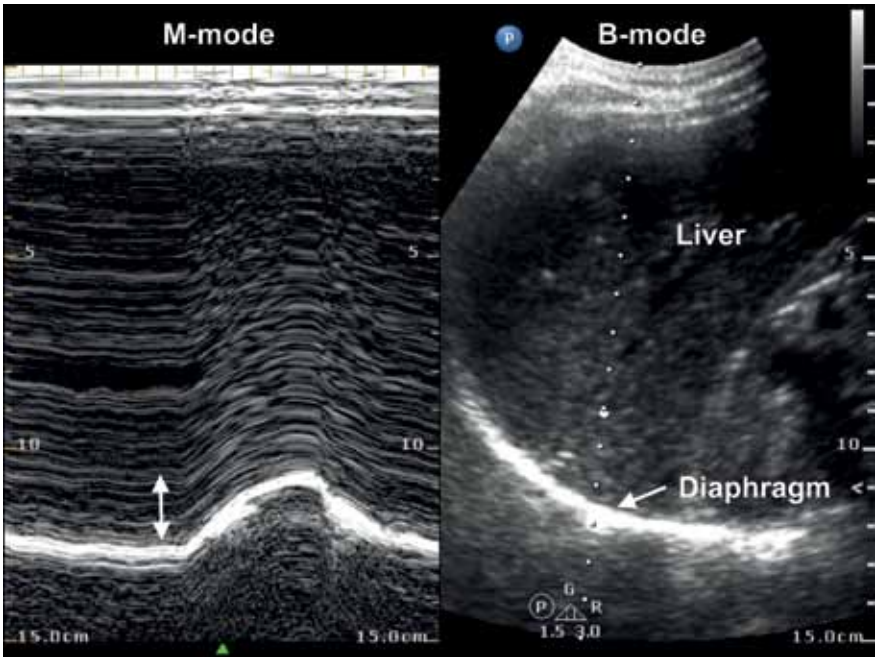


**Figure 1.**
B-mode (right) and M-mode (left) ultrasound images of the diaphragm. The M-mode image shows downward diaphragm excursion during inspiration, i.e. towards the ultrasound probe positioned subcostally.

way, diaphragm weakness is not masked by increased accessory muscle activity during the SBT, which may explain the excellent predictive results of this parameter (DiNino et al. 2014).

## Application: monitoring diaphragm activity

When the diaphragm is activated during tidal breathing, it shortens and hence thickens. This tidal thickening is visualised on ultrasound as diaphragm thickening. Hence, diaphragm thickening fraction measurements can be used as a marker of inspiratory effort and diaphragm contractile activity, even under mechanical ventilation. Diaphragm activity during mechanical ventilation is a key determinant of the risk of diaphragm injury. Both inappropriately low or excessive levels of diaphragm activity predict the risk of deleterious changes in diaphragm thickness and poor clinical outcomes (Goligher et al. 2018). Insufficient activity leads to rapid disuse atrophy (Levine et al. 2008; Goligher, Fan et al. 2015; Goligher et al. 2018); some evidence suggests that excessive respiratory muscle loading may result in inflammation, injury and dysfunction (Reid et al. 1994; Jiang et al. 2012), although it is unclear whether this happens frequently in the clinical setting.

Monitoring diaphragm activity by ultrasound might be used to guide the titration of ventilatory support. By targeting support levels producing relatively normal levels of respiratory effort (thickening fraction in the range of 15-30%), diaphragm atrophy and injury might be prevented. This concept is referred to as diaphragm-protective ventilation (Heunks and Ottenheijm 2018). A recent study found that the length of ICU stay, the duration of ventilation, and the risk of complications of respiratory failure (prolonged ventilation, reintubation, tracheostomy or death) were minimised when patients' thickening fraction averaged 15-30%—similar to that of healthy subjects breathing at rest—during the first 3 days of ventilation (Goligher et al. 2018). This may represent the optimal level of spontaneous breathing during mechanical ventilation to protect the diaphragm from injury (Tobin et al. 2010). Ultrasound measurements can detect adequate, insufficient or excessive inspiratory effort (see **Figure 2**) (Umbrello et al. 2015).

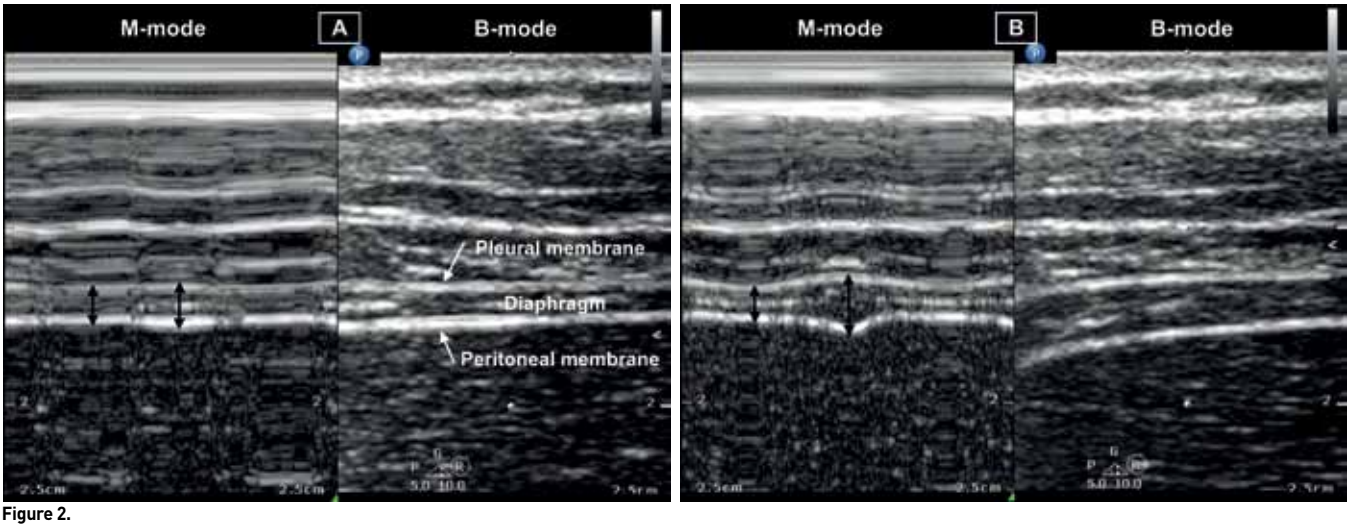


**Figure 2.**
B-mode (right) and M-mode (left) ultrasound images of the diaphragm, measured at the zone of apposition. Measurements of the thickness (black vertical lines) during expiration (left) and inspiration (right). Figure A shows reduced diaphragm contractile activity with a small change in thickness during inspiration (thickening fraction = 13%), Figure B shows adequate diaphragm contractile activity with a larger change in thickness during inspiration (thickening fraction = 70%).

Ultrasound can also be used to diagnose patient-ventilator dyssynchrony (Thille et al. 2006; Matamis et al. 2013), as it provides real-time information of contractile activity. Recognising and treating dyssynchrony may help to improve outcomes, as frequent dyssynchrony strongly predicts poor clinical outcomes (Vaporidi et al. 2016; Blanch et al. 2015).

## Future of diaphragm ultrasound

Several emerging ultrasound techniques have been evaluated for their potential to further evaluate the diaphragm. These include speckle tracking, which uses naturally occurring speckle patterns to assess tissue deformation and motion. Originating from cardiac imaging, it has been used to measure diaphragm muscle strain (Ye et al. 2013; Hatam et al. 2014). It may provide a novel noninvasive technique for bedside evaluation of respiratory workload, but further research is required to validate this technique.

Changes in diaphragm tissue structure apart from atrophy might be detected by assessing changes in diaphragm echodensity, which reflects the development of muscle oedema, inflammation and necrosis (Puthucheary et al. 2015). These provide insights on muscle quality apart from muscle bulk. This technique has been described for imaging quadriceps muscle; it has not yet been described for diaphragm ultrasound. Other ultrasound techniques including 3D imaging and elastography have yet to find their way into the ICU and clinical practice.

## Conclusion

Mechanical ventilation can injure the diaphragm, resulting in significant morbidity and mortality in critically ill patients. Optimising diaphragm activity during mechanical ventilation is important to mitigate diaphragm dysfunction. Ultrasound has the capability to detect structural changes in the diaphragm (thickness and quality), assess inspiratory effort, diagnose diaphragm weakness, predict liberation from ventilation, and possibly detect patient-ventilator dyssynchrony. Widespread implementation of diaphragm ultrasound in clinical practice has the potential to improve outcome by optimising ventilator management based on patient effort and synchrony, guiding assessment of the difficult-to-wean patient, and informing decisions about liberation from mechanical ventilation. Diaphragm ultrasound can also provide crucially important mechanistic insights for research studies: measurements of thickness, echodensity, thickening fraction, and maximal thickening may provide clinically relevant physiological biomarkers of disease and treatment effects. Future trials are required to explore how to facilitate diaphragm-protective ventilation and whether this new paradigm for ventilation improves the outcome for ventilated patients. ■

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# Imaging and ICU

## Advice from a radiologist

For the Imaging issue, *ICU Management & Practice* spoke to radiologist Dr. Marcelo Sanchez about radiology-ICU collaboration.

**How can communication between radiology and ICU be optimised as both specialities become ever more complex?**

The collaboration must be maintained by establishing protocols and consensus on image indications for the clinical processes analysed in the ICU. The best communication system is to organise multidisciplinary clinical board sessions to evaluate the cases and to create guidelines for each clinical situation. This communication is also important because clinicians consider all the ICU exams as urgent, even follow-up exams. It is important to talk not only about the indications but also about when the exam could be done. It is important not to overload the on-call staff with urgent exams that are not really urgent.

**What are the financial considerations?**

The imaging budget must be adjusted to the indications established in the clinical guidelines by consensus and exceptions must be analysed to try to correct them by following up and avoiding rejecting imaging requests. We do not refuse imaging due to financial considerations; we can only discuss the medical indication.

**What imaging should be done at the bedside, and what should be done in the radiology department?**

The ICU doctors don't like to move their patients, but currently, only x-rays and ultrasound studies should be performed at the patient's bedside and CT or MRI studies in the radiology department. However, with new technological advances and the possibility of performing portable CT studies it will be possible to bring the radiology service closer to the ICU. ■

# Abdominal point-of-care ultrasound in critical care

## The secrets of the abdomen

Overview of abdominal point-of-care ultrasound use in the ICU, potential diagnoses and findings common to the critical care patient population.

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The use of point-of-care ultrasound (POCUS) in critical care as a diagnostic and monitoring tool is rapidly expanding. While its role in cardiovascular and respiratory assessment is well established (within critical care), abdominal ultrasonography is less so; perhaps because of the myriad of potential diagnoses that can be made and the fact that the abdomen is often less accessible due to gaseous interposition. Regardless of modality, the key difference between radiology department scans and scans performed by intensivists is that the latter are more focused and aim to answer a specific clinical question in the context of a specific clinical situation.

It is without the scope of this article to describe every single (potential) use of abdominal POCUS; the aim is to provide an overview of the potential diagnosis and findings common to the critical care patient population.

## Basic B-mode ultrasound

### 1. Trauma

One of the earliest uses of ultrasound (US) outside of radiology was in the detection of intra-abdominal free fluid (or blood) in the context of trauma. The Focused Assessment with Sonography in Trauma (FAST) scan has been consistently included as part of the Advanced Trauma Life Support (ATLS) course over the latest editions (Royal College of Surgeons 2017). The original FAST scan included assessment of the hepato-renal recess (right upper quadrant a.k.a Morison's pouch), the spleno-renal recess (left upper quadrant) and the pelvis for the presence of free fluid/blood (Carroll et al. n.d.). This has been expanded to include the subcostal views (pericardial fluid/tamponade), anterior thoracic views (to rule out pneumothorax) and the detection of pleural fluid in the so-called extended FAST or eFAST (123sonography.com n.d.) (**Figure 1**).

The sensitivity and specificity of FAST for the detection of free intraperitoneal fluid were 64–98% and 86–100%, respectively (Bloom and Gibbons 2018). This range may be explained by differences in the levels of clinical experience and in the reference standards.

### 2. Abdominal free fluid

Ultrasound allows for the identification of free fluid, quantification of the volume and potentially, the underlying aetiology.

The differential diagnosis of the presence of abdominal free fluid is summarised in **Table 1**. In the critically ill the main cause for abdominal fluid is in the setting of sepsis, capillary leak and massive fluid resuscitation, as seen in severely burned patients. The aetiology of spontaneous haemoperitoneum can vary, and the causes may be classified as gynaecologic, hepatic, splenic, vascular, or coagulopathic conditions.

US is not sensitive at identifying a focus of extravasation from a vessel or organ (Schmidt et al. 205). Therefore, FAST may be an option for the initial evaluation of a patient to detect haemoperitoneum in non-trauma patients, but it does not replace computed tomography (CT) scanning.

### 3. Assessment of gastric content

Dysfunctional gastric emptying in critically ill patients can contribute to complications during procedures related to airway management and can result in unsuccessful enteral feeding as well as an increased risk of aspiration (Marik 2001). A 6-hour fasting period (2 hours for clear fluid) has been recommended for patients undergoing elective surgery to reduce the risk of aspiration during anaesthesia (s.n. 2017). In the ICU, gastric emptying is frequently altered and influenced by several factors, including age, diagnosis on admission (Hsu et al. 2011) underlying disease processes (e.g. diabetes, porphyria, shock) (Nguyen et al. 2007), therapeutic interventions (e.g. mechanical ventilation), medications (e.g. opioids, sedatives, neuromuscular blockers, vasopressors) (Nimmo et al. 1975; Steyn et al. 1997), electrolyte and metabolic disturbances and mechanical ventilation (Mutlu et al. 2001).

Epidural anaesthesia, on the contrary, improves gastric emptying and peristalsis. The measure of the antral cross-sectional area (CSA) by US is feasible in most critically ill

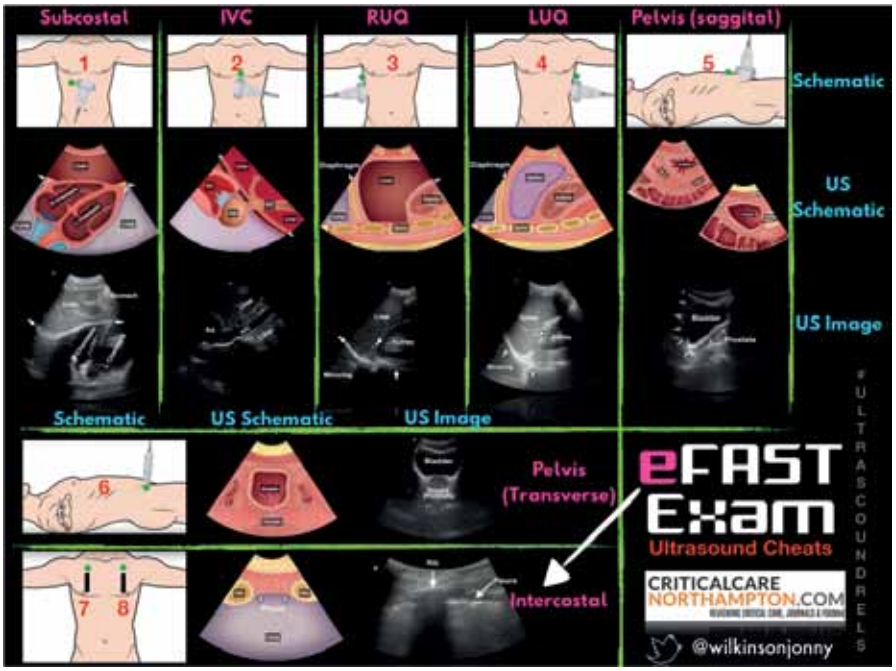
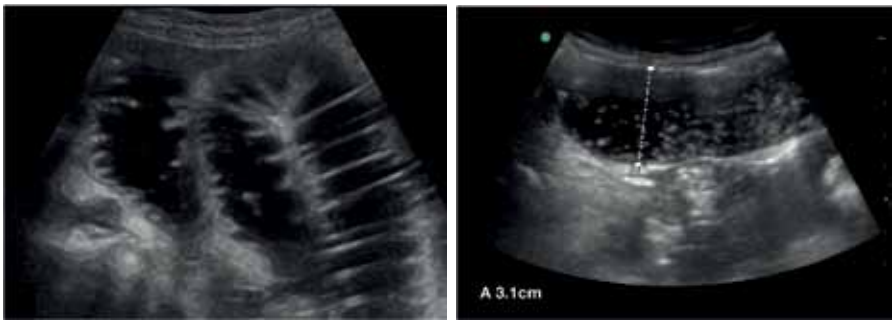



**Figure 1.** The eFAST Exam




a) Visible valvulae conniventes and hypoechoic dilated loops of small bowel

b) 3cm dilated loop of bowel with pathological air visible in a to-and-fro motion due to lack of peristalsis

**Figure 2.** Patterns of small bowel obstruction

patients and would allow for direct visualisation of stomach content. On average, a CSA > 15-25 $cm^2$ corresponds to a gastric residual volume (GRV) > 300 mL. The same principle has been studied with regard to assessment of preoperative fasting status amongst surgical patients (Van der Putte and Perlas 2014; Perlas et al. 2009).

Gastric US can also identify other pathologies such as gastric tumours (carcinomas and rarely teratomas), hypertrophic pyloric stenosis and even bezoar related to enteral nutrition.

Normal stomach wall anatomy consists of five layers, referred to as the gut signature:

1. Serosa (hyperechogenic)
2. Muscularis propria (hypoechogenic)
3. Submucosa (hyperechogenic)
4. Muscularis mucosa (hypoechogenic)
5. Mucosa (hyperechogenic)

**4. Bowel obstruction**

Features of the bowel which can be assessed using US include:

- Wall thickness
- Diameter and intraluminal contents
- Peristalsis
- Vascularity

The diameter of the bowel and its contents may vary according to site, fasting/feeding state and bowel function. In adults, the normal small bowel measures <30mm in diameter and the normal large bowel <60 mm in diameter (Reintam Blaser et al. 2012). Dilated loops may show thickened walls (normally up to 3 mm in the small bowel), or thickened vavulae conniventes (normally up to 2mm in the large bowel). The exceptions to this are the duodenal bulb and rectum, which are less than 3 and 4mm in thickness respectively (Lichtenstein et al. 2014). Ultrasound patterns can aid in the differentiation of small from large bowel (**Table 2**).

Assessment of bowel peristalsis is difficult and subjective, but may provide useful information in several intestinal diseases. Increased small bowel peristalsis has been described in coeliac disease and acute mechanical bowel obstruction (increased to-and-fro motion of the bowel contents) (Hefny et al. 2012). In later phases, one may detect a fluid-filled lumen, thinning and spasm of the bowel wall, evidence of extraluminal fluid and decreased or absent peristalsis.

**Types of peristalsis:**

- Absent peristalsis
- Present ineffective peristalsis
- Present effective peristalsis
- Augmented peristalsis

**5. Viscus perforation**

Physiologic air can be seen in the lumen of the bowel as small stars. Larger air bubbles can appear as hyperechoic stripes generating comet tail artefacts (these are rare in the small bowel but frequent in the large bowel), much like a linear view of the lung would look. Air artefacts can emanate from the thoracic cavity and the lung over the liver. Pathological air, however, may produce an enhanced peritoneal stripe sign (EPSS), reverberation artefacts and ring-down artefacts (**Figures 2a and 2b**) (Hoffmann et al. 2012).

**6. Renal dysfunction**

International guidelines recommend that all patients who present in acute renal failure undergo an ultrasound examination to ascertain its cause (Kidney Disease: Improving Global Outcomes 2012). Hydronephrosis due to obstructive uropathy is a reasonably straightforward diagnosis to make.

More advanced techniques include the assessment of blood flow within the renal artery and vein using Doppler analysis.

Analysis of the urinary bladder should be performed as well. The bladder can be empty,

filled or distended (globus). The position of the bladder catheter balloon can be checked, as well as the presence of hyperechogenic structures (debris, tumour, blood clot etc).

**7. Liver and spleen**

Ultrasound of the liver is divided into general US views including anatomic views of the liver, gallbladder and biliary tree. Pathology within these organs e.g. acute liver failure, can result in intensive care admission, but is beyond the scope of this paper.

## Advanced modalities

**1. Doppler and colour Doppler techniques**

Doppler US is used to assess the signal from visceral vessels that supply the gastrointestinal (GI) tract and smaller vessels within the intestinal wall. Although the technique cannot be used to assess capillary flow, it can be used to analyse all the major visceral vessels e.g. renal, hepatic, mesenteric. It has to be noted that normal bowel wall perfusion cannot be demonstrated by colour or power Doppler. The presence of flow in the bowel wall points towards pathologic perfusion (e.g. hyperaemia in actively inflamed segments, as seen in appendicitis).

Commonly used measurements which can be performed include:

- Systolic, diastolic and mean velocities
- Pulsatility index
- Resistance index (peak systolic velocity – end diastolic velocity)/peak systolic velocity
- Blood flow volume

**GI tract blood flow**

Colour Doppler allows for the assessment of mural flow, the absence of which is a sign of ischaemia. Unfortunately, this finding is only reported in 20–50% of patients with a proven diagnosis of ischaemic colitis (Danse et al. 2000a; Danse et al. 2000b). Doppler US can show stenosis, emboli, and thrombosis in the near visible parts of the coeliac trunk, the superior mesenteric artery (SMA) and the inferior mesenteric artery (IMA). In the early phase of bowel ischaemia, US examinations may show SMA occlusion, hyperaemic segments and bowel spasm. Collateral vessels cannot be reliably displayed using ultrasound. Systolic velocities of more than 250–300 cm/s

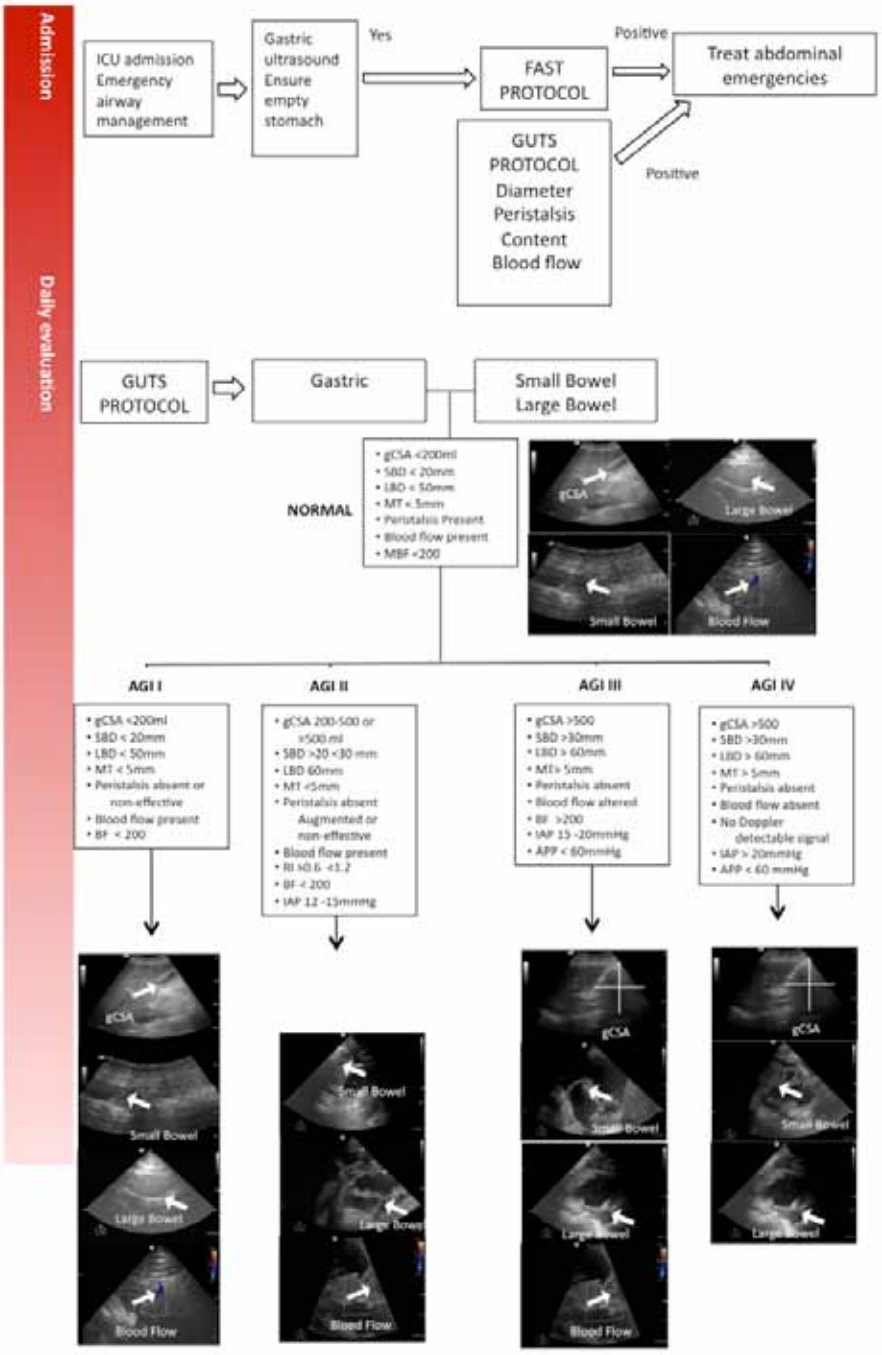



**Figure 3.** gCSA gastric cross sectional area, SBD small bowel diameter, LBD large bowel diameter, MT mucosal thickness, BF blood flow, IAP intrabdominal pressure, RI resistive index

are sensitive indicators of severe mesenteric arterial stenosis (Hamada et al. 2014; Koenig et al. 2011). The spectral analysis of Doppler signals of arteries supplying the GI tract (truncus coeliacus, superior and inferior mesenteric arteries) and the vessels draining the intestine, can be used to estimate bowel perfusion (see below). Assessment in transverse and longitudinal plane should be performed. Low flow states can also be identified by the presence of spontaneous contrast and turbulent flow in the large vessels.

### Hepatic blood flow

**Portal vein:** the normal main portal vein (MPV) is gently undulating with peak systolic velocities ranging between 20 cm/s and 40 cm/s. A low flow velocity of <16 cm/s in addition to a calibre increase in the MPV are diagnostic features of portal hypertension (PH). Further worsening of PH leads to a to-and-fro flow pattern, whereby the nearly stagnant blood column in the portal veins is seen to shift into and out of the liver with the respiratory cycle. In the end stages, stagnation of the blood column can lead to thrombosis or progress to a frank flow reversal or non-forward portal flow (NFPF). This is considered to have grave prognostic significance, indicating severe and irreversible liver failure (Wachsberg et al. 2002).

**Hepatic vein:** the normal flow is triphasic with two hepatofugal phases related to atrial and ventricular diastole. Fibrotic or inflammatory changes may create a monophasic flow pattern. Early waveform changes in cirrhosis patients include spectral broadening and dampening of the normal, retrograde, pre-systolic wave of the hepatic vein waveform. Later, the normal triphasic waveform pattern may be diminished or replaced with a monophasic pattern. Therefore the monophasic hepatic vein waveform indicates relatively high portal pressures (Ralls 1990).

**Hepatic artery:** hepatic arterial resistance changes with increasing portal pressure values, but hepatic arterial resistive indices correlate poorly with the severity of cirrhosis and will not be further discussed here.

### Renal blood flow

Doppler US can be used to assess renal perfusion. Normal resistive index (RI) is approximately 0.58 ± 0.10 and values >0.70 are considered to be abnormal. A renal Doppler RI may also help in detecting early renal dysfunction or predicting short-term reversibility of acute kidney injury (AKI) in critically ill patients. A recent meta-analysis suggested that RI may be a predictor of persistent AKI in critically ill patients with a pooled sensitivity and specificity of 0.83 (95% CI, 0.77-0.88) and 0.84 (95% CI, 0.79-0.88) (Ninet et al. 2015).

Increased renal resistive index (RRI) has been proven to be an independent predictor of worse cardiovascular and renal outcomes, especially when combined with reduced glomerular filtration rate (GFR), thus providing a useful diagnostic complement to the assessment of renal function in these patients. High RRI has also been correlated with the presence of hypertensive and atherosclerotic organ damage. Values >0.80 have been reported to be predictive of all-cause mortality in chronic kidney disease patients and may indicate impending renal transplant failure in this patient subset (Barozzi et al. 2007; Guinot et al. 2013; Ninet et al. 2015; Schnell et al. 2012).

**Table 1.** Causes of abdominal free fluid

| Common causes | Other Causes |
|---|---|
| Malignant disease<br>Cardiac failure<br>Hepatic failure<br>Sepsis, capillary leak, fluid overload Hypoproteinaemia – nephrotic syndrome, malnutrition | Hepatic venous occlusion<br>Infection – tuberculosis<br>Lymphatic obstruction<br>Pancreatitis |

**Table 2.** Differentiation between small and large bowel

| Features | Small Bowel | Colon |
|---|---|---|
| **Location** | Central | Peripheral (picture frame) |
| **Appearance** | Folds (lesser distally) | Haustra |
| **Contents** | Fluid or dry<br>Minimal air | Feces<br>Air |
| **Spontaneous peristalsis** | Should be seen in healthy segments | Rarely |
| **Easy to compress and displace by US probe** | Yes, easily | Yes for mesenteric segments |

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> "aim to answer a specific clinical question in the context of a specific clinical situation"

## Gastrointestinal and urinary tract sonography (GUTS) protocol

Gastrointestinal function can be assessed with US, using a combination of anatomical, functional and blood flow evaluation (Schmidt et al. 2005).

1. **Function:** peristalsis, bowel motility, gastroparesis, small bowel ileus, large bowel paralysis
2. **Dimensions:** bowel dilatation, bowel obstruction, Ogilvie syndrome, bacterial overgrowth, toxic megacolon, bowel wall oedema, abdominal wall oedema
3. **Collections:** bowel content (blood, liquid, air, solid), haematoma, gastrointestinal bleeding, ascites
4. **Perfusion:** bowel ischaemia, hepatosplanchnic perfusion, shock state (spontaneous contrast), renal resistive index, abdominal perfusion pressure (APP) = mean arterial pressure (MAP)-intraabdominal pressure (IAP)

This approach is summarised by the GUTS (Gastrointestinal and Urinary Tract Sonography) protocol (**Figure 3**). The structured and stepwise approach may lead to improved practical management of adult ICU patients with acute gastrointestinal injury (AGI), as graded by the European Consensus Definitions (Reintam Blaser et al. 2012). Such a management strategy has not been shown to improve patient outcome, however.

The European Consensus Definition of AGI suggests a graded severity score:

**Table 3.** US study of the normal GI tract

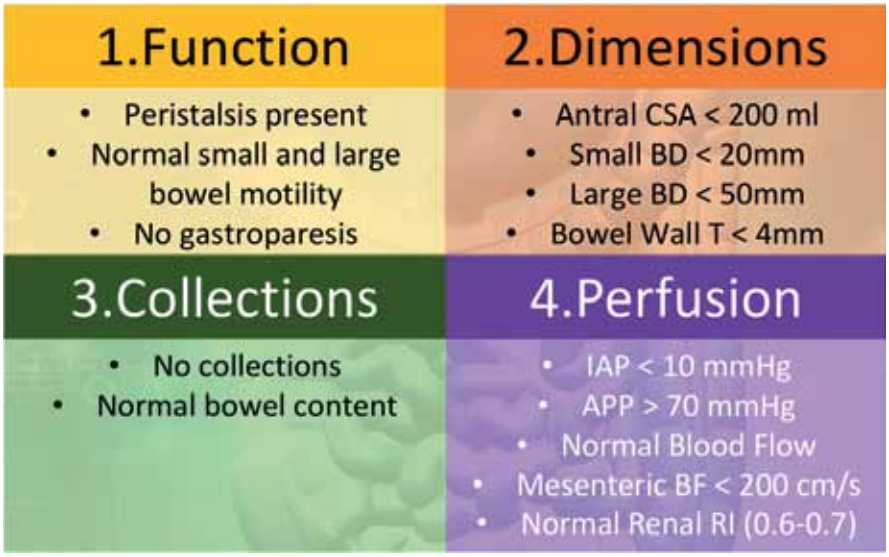
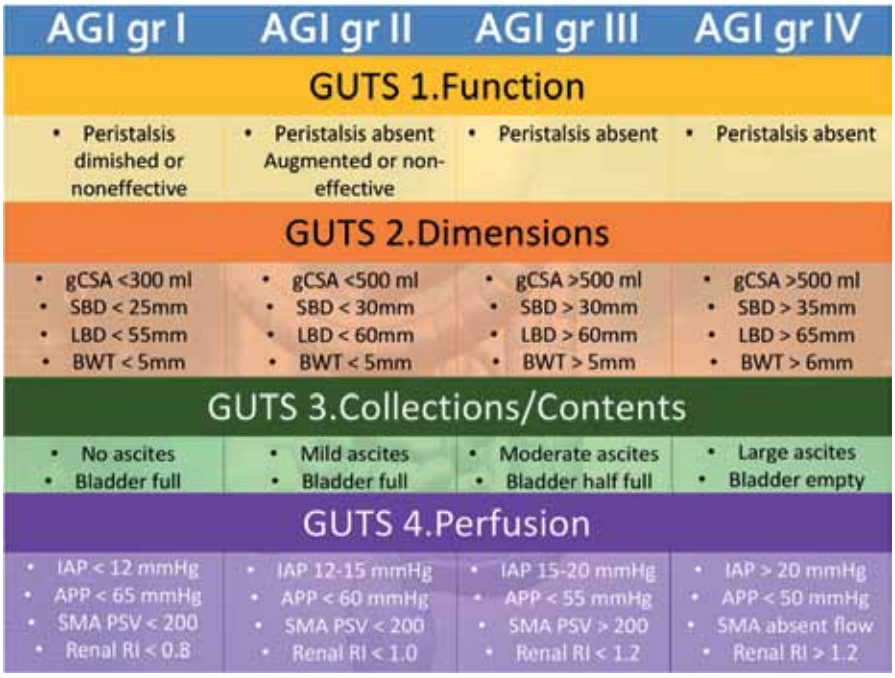



**Table 4.** GUTS classification for AGI




1. AGI grade I represents a self-limiting condition with increased risk of developing GI dysfunction or failure
2. AGI grade II (GI dysfunction) represents a condition requiring interventions to restore GI function
3. AGI grade III (GI failure) represents a condition when GI function cannot be restored with interventions
4. AGI grade IV represents a dramatically manifesting GI failure, which is immediately life-threatening (e.g. abdominal compartment syndrome with organ dysfunction) (Reintam Blaser et al. 2012).

## Future works

### Contrast-enhanced ultrasound

Contrast-enhanced ultrasound (CEUS) involves the use of contrast agents containing gas-filled microbubbles administered intravenously, producing an image with greater contrast and/or highlighting more vascular areas. Although reasonably well established in radiology, and more recently cardiology departments, its use in intensive care is in its infancy. Unlike CT contrast agents, CEUS appears safe for patients with renal dysfunction and the modality itself remains free of radiation exposure to patients. Possible use within critical care includes enhanced echocardiography and in blunt abdominal trauma to assess solid-organ injuries (Dietrich 2017).

### Doppler analysis as a marker of fluid status and venous congestion

As mentioned, Doppler analysis of the vasculature of specific abdominal organs allows for assessment of its perfusion. Some early work showed that this modality could also be used as a marker of systemic vascular congestion (Lewis et al. 1989).

## Conclusion

This paper summarises the multiple uses of abdominal US on the ICU and highlights future work and development. It must be remembered however that despite the myriad of potential diagnosis, utilisation and interpretation of such techniques requires training and experience.

### Acknowledgements and conflicts of interest

Jonny Wilkinson is a member of the International Fluid Academy (IFA) faculty. Manu Malbrain is founding President of WSACS (The Abdominal Compartment Society) and current Treasurer, he is also member of the medical advisory Board of Getinge (former Pulsion Medical Systems) and Serenno medical, and consults for ConvaTec, Acelity, Spiegelberg and Holtech Medical. He is co-founder and member of the executive committee of the International Fluid Academy (IFA). Adrian Wong is a member of the executive committee of the IFA. ■

### Abbreviations

FAST Focused Assessment with Sonography in Trauma
GI gastrointestinal
POCUS point-of-care ultrasound
US ultrasound

## References

**For full references, please email editorial@icu-management.org or visit https://iii.hm/qp6**

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# Multimodal neuromonitoring catheter insertion

## Secondary complications

Reports on secondary complications arising from insertion of a multimodal monitoring sensor using a dual lumen introducer kit in patients with subarachnoid haemorrhage, head injury or intracranial haemorrhage.

Maintenance of sufficient cerebral oxygen supply to meet metabolic demand is a key goal in managing patients with acute brain injury and in perioperative settings. A discrepancy between oxygen supply and demand can lead to cerebral hypoxia/ischaemia and deleterious outcome, with time-critical windows to prevent or minimise permanent ischaemic neurological injury.

As clinical manifestations of cerebral hypoxia/ischaemia may remain hidden in unconscious or sedated patients, brain monitoring is required to detect impaired cerebral oxygenation in such circumstances (Kirkman and Smith 2016).

## Cerebral oxygenation monitoring methods

- **Jugular venous oxygen saturation monitoring:** this was the first bedside monitor of cerebral oxygenation; however, other monitoring tools are superseding its use.
- **Near-infrared spectroscopy:** these are commercial devices that measure regional cerebral oxygen saturation and enable simultaneous measurement of multiple regions of interest, although its inclusion in routine clinical practice is not widespread (Ghosh et al. 2012).
- **Brain tissue oxygen pressure monitoring:** In recent years, there has been an increasing trend towards direct measurement of partial brain tissue oxygen pressure ($P_{ti}O_2$); furthermore, this offers the most solid evidence of all cerebral oxygen monitors (Bouzat et al. 2013).

## Technical aspects

$P_{ti}O_2$ catheters, which are inserted into subcortical white matter through single or multi-lumen bolts via a burr hole or during a craniotomy, are similar in size to intraparenchymal ICP monitors.

$P_{ti}O_2$ is a localised measurement; the region of interest monitored by a $P_{ti}O_2$ probe is approximately 17mm. Precise insertion can be technically challenging or impossible, in addition to the risk of inadvertent intralesional placement, which does not provide useful information. A major caveat for $P_{ti}O_2$ monitoring is that the heterogeneity of brain oxygenation, even in undamaged areas, is well recognised (Van den Brink et al. 2000).

> **"$P_{ti}O_2$ catheters are similar in size to intraparenchymal ICP monitors"**

## Study purpose, materials and methods

This study analysed complications arising from insertion of the multimodal monitoring sensor using a dual lumen introducer kit—Integra® Licox® Brain Tissue Oxygen Monitoring (Integra LifeSciences).

All patients in León Hospital ICU diagnosed with subarachnoid haemorrhage (SAH), head injury or intracranial haemorrhage (ICH), and who had been neuro-monitored either solely with ICP or with ICP+ $P_{ti}O_2$ were studied retrospectively for one year (from March 2017 to March 2018). We analysed the presence of haemorrhage associated with the catheter, infection and bone fragments in the brain.

## Results

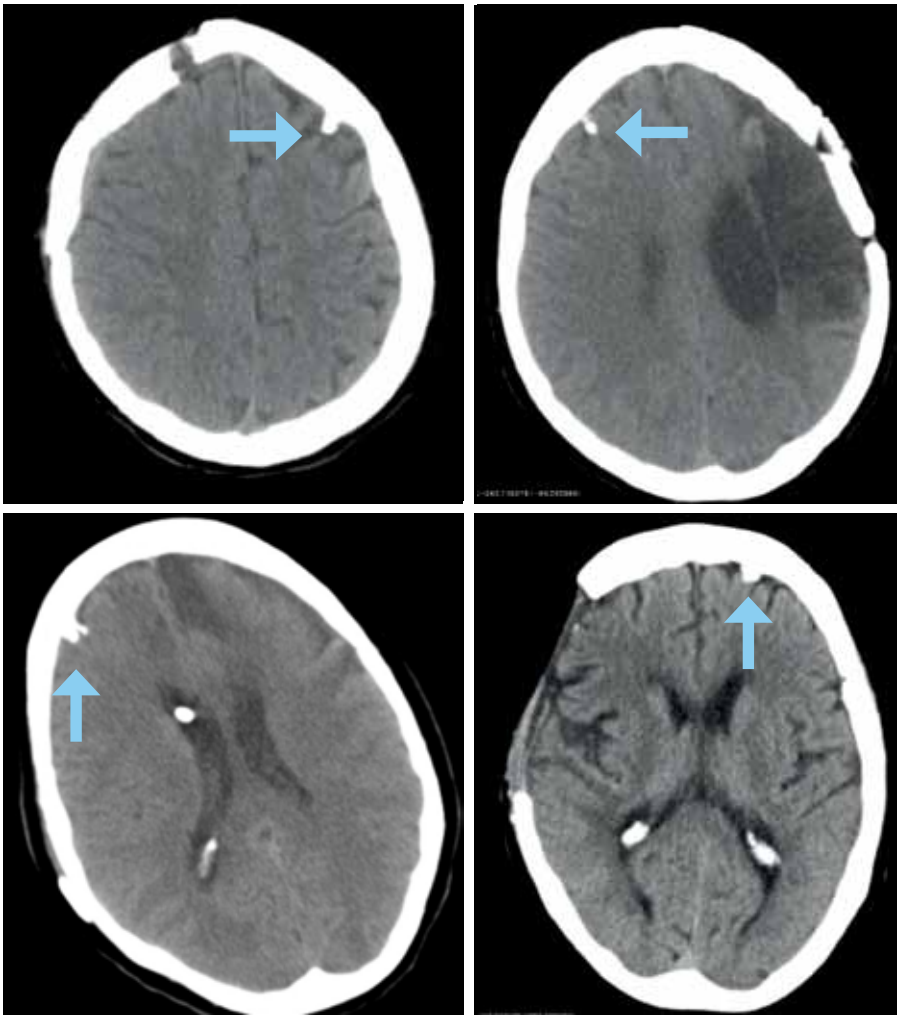
During the study period 126 patients were admitted with a diagnosis of head injury, subarachnoid or intraventricular haemorrhage. Twenty-one of these patients were monitored (16.6%); 20 underwent multimodal monitoring, and only one was fitted with just an ICP sensor.

Fourteen patients (70%), monitored with a ICP+ $P_{ti}O_2$ sensor, were found to have a bone fragment in the brain on undergoing a control CT after removal of the sensors. In another five patients, they either did not present with this complication or the control CT was not performed because they were discharged. Only one patient presented with a haematoma in the catheter trajectory. The only patient monitored with an ICP sensor had no bone fragments.

No infections whatsoever were associated with the sensor under any circumstance.

In 9 out of 20 patients monitored with ICP+ $P_{ti}O_2$, figures were normal for both ICP and $P_{ti}O_2$.

A neurosurgical team followed up these patients, and no infectious complications



The images show the CT scan cuts of 4 patients where the presence of bone fragments can be observed

in the bone fragment area or untreatable seizures were observed. Nevertheless, it was impossible to follow up all those patients long-term.

On reviewing patients monitored solely with an ICP sensor, bone fragments have never been observed in the same.

## Discussion

We did not find any publication describing the presence of bone fragments as a complication, so we were unable to make a comparison.

### Technical considerations

The drill used for inserting a $P_{ti}O_2$ +ICP Integra® Licox® Brain Tissue Oxygen Monitoring (Integra LifeSciences) has a diameter of 6.3 mm; sheet geometry and cutting grooves mean that on drilling the bone, fragments enter the brain. It would seem a controlled delicate dissection is not possible.

According to Dings et al. (1997), this technique is considered relatively safe with a low haematoma incidence (<2% usually small and clinically insignificant). The most common technical complication described was dislocation or drift whose frequency may reach 13.6%. No infections have been described.

> "long-term complications of these lesions have yet to be determined"

Advances in $P_{ti}O_2$ technology should lead to improved techniques, since the addition of a further lesion (bone fragment) in an already damaged brain should not be acceptable.

## Conclusions

Insertion of ICP+$P_{ti}O_2$ sensors using the dual lumen insertion technique Integra® Licox® Brain Tissue Oxygen Monitoring (Integra LifeSciences) is associated with a high rate of intra-cerebral bone fragments. Long-term complications of these lesions have yet to be determined. ■

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# Required and preferred scanner features for different ultrasound applications

## Executive summary

Minimum requirements, preferred features, and other advantageous features are identified for ultrasound systems for common exam types.

Ultrasound is used for a wide variety of clinical applications, each requiring a somewhat different set of sonographic capabilities. A scanner's array of available features is a key factor in determining its appropriateness for a given application. Listed below are common ultrasound applications. For each one, we provide ECRI Institute's recommendations about the necessary transducer types, along with the following:

- Minimum requirements—the essential functions needed to perform the application
- Preferred features—highly desired capabilities that make scanning or image interpretation easier, make operation more convenient, or improve the use of the scanner for the application in some other significant way
- Other advantageous features—features that enhance the scanner's set of capabilities for the application but that are of lesser importance

### Abdominal (comprehensive)

Imaging abdominal organs is one of the oldest and most common ultrasound procedures. Diagnoses of diseases, cysts, and tumours can be made from the anatomical information—such as size, texture, and location—provided by ultrasound scans. Biopsies of abdominal organs can be performed under ultrasound guidance. Colour Doppler imaging (CDI) permits further diagnosis by providing information on blood flow. Comprehensive abdominal studies require a full-featured scanner typically used by experienced (credentialled) sonographers.

Transducer. Sector transducer (convex or vector; adult, 3 to 5 MHz; paediatric, >7 MHz)

Minimum requirements. Real-time 2D (B-mode) capability, CDI, DICOM compatibility, digital calipers, pulsed-wave (PW) Doppler

Preferred features. Power Doppler imaging (PDI), harmonic imaging, transducer needle-guide attachment

Other advantageous features. Cine-loop, elastography, extended field of view, frame averaging, frequency compounding, multiplanar reconstruction, multislice 3D, spatial compounding, volume rendering (either freehand 3D or real-time 3D [4D]), fusion imaging

### Abdominal (limited)

Limited abdominal studies include detection of fluid collections caused by abdominal trauma (by means of a focused assessment with sonography for trauma, or FAST exam), gallstones, aortic aneurysms, and noncardiac studies of the thorax (e.g. pleural effusion). Studies can be performed with a system containing only basic features. The study is often performed at the point of care and is typically performed by a physician.

Transducers. Recommended minimum: any sector transducer (3 to 5 MHz); acceptable: curved linear-array transducer (3 to 5 MHz)

Minimum requirements. Real-time 2D B-mode capability, digital calipers

Preferred features. Battery operation for portable studies, CDI (PDI also acceptable), image and video storage capability

Other advantageous features. PW Doppler, Wi-Fi connectivity

### Cardiac (comprehensive)

Cardiac ultrasonography, or echocardiography, involves assessing the structure and function of the heart and imaging the cardiac valves and heart chambers to measure wall motion and wall thickness. Cardiac ultrasound can call on the full range of a scanner's Doppler capabilities to examine flow and turbulence throughout the heart and great vessels. Cardiac analysis packages measure and automatically calculate quantitative values to aid diagnosis. The unit normally produces an ECG to allow the images to be referenced to the cardiac cycle. A comprehensive cardiac study requires a full-featured scanner typically used by experienced (credentialled) echocardiographers. Examinations include comprehensive adult and paediatric echocardiography.

Transducers. Pedoff (continuous-wave [CW] Doppler, 1.5 to 3 MHz) transducer; small-footprint* sector transducer (phased-array, vector-array, or microconvex-array; adult, 2 to 4 MHz; paediatric, >7 MHz)

Minimum requirements. Real-time 2D



* A transducer's footprint describes the area of the scanning surface that contacts the patient.

B-mode capability, cardiac analysis package, CDI, CW Doppler, DICOM compatibility, digital calipers, ECG, M-mode, PW Doppler, cine-loop

Preferred features. Contrast-specific imaging, transoesophageal echocardiography (TEE) transducer (single-plane), strain imaging, stress-echo calculation package

Other advantageous features. Multiplanar reconstruction, multislice 3D, stress echo, TEE transducer (biplane or multiplane), volume rendering (real-time 3D [4D]), intracardiac echocardiography (ICE) capability

## Cardiac (limited)

A limited cardiac study includes assessment of basic cardiac activity as well as detection of pericardial effusion. A limited study can be performed with a system containing only basic features. A portable system could be used in a number of locations: a patient's bedside, the intensive care unit or cardiac care unit, the catheterisation lab, or an off-site clinic. The study is often performed at the point of care and is typically performed by a physician.

Transducer. Small-footprint sector transducer (phased-array, vector-array, or microconvex-array; 2 to 4 MHz)

Minimum requirement. Real-time 2D B-mode capability

Preferred features. Battery operation for portable studies, CDI, cine-loop, digital calipers, image and video storage capability

## Intraoperative

Ultrasound is used for various intraoperative procedures such as laparoscopy and biopsy guidance. Some of these procedures require scanners that are designed and equipped for intraoperative applications. Because of the variety of intraoperative studies that may be performed, user assessment is very important when choosing features (mainly transducers) for these applications.

Transducer. Intraoperative transducer (application-specific)

Minimum requirement. Real-time 2D B-mode capability

Preferred features. CDI, PW Doppler

Other advantageous features. Fusion imaging capability, needle-guidance software, 3D/4D imaging capability

## OB/GYN (comprehensive)

Gynaecologic ultrasonography is used to assess for a variety of gynaecologic abnormalities, including infertility. During a comprehensive obstetric study, ultrasonography is used to detect the presence and condition of the fetus, as well as to investigate the blood supply to the fetus and the fetus's growth throughout pregnancy. Ultrasonography is also useful in guiding amniocentesis and other invasive procedures. Obstetric analysis packages provide a variety of commonly used gestational age, fetal weight, and fetal growth calculation methods, and some are also capable of report generation. Endovaginal transducers are used with gynaecologic and early obstetric imaging. Comprehensive OB/GYN studies require a full-featured scanner typically used by experienced (credentialled) sonographers.

Transducers. Endovaginal transducer (>7 MHz); convex or sector transducer (3 to 5 MHz)

Minimum requirements. Real-time 2D B-mode capability, CDI, DICOM compatibility, digital calipers, M-mode, obstetric analysis package

Preferred features. Cine-loop, transducer needle-guide attachment

Other advantageous features. Extended field of view, multiplanar reconstruction, multislice 3D, volume rendering (either freehand 3D or real-time 3D [4D]), needle-enhancement software, automated measurement capabilities

## OB/GYN (limited)

Limited obstetric and gynecologic studies may be used to determine the presence, position, and viability of the fetus, as well as to verify gestational age. Determining amniotic fluid levels and pelvic morphology and assessing for ectopic pregnancy are also possible. Limited OB/GYN studies can be performed with a system containing only basic features. The study is often performed at the point of care and is typically performed by a physician or nurse.

Transducers. Recommended minimum: convex sector transducer (3 to 5 MHz); acceptable: linear-array transducer (3 to 5 MHz); preferred: endovaginal transducer (>7 MHz)

Minimum requirement. Real-time 2D B-mode capability

Preferred features. Battery operation for portable studies, digital calipers, CDI or PDI

Other advantageous features. PW Doppler, Wi-Fi connectivity, image and video storage

## Prostate

Endorectal transducers are available on some scanners for prostate screening and biopsy guidance. Prostate studies are typically performed by physicians or experienced (credentialled) sonographers.

Transducer. Endorectal transducer (>7 MHz)

Minimum requirements. Real-time 2D capability, CDI, DICOM compatibility, digital calipers, transducer needle-guide attachment

Preferred feature. PDI

Other advantageous features. Multiplanar reconstruction, multislice 3D, volume rendering (either freehand 3D or real-time 3D [4D])

## Small parts

Some scanners are equipped with high-frequency (>7 MHz) transducers for use in thyroid, breast, scrotal, neonatal brain, and musculoskeletal imaging. Small-parts studies require a full-featured system typically used by experienced (credentialled) sonographers. Because of the variety of small-parts studies that may be performed, user assessment is very important when choosing features (e.g. transducers, needle guides) for these applications.

Transducers. Linear-array transducer for thyroid, breast, scrotal, and musculoskeletal imaging (>7 MHz); small-footprint sector transducer for neonatal brain studies (phased-array, vector-array, microconvex-array; >7 MHz); flat linear-array transducer for very superficial applications (e.g. to image the skin, subdermis, and some ligaments) (>10 MHz)

Minimum requirements. Real-time 2D capability, CDI, DICOM compatibility, digital calipers

Preferred features. PDI, harmonic imaging, transducer needle-guide attachment

Other advantageous features. Elastography for breast studies, extended field of view for thyroid and musculoskeletal studies,

frame averaging, frequency compounding, multiplanar reconstruction, multislice 3D, spatial compounding, volume rendering (either freehand 3D or real-time 3D [4D])

## Transoesophageal echocardiography

In addition to its use in cardiology—see Cardiac (comprehensive), p.268—TEE is also occasionally used outside the cardiology department by anaesthesiologists for cardiac monitoring during surgical procedures.

Transducers. Single-plane TEE transducer; advantageous: biplane or multiplane TEE transducer

Minimum requirement. Real-time 2D capability

## Vascular (comprehensive)

Vascular ultrasonography affords the clinician flow profiles of vessels throughout the body to diagnose arterial and venous abnormalities and identify their causes.

Comprehensive vascular studies include complete peripheral, cerebrovascular, and extracranial imaging with complete vascular analysis (2D and Doppler). Vascular analysis packages can make measurements and calculations automatically. A vascular study requires a full-featured scanner, typically used by experienced (credentialled) sonographers. Vascular studies are performed in a hospital department's radiology-based ultrasound lab, in a vascular surgery ultrasound lab, or in cardiology. These exams may be performed at the patient's bedside in general care areas and in the intensive care unit.

Transducers. Recommended minimum: linear-array transducer (>7 MHz); acceptable: vector-array transducer (>7 MHz); preferred: steered linear-array transducer (>7 MHz), curved linear array transducer (3 to 5 MHz)

Minimum requirements. Real-time 2D capability, CDI, PDI, DICOM compatibility, digital calipers, PW Doppler, vascular analysis package

Preferred features. Cine-loop, CW Doppler

Other advantageous features. Volume rendering (freehand 3D or real-time 3D [4D])

## Vascular access

Vascular access is a special application that involves ultrasonic guidance for vascular surgical procedures, peripherally inserted central catheter (PICC) line placement, and biopsies. Scanners are often dedicated to this application, and there is a growing list of related studies performed with these systems, including bedside deep-vein thrombosis exams, pseudoaneurysm repair guidance, vein mapping prior to harvest or dialysis fistula creation, and intraoperative arterial monitoring. Because of the variety of vascular access studies that may be performed, user assessment is very important when choosing features (mainly transducers) for these applications. These procedures are typically performed at the point of care and are usually performed by physicians or nurses.

Transducers. Recommended minimum: linear-array transducer (>7 MHz); acceptable: convex-array transducer (>7 MHz)

Minimum requirement. Real-time 2D capability

Preferred features. Battery operation for portable studies, CDI or PDI, digital calipers ■

# Advances in monitoring expired $CO_2$ in critically ill patients

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Reviews the potential uses and pitfalls of capnography in critically ill patients, especially for haemodynamic and respiratory monitoring.

Expired $CO_2$ can be easily monitored in the intensive care unit (ICU), especially in patients under invasive mechanical ventilation, using infrared measurement by sampling mainstream expiratory flow using an in-line chamber, or sidestream expiratory flow (by continuous aspiration through a sampling line connected between the intubation tube and the Y-piece of the ventilator).

Expired $CO_2$ is determined by three parameters:

1. $CO_2$ production ($CO_2$) mainly due to tissue metabolic activity
2. $CO_2$ transport related to cardiac output (CO) and haemoglobin level
3. $CO_2$ clearance by alveolar ventilation.

Given its high diffusive capacity, $CO_2$ is easily eliminated by alveolar ventilation, although end-tidal $CO_2$ partial pressure ($PEtCO_2$) is higher than alveolar $CO_2$ partial pressure ($PACO_2$) due to ventilation-perfusion mismatch. The gradient between $PEtCO_2$ and arterial $CO_2$ partial pressure ($PaCO_2$) is usually low (3-5 mmHg) but increases with increasing alveolar dead space, even though $PEtCO_2$ remains highly correlated with $PaCO_2$.

By allowing a combined analysis of respiratory, haemodynamic and metabolic status, capnography is a versatile tool with developing clinical applications in the ICU. While capnography is commonly used in the operating room, this technique may be underused in the ICU (Cook et al. 2011; Georgiou et al. 2010; Ono et al. 2016). The aim of this paper is to highlight the advances and the usefulness of expired $CO_2$ monitoring in the specific ICU setting.

## Capnography and respiratory intensive care

### *Airway management*

Capnography is a reliable tool to confirm the correct placement of endotracheal (Guggenberger et al. 1989) or supraglottic devices, given the lack of significant $CO_2$ production in the oesophagus. Despite a high diagnostic performance (Silvestri et al. 2005), false negatives are encountered in the cardiac arrest setting (Heradstveit et al. 2012) or as a consequence of technical pitfalls (leaks around endotracheal cuff (Dunn et al. 1990), kinking of the sampling line, ventilator failure…). False positives may happen if the stomach contains $CO_2$ (e.g. in patients receiving noninvasive ventilation for hypercapnic respiratory failure). Finally, despite recommendations for systematic use during intubation in the ICU, the clinical impact of this strategy remains to date unknown in the ICU setting. Indeed, most of the recommendations are made from the NAP 4 audit (Cook et al. 2011), which showed that 74% of deaths related to airway issues in the ICU (tube displacement, oesophageal intubation) were associated with the lack of capnography.

### *Dead space measurement and volumetric capnography*

Partial pressure of expired $CO_2$ is usually plotted against time on a capnogram, allowing assessment of $PEtCO_2$. Partial pressure of expired $CO_2$ may also be plotted as a function of expired tidal volume to provide volumetric capnography. An ideal volumetric capnography curve can be described in three expiratory phases (**Figure 1**) (Verscheure et al. 2016):

- **Phase 1** - exhaled $CO_2$ amounts to zero and reflects the lack of $CO_2$ content in the conducting airways
- **Phase 2** - $CO_2$ increases linearly, reflecting mixing of $CO_2$ content of distal airways and alveoli close to the main airways
- **Phase 3** - $CO_2$ reaches a slowly rising plateau (reflecting alveolar gas compartment), whose slope is an indication of ventilation-perfusion mismatch. Both anatomical ($VD_{aw}$) and alveolar dead space ($VD_{alv}$) can be computed by combining capnography and arterial blood sampling using graphical analysis of the volumetric capnography curve (Fletcher et al. 1981). Assuming $PaCO_2$ approximates $PACO_2$, physiological dead space ($VD_{phys}$) can also be computed using the Enghoff modification of the Bohr equation, as follows:

  $VD_{phys}$ Bohr-Enghoff = $(PaCO_2 - PACO_2)/PaCO_2$ with $PACO_2$ = mean expired $CO_2$ partial pressure.

However, $VD_{phys}$ assessed with the Bohr-Enghoff equation overestimates the true $VD_{phys}$, since venous admixture and low ventilation-perfusion areas increase the difference between $PaCO_2$ and $PACO_2$. It

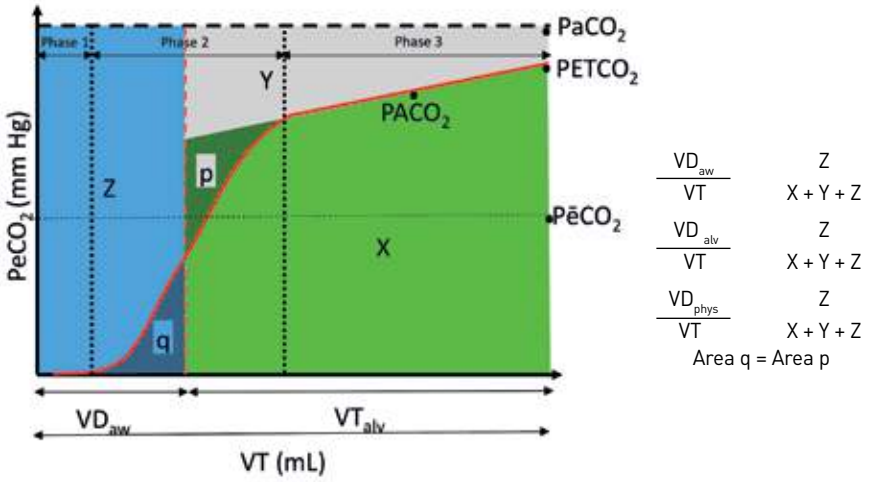


**Figure 1.** Typical volumetric capnography curve

**Phase 1:** emptying of conducting airways; **phase 2:** emptying of distal airways and alveoli close to the main airways; **phase 3:** emptying of alveolar gas compartment. Right side of rectangle Z is defined such as area q equals area p (Fletcher et al. 1981). Area X (green-filled), Y (grey-filled) and Z (blue-filled) are used to compute anatomical, alveolar, and physiological dead space using Fletcher's approach (Fletcher et al. 1981).
$PaCO_2$ arterial $CO_2$ partial pressure $PeCO_2$ expired $CO_2$ partial pressure $PeCO_2$ mean expired $CO_2$ partial pressure $PEtCO_2$ end-tidal $CO_2$ partial pressure $VD_{aw}$ anatomical dead space $VD_{alv}$ alveolar dead space VT tidal volume $VT_{alv}$ alveolar tidal volume

was recently shown that the midportion of phase 3 is a reliable estimator of $PACO_2$ (Tusman et al. 2011), allowing a continuous assessment of true physiological dead space, without arterial blood sampling, using Bohr's original equation, as follows:

$VD_{phys}\ B_{ohr} = (PACO2\text{-}PeCO2)/PACO2$.

$VD_{phys\ Bohr}$ as assessed by volumetric capnography has been shown to be closely related to dead space measurement using the multiple inert gas technique (Tusman et al. 2011), and is not impacted by the effect of shunt or low ventilation-perfusion areas.

Finally, plotting the volume of expired $CO_2$ as a function of expired tidal volume allows computation of $VD_{alv}$ (Fletcher et al. 1981) and alveolar ejection volume (Romero et al. 1997), defined at the predicted point where alveolar emptying begins (**Figure 2**), as an attempt to better quantify phase 3 of the volumetric capnography curve.

The following clinical applications of volumetric capnography have been reported:

- Nuckton et al. (2002) reported that dead space (computed from the Bohr-Enghoff equation) was strongly associated with acute respiratory distress syndrome (ARDS) mortality. In addition, Gattinoni et al. (2003) showed that decrease of dead space during prone position was associated with lower ARDS mortality. Alveolar ejection volume is also associated with ARDS mortality (Lucangelo et al. 2008), with the advantage of being independent of ventilatory settings (Romero et al. 1997). Whether strategies aiming to minimise deadspace decrease ARDS mortality remains however unknown.
- As early as 1975, Suter et al. (1975) showed that the "best positive end-expiratory pressure (PEEP)" (i.e. PEEP level associated with the highest oxygen transport) was associated with the lowest dead space (computed from the Bohr-Enghoff equation with a correction for the effect of shunt [Kuwabara et al. 1969]). Increase in dead space below and above the best PEEP level was interpreted as evidence of lung overdistension (and hence compression of alveolar vessels) at low and high lung aerated volume.
- Increased dead space fraction has been reported as an excellent predictor of extubation failure in a single study on ICU adult patients (González-Castro et al. 2011), a finding that should be confirmed before application in clinical practice.

> "capnography is a versatile tool with developing clinical applications in the ICU"

However volumetric capnography presents the following limitations: measurement errors due to air leaks (e.g. during noninvasive ventilation) or obstruction of airway adaptor by secretions or condensation droplets, requirement of sufficient expiratory time in order to allow complete $CO_2$ exhalation, deviation from the ideal 3 phases curve in some clinical situations, dependency to ventilatory settings etc.

### $PaCO_2$ surrogate

$PEtCO_2$ can be used as a surrogate of $PaCO_2$, e.g. after changing ventilatory settings, assuming the $PEtCO_2$-$PaCO_2$ gap remains constant over time (i.e. hypothesising that the dead space remains constant). It was shown as a cost-effective intervention (Rowan et al. 2015) with a reduction of a third of blood gases analyses and a saving of $880,496 over 6 months in an American paediatric ICU. In specific populations where tight control of $PaCO_2$ is important (e.g. patients with brain injury), $PEtCO_2$ monitoring can be useful as it allows a continuous noninvasive estimation of $PaCO_2$. It should, however, be stressed that interventions that can alter dead space (e.g. bronchodilators, major change of PEEP level and so on) should prompt the verification of the $PEtCO_2$-$PaCO_2$ gap. Furthermore, it may be unsafe to use only $PEtCO_2$ for the setting of the ventilator, given that some patients with unknown enlarged $PEtCO_2$-$PaCO_2$ gap might suffer from severe iatrogenic hypercapnia.

## Capnography and haemodynamic intensive care

### Cardiac arrest

The use of capnography in the cardiac arrest setting has been well documented and is recommended in both American and European resuscitation guidelines (Link et al. 2015; Soar et al. 2015). In this setting, capnography is a versatile tool that can help

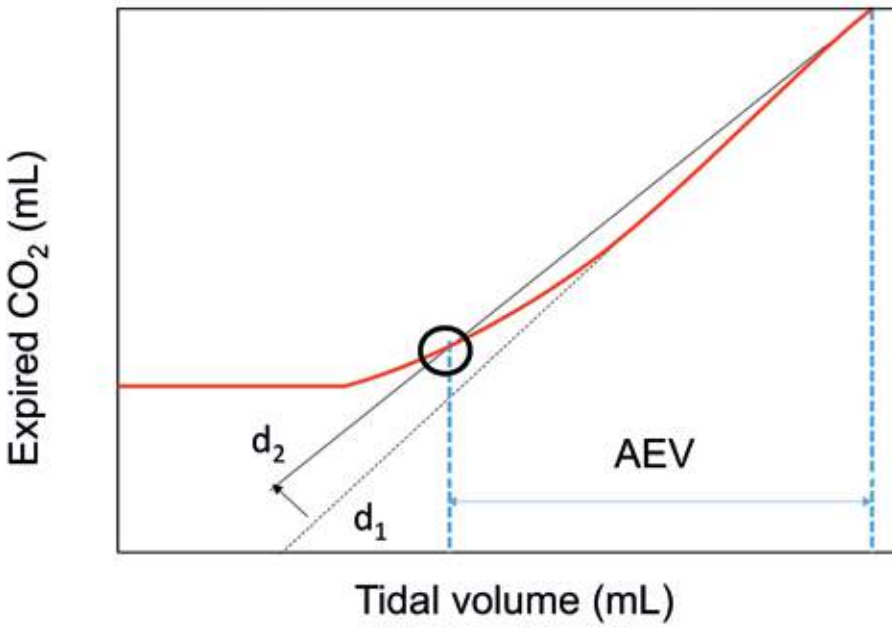


**Figure 2.** Plot of the expired volume of $CO_2$ as a function of expired tidal volume to compute alveolar ejection volume.

Alveolar ejection volume is computed as follows (Romero et al. 1997): first, a regression line (dotted black line $d_1$) is computed from the rightmost linear part of the curve, whose slope b is recorded. Second, a straight line (solid black line $d_2$) is drawn from the maximum value of expired $CO_2$ at end-expiration, with a slope amounting to 0.95 times slope b, to account for dead space contamination (dead space allowance). Finally, the intersection of the experimental curve and line $d_2$ is expected to represent the beginning of alveolar gas ejection.
AEV = alveolar ejection volume

the management of cardiac arrest patients (Heradstveit et al. 2014).

First, as described above, it can confirm the correct placement of an endotracheal tube. Second, capnography may assess the quality of cardiac resuscitation, which is correlated with the $PEtCO_2$ level, since $PEtCO_2$ is related to cardiac output. Hence it is recommended (Paiva et al. 2018) to achieve a $PEtCO_2$>20 mmHg during resuscitation. Third, capnography may help to detect the return to a spontaneous circulation if a sudden rise of $PEtCO_2$ occurs. Fourth, initial low values or failure to maintain "correct" values of $PEtCO_2$ are associated with worse outcome (Levine et al. 1997), and may help the decision to terminate resuscitation or help to triage patients with refractory cardiac arrest eligible for extracorporeal life support (Conseil français de réanimation cardiopulmonaire et al. 2009).

### Cardiac output surrogate

As $PEtCO_2$ is highly correlated to CO and monitored on a breath-by-breath basis (Weil et al. 1985), it may be used as a surrogate for continuous cardiac output monitoring over short periods, assuming $CO_2$ production and elimination remain constant. In this connection, some authors recently investigated whether $PEtCO_2$ variations could be used to track CO changes related to change in cardiac loading conditions (Monnet et al. 2012). In a study on 65 mechanically ventilated patients with acute circulatory failure, $PEtCO_2$ increased by at least 5% during a passive leg raising manoeuvre predicted fluid responsiveness with 100% specificity and a sensitivity of 71%. For patients under veno-arterial extracorporeal membrane oxygenation (ECMO), $PEtCO_2$ might reflect transpulmonary (or native) cardiac output. Naruke et al. (2010) reported that patients that were successfully weaned from veno-arterial ECMO exhibited a rise of $PEtCO_2$ of at least 5 mmHg after reduction of ECMO flow, which was interpreted as a rise of native CO. If confirmed, this method could allow a more precise screening of patients who could be safely weaned from ECMO.

CO can be measured noninvasively with the differential Fick method, using measurements of $CO_2$ elimination ($VCO_2$) and $PEtCO_2$ on a breath-by-breath basis before and during a $CO_2$ rebreathing manoeuvre (Jaffe 1999). Since cardiac output is computed from expired $CO_2$, blood flow from non-ventilated lung regions is not accounted for and a correction for shunt fraction has to be performed using arterial oxygen saturation assessed by a pulse oximeter and an iso-shunt diagram (Rocco et al. 2004). The NICO® system is a commercially available device based on this technique, using a rebreathing loop controlled by a pneumatic valve inserted at the Y-piece level. This technique has an acceptable reliability (Gueret et al. 2006) in cardiac surgery patients, but a lack of reliability in conditions of high intrapulmonary shunt (Rocco et al. 2004). In addition, the technique is hampered by several additional limitations: CO monitoring is not continuous (1 measurement every 3 minutes) making the technique unsuitable to assess fluid responsiveness by the passive leg raising test or other postural tests (Yonis et al. 2017); the technique is contraindicated in patients requiring strict control of $PaCO_2$ (e.g. brain-injured patients); haemodynamic and respiratory instability (with rapidly changing $VCO_2$ between the basal and rebreathing phase) may decrease the reliability of the CO measurement. The ideal patient for this technique would be mechanically ventilated, with no active breathing and no pulmonary disease, which probably makes the technique suitable for intraoperative monitoring.

## Capnography for metabolic intensive care

As highlighted in the introduction, $PEtCO_2$ is highly correlated to $VCO_2$. The analysis of $VCO_2$ and oxygen consumption ($VO_2$) allows estimation of the energy expenditure, through indirect calorimetry (Oshima et al. 2017). This method is the gold standard for the estimation of the daily nutrition needs in the ICU, and is now implemented in some ICU ventilators. However, to be accurate, indirect calorimetry should be done under respiratory and haemodynamic stable conditions, in aerobic condition, and with $FiO_2$ below 60%. Some authors have proposed a new estimation of energy expenditure using only

$VCO_2$ assessed by a commercial ventilator (Stapel et al. 2015), by computing respiratory quotient of the administered nutrition using the Weir formula to compute $VO_2$ (Weir 1949). The reliability of this method was acceptable, with a less than 10% overestimation of energy expenditure. Whatever the method to determine energy expenditure, no study has, to date, explored the impact of its use on ICU outcome as compared to traditional predictive equations including anthropometric parameters.

## Capnography for intrahospital transport

The use of $PEtCO_2$ for intrahospital transport mechanically ventilated patients is highly recommended in the United Kingdom and in selected patients in France (Intensive Care Society 2016; Quenot et al. 2012). This recommendation is based on the frequency of airway related adverse events (hypoxia, extubation, ventilator failure etc.). As for the intubation procedure, strong evidence is lacking, and recommendations are based on observational studies and expert opinions.

## Conclusion

In this review, we have highlighted the possible applications of capnography in the ICU. The versatility of this tool also makes its frailty. However, it often requires that the patient is haemodynamically stable, passively ventilated, with no change in energy expenditure. ICU patients do not fulfil these criteria most of the time. Finally, we are lacking studies showing improvement of critically ill patients' outcome by using any of the $CO_2$ monitoring tools. Whether this statement will remain true in the future depends on the will of critical care teams to embrace this technology, study it, and ultimately... use it! ■

**Conflicts of interest**

Mehdi Mezidi declares that he has no conflict of interest. Jean-Christophe Richard declares that he has no conflict of interest.

**Abbreviations**

ARDS acute respiratory distress syndrome
CO cardiac output
$CO_2$ carbon dioxide
ECMO extracorporeal membrane oxygenation
ICU intensive care unit
$PACO_2$ $CO_2$ alveolar partial pressure
$PaCO_2$ $CO_2$ arterial partial pressure
$PeCO_2$ mean expired $CO_2$ partial pressure
PEEP positive end-expiratory pressure
$PEtCO_2$ end-tidal $CO_2$ partial pressure
$VCO_2$ $CO_2$ production
$VD_{alv}$ alveolar dead space
$VD_{aw}$ anatomical dead space
$VD_{phys}$ physiological dead space
$VO_2$ $O_2$ consumption

## References

**For full references, please email editorial@icu-management.org or visit https://iii.hm/qp9**

# How to manage severe dengue infection

A review of diagnosis and treatment of dengue, a mosquito-borne febrile illness caused by flavivirus with a clinical spectrum ranging from self-limited fever to dengue haemorrhagic fever with shock.

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Dengue is a febrile illness, caused by one of the serotypes of Flavivirus (DENV1-4), transmitted by *Aedes aegypti* and *Aedes albopictus* mosquitoes during a blood meal (Simmons et al. 2012; Guzman et al. 2015; Pai-Dhungat et al. 2013). The vectors live in an urban habitat and are daytime feeders. *Aedes albopictus* is now spreading to North America and Europe due to international trade. The island of Madeira, Portugal, and five other European countries have witnessed an outbreak of dengue (Guzman et al 2015).

The World Health Organization (WHO) currently estimates there may be 50-200 million dengue infections worldwide every year. Half of the world's population living in endemic areas is at risk (Pai-Dhungat et al. 2013). Recovery from infections in one serotype provides lifelong immunity against that serotype. However, cross immunity is only partial and temporary. Subsequent infection by either serotype increases the risk of developing severe dengue.

## Clinical features

As per the WHO 1997 classification, dengue comprises a clinical spectrum, which consists of

- Dengue fever (breakbone fever)
- Haemorrhagic fever and
- Dengue shock syndrome (WHO 1997)

The revised WHO classification scheme (2012) consists of

- Dengue without warning signs
- Dengue with warning signs
- Severe dengue

Expanded dengue comprises unusual or atypical manifestations of dengue which can happen in the absence of plasma leakage.

### Clinical features of dengue fever without warning signs

- Fever which lasts 5 to 7 days
- Myalgia/arthralgia
- Retro-orbital pain
- Rash
- Haemorrhagic manifestations – Petechie, ecchymosis, mucosal bleed, positive tourniquet test
- Leucopaenia and thrombocytopaenia

### Clinical features of dengue with warning signs

- Abdominal pain
- Persistent vomiting
- Mucosal bleed
- Lethargy
- Hepatomegaly
- Rapid decline in platelet count

The differentiating features of dengue with warning signs consist of haemoconcentration with a more than 20% rise in haematocrit, pleural effusion and ascites secondary to plasma leakage because of increased vascular permeability.

### Clinical features of severe dengue

- Severe plasma leakage leading to cold clammy skin, thready pulse, narrowed pulse pressure, shock, fluid accumulation with respiratory distress
- Severe bleeding
- Organ involvement
- Liver: aspartate aminotransferase (AST) or alanine aminotransferase (ALT) ≥ 1000
- Central nervous system (CNS): Impaired consciousness
- Heart and other organ involvement

### Expanded dengue

Additional manifestations of dengue virus infection may include liver failure, CNS involvement, myocardial dysfunction, acute kidney injury and other organ involvement. Neurological manifestations include encephalopathy and seizures, stroke, Guillain-Barre syndrome, transverse myelitis, mono and poly neuropathies (Solomon et al. 2000). Diagnosis is by serological testing, culture and detection by polymerase chain reaction (PCR) in cerebral spinal fluid. Cardiovascular manifestations include myocardial impairment, arrhythmias and fulminant myocarditis (Miranda et al. 2013). Haemophagocytic lymphohistiocytosis is described in association with dengue virus infection.

## Pathogenesis

After the virus is introduced into the skin by an infected mosquito, viraemia is detected from 6 to 18 hours before onset of symptoms and ends as the fever results. Both innate and adaptive immune responses play a role in clearance of infection. Virus-specific T lymphocytes response and antibody-dependent

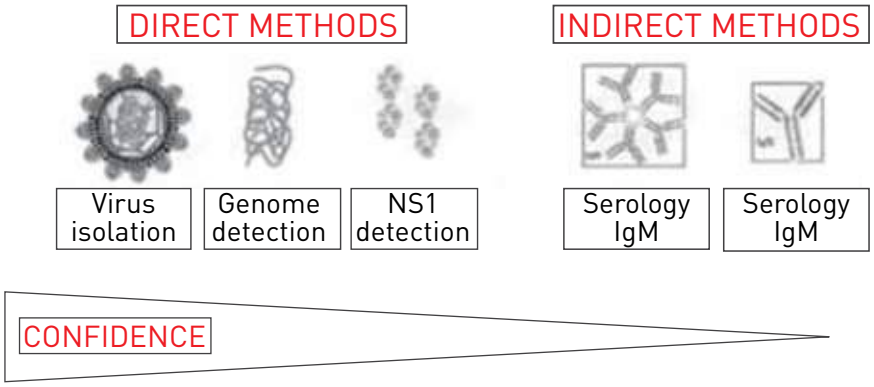



**Figure 1**. Laboratory tests for diagnosis of dengue virus infection



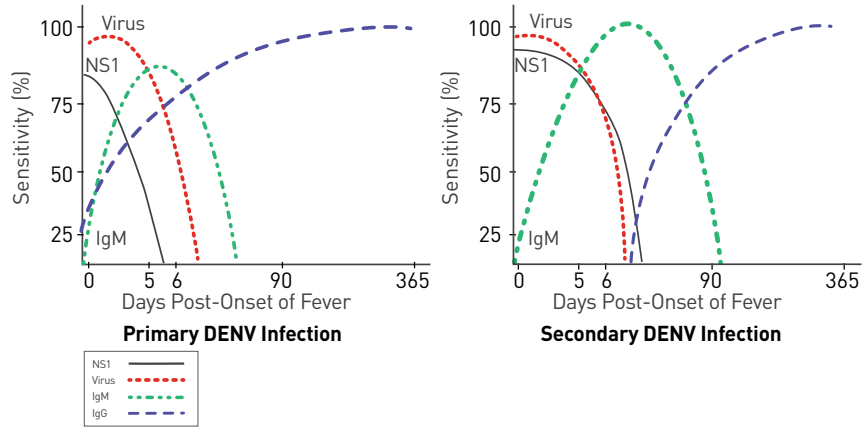



**Figure 2.** Dengue antibody response in primary and secondary infection (CDC 2010)

enhancement of infection decide severity of the infection. Plasma leakage, haemoconcentration and abnormalities in homeostasis characterise severe dengue.

A transient and reversible imbalance of inflammatory mediators, cytokines and chemokines occurs during severe dengue, probably driven by a high early viral burden, and leading to dysfunction of vascular endothelial cells, derangement of the haemocoagulation system, then to plasma leakage, shock and bleeding.

## Management

Step I – Overall assessment

- History, onset of symptoms, past medical and family history
- Physical examination, including full physical and mental assessment
- Investigation, including routine laboratory tests and dengue-specific laboratory tests

Step II – Diagnosis, differentials, assessment of disease phase and severity

Step III – Management

- Disease notification
- Management decisions: Depending on the clinical manifestations and other circumstances, patients may either be:
  - Sent home (Group A) or
  - Referred for in-hospital management (Group B) or
  - Require emergency treatment and urgent referral (Group C)

**Laboratory tests**

See **Figure 1**.

- Directly by detection of viral components in serum—high specificity but labour-intensive and costly
- Indirectly by serology—lower specificity but more accessible and less costly

***1. Direct methods***

During the first week of illness:

- Reverse transcription polymerase chain reaction (RT-PCR) assay for detection of viral nucleic acid
- Nonstructural protein 1 antigen test (NS1Ag): sensitivity 90% in primary infection and 60-80% in secondary infection

***2. Indirect methods* (Figure 2)**

- Immunoglobin M antibody (IgM Ab): Detected as early as 4 days after onset of illness
- Immunoglobin G antibody (IgG Ab): In primary infection there is slow rise and low titres, detected after 7 days of onset of illness. In secondary infection, there is rapid rise in titres beginning 4 days after onset of illness.

The ratio of IgG: IgM >1:1.10 on day 2 of illness helps to diagnose secondary dengue infection (Changal et al. 2016).

***3. Direct virus isolation through cultures with delayed results***

***4. Dengue viral proteins detected in tissue samples using immunohistochemical staining***

Liver tissues have highest yield. This is rarely indicated.

**Differential diagnoses**

- Viral haemorrhagic fevers like Ebola, Lassa, Yellow fever, Hanta, Crimean congo, Severe fever with thrombocytopaenia syndrome virus (SFTSV)
- Chikungunya
- Malaria
- Typhoid fever
- Leptospirosis
- Rickettsial infection
- Zika virus
- Sepsis due to bacteraemia

## Dengue case management

Treatment according to groups A to C:

**Group A:** Patients who may be sent home (outpatient management)

1. Bed rest and frequent oral liquids
2. Paracetamol (10mg/kg/dose) not more

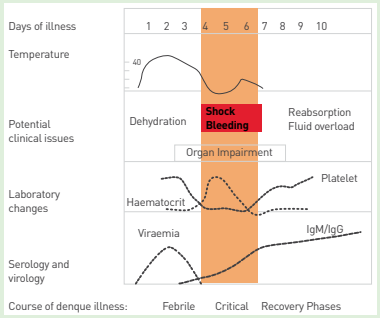
# Dengue Case Management

## Assessment

**Presumptive Diagnosis:**
Live in / travel to endemic area plus
Fever and two of the following:
- Anorexia and nausea
- Rash
- Aches and pains
- Warning signs
- Leukopaenia
- Tourniquet test positive

Lab.confirmed dengue *(important when no sign of plasma leakage)*

**Warning signs:**
- Abdominal pain or tenderness
- Persistent vomiting
- Clinical fluid accumulation
- Mucosal bleed
- Lethargy; restlessness
- Liver enlargement >2cm
- Laboratory: Increase in HCT concurrent with rapid decrease of platelet count




## Classification

negative → Co-existing conditions Social circumstances → positive / negative → **Dengue without warning signs**

positive → **Dengue with warning signs**

positive → **Severe Denque**

## Management

### Group A
**May be sent home**

**Group criteria**
Patients who do not have warning signs
AND
who are able:
- To tolerate adequate volumes of oral fluids
- To pass urine at least once every 6 hours

**Laboratory tests**
- Full blood count (FBC)
- Haematocrit (Hct )

**Treatment**
Advice for:
- Adequate bed rest
- Adequate fluid intake
- Paracetamol, 4 gram max. per day in adults and accordingly in children
- Patients with stable Hct can be sent home

**Monitoring**
- Daily review for disease progression:
  - Decreasing WBC
  - Defervescence
  - Warning signs (until out of critical period)
- Advice for immediate return to hospital if development of any warning signs
- Written advice of management (e.g. home care card for dengue)

Discharge criteria:
-> all of the following criteria must be present

### Group B
**Referred for in-hospital care**

**Group criteria**
Patients with any of the following features:
- Co-existing conditions such as pregnancy, infancy, old age, diabetes mellitus
- Social circumstances such as living alone, living far from hospital

**OR**
Existing warning signs:
- Abdominal pain or tenderness
- Persistent vomiting
- Clinical fluid accumulation
- Mucosal bleeding
- Lethargy/restlessness
- Liver enlargement >2cm
- Laboratory: increase in Hct

**Laboratory tests**
- Full blood count (FBC)
- Haematocrit (Hct)

**Treatment**
- Encouragement for oral fluids
- If not tolerated, start intravenous fluid therapy 0.9% saline or Ringer Lactate at maintenance rate

**Monitoring**
- Temperature pattern
- Volume of fluid intake and losses
- Urine output – volume and frequency
- Warning signs
- Hct, white blood cell and platelet counts

**Treatment**
- Obtain reference Hct before fluid therapy
- Give isotonic solutions such as 0,9% saline, Ringer lactate, start with 5-7mL/kg/hr for 1-2 hours, then reduce to 3-5mL/kg/hr for 2-4 hr, and then reduce to 2-3mL/kg/hr or less according to clinical response

**Reassess clinical status and repeat Hct**
- If Hct remains the same or rises only minimally -> continue with 2-3 mL/kg/hr for another 2-4 hours
- If worsening of vital signs and rapidly rising Hct -> increase rate to 5-10 mL/kg/hr for 1-2 hours

**Reassess clinical status, repeat Hct and review fluid infusion rates accordingly**
- Reduce intravenous fluids gradually when the rate of plasma leakage decreases towards the end of the critical phase.

**This is indicated by:**
- Adequate urine output and/or fluid intake
- Hct decreases below the baseline value in a stable patient

**Monitoring**
- Vital signs and peripheral perfusion (1-4 hourly until patient is out of critical phase
- Urine output (4-6 hourly)
- Hct (before and after fluid replacement, then 6-12 hourly)
- Blood glucose
- Other organ functions (renal profile, liver profile, coagulation profile, as indicated)

- No fever for 48 hours
- Improvement in clinical picture
- Increasing trend of platelet count
- No respiratory distress

### Group C
**Require emergency treatment**

**Group criteria**
Patients with any of the following features.
- Severe plasma leakage with shock and/or fluid accumulation with respiratory distress
- Severe bleeding
- Severe organ impairment

**Laboratory tests**
- Full blood Count (FBC)
- Hae matocrit (Hct)
- Other organ function tests as indicated

**Treatment of compensated shock:**
- Start IV fluid resuscitation with isotonic crystalloid solutions at 5-10 mL/kg/hr over 1 hr
- Reassess patient's condition

**If patient improves:**
- IV fluids should be reduced gradually to 5-7 mL/kg/hr for 1-2 hr, then to 3-5 mL/kg/hr for 2-4 hr, then to 2-3 mL/kg/hr for 2-4 hr and then reduced further depending on haemodynamic status
- IV fluids can be maintained for up to 24 - 48 hours

**If patient still unstable:**
- Check Hct after first bolus
- If Hct increases/ still high (>50%), repeat a second bolus of crystalloid solution at 10-20 mL/kg/hr for 1 hr
- If improvement after second bolus, reduce rate to 7-10 mL/kg/hr for 1-2 hr, continue to reduce as above
- If Hct decreases, this indicates bleeding and need to cross-match and transfuse blood as soon as possible

**Treatment of hypotensive shock**
- Initiate IV fluid resuscitation with crystalloid or colloid solution at 20 mL/kg as a bolus for 15 min
- If patient improves
- Give a crystalloid /colloid solution of 10 mL/kg/hr for 1 hr, then reduce gradually as above

**If patient still unstable**
- Review the Hct taken before the first bolus
- **If Hct was low** (<40% in children and adult females, < 45% in adult males) this indicates bleeding, the need to crossmatch and transfuse (see above)
- **If HCT was high** compared to the baseline value, change to IV colloids at 10-20 ml/kg as a second bolus over ½ to 1 hour; reassess after second bolus
- **If improving** reduce the rate to 7-10 mL/kgt/hr for 1-2 hours, then back to IV crystalloids and reduce rates as above
- **If condition** still unstable, repeat Hct after second bolus
- **If Hct decreases**, this indicates bleeding, see above
- **If Hct increases**/ remains high (> 50%), continue colloid infusion at 10-20 mL/kg as a third bolus over 1 hr, then reduce to 7-10 mL/kg /hr for 1-2 hours, then change back to crystalloid solution and reduce rate as above

**Treatment of haemorrhagic complications:**
- Give 5-10 mL/kg of fresh packed red cells or 10-20 mL/kg fresh whole blood

- Stable haematocrit without intravenous fluids

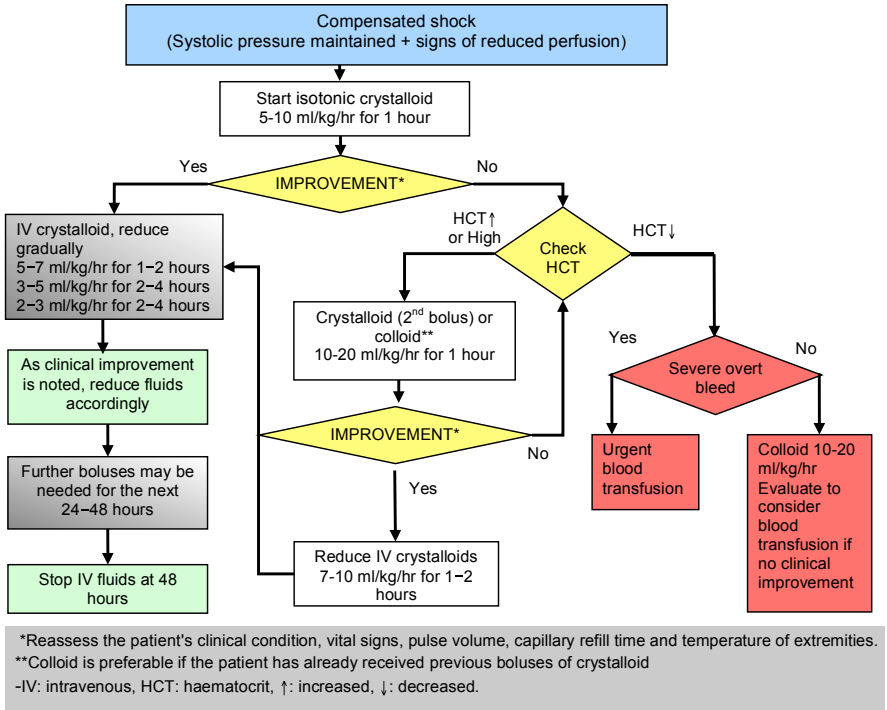



**Figure 4.** Algorithm for fluid management of compensated shock



than 3-4 times/day in chidren and not more than 3g/day in adults. Tepid water sponging if high grade fever persists

3. Patients with more than 3 days of illness need to be reviewed daily for disease progression (Look for leukopaenia, thrombocytopaenia, increasing Hct, defervescence and warning signs).

**Group B:** Patients with warning signs, co-existing conditions and those with social circumstances need inhospital management for close observation.

Warning signs: no clinical improvement, deterioration around the time of defervescence, abdominal pain, vomiting, cold peripheries, obtundation, bleeding, breathlessness, oligo-anuria. Refer to **Figure 3** (previous page) for fluid management of Group B patients.

**Group C:**

- Patients with severe plasma leakage causing shock, third spacing, respiratory distress
- Severe haemorrhages
- Severe organ impairment

Further divided into patients with compensated and uncompensated shock (**Figures 4-5**).

## When to stop IV fluids

- Signs of cessation of plasma leakage
- Stable haemodynamics
- Decreasing haematocrit with stable haemodynamics
- Apyrexia for > 24-48 hours
- Resolving abdominal symptoms
- Improving urine output

Prophylactic transfusion of platelet concentrates in absence of bleeding, even if profound thrombocytopaenia and use of steroids, unless proven haemophagocytic syndrome, has not been shown to improve outcome (Dondorp 2016).

## Treatment of haemorrhagic complications

- Strict bed rest and protection from trauma
- Avoid intramuscular injections
- Cautious insertion of urinary/nasogastric tubes/central line insertion under ultrasound guidance
- Stop the bleeding
- 5-10mL/kg of fresh packed red blood cells (PRBCs)
- Platelet transfusion (if <10,000 or active bleeding) and occasionally fresh frozen plasma (FFP).
- Vitamin K if international normalised ratio (INR) deranged or liver disease
- In gastrointestinal bleeds, H2 blockers/proton pump inhibitors (PPIs) but doubtful efficacy

### Risk factors

- Patients with refractory shock
- Patients on non-steroidal anti-inflammatory agents, anticoagulant therapy
- Patients with pre-existing peptic ulcer disease

## Glucose control

Both hypoglycaemia and hyperglycaemia can occur in the same patient during critical phases.

## Electrolyte and acid base imbalances

- Hyponatraemia secondary to GI losses or use of hypotonic solutions
- Hypo- or hyperkalaemia in association with acute kidney injury or gastrointestinal losses or stress-induced hypercortisol state.
- Hypocalcaemia: after massive blood transfusions or use of sodium bicarbonate
- Hypophosphataemia
- Hyperuricaemia
- Lactic acidosis secondary to tissue hypoxia and hypoperfusion
- Hyperchloraemic metabolic acidosis due to administration of large volume of normal saline

## Complications

- Prolonged shock
- Severe bleeding with disseminated intravascular coagulation
- Fluid overload
- Respiratory distress and failure
- Multiorgan failure (MOF)
- Abdominal compartment syndrome
- Irreversible shock and death
- Co-infections and nosocomial infection: Gram-negative sepsis, co-existing tropical diseases like malaria, leptospira, typhus,enteric fever, chikungunya
- Haemophagocytic syndrome: Manifested as persistent high-grade fever, cytopaenia and MOF associated with macrophage activation, haemophagocytosis and hypercytokinaemia with raised serum ferritin levels.

- Diagnosed by bone marrow biopsy demonstrating haemophagocytic activity
- Treatment mainly with steroids (Methylprednisolone) and IV immunoglobulin

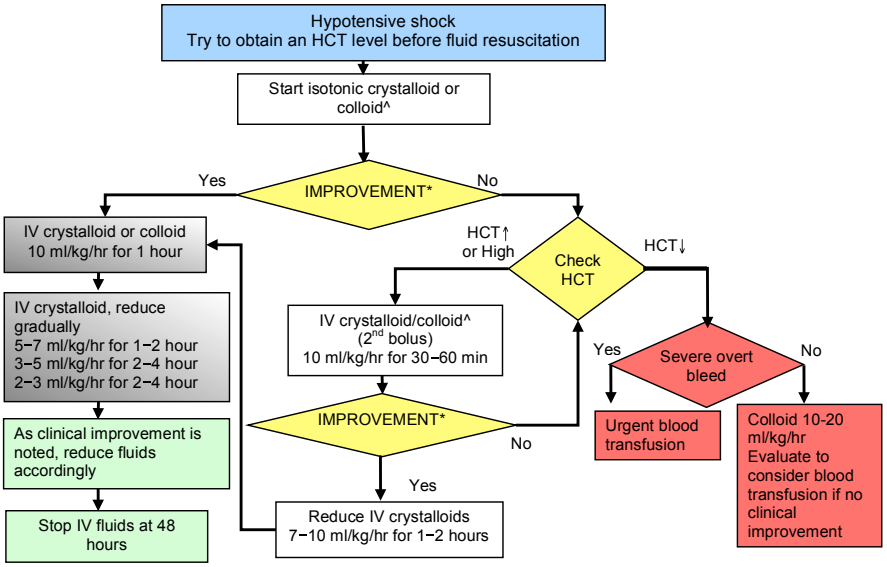
## Dengue prevention

Prevention includes mosquito control, personal protective measures and vaccination.

- **Mosquito control:**
  - Reducing breeding sites
  - Larva control
  - Use of insecticide
  - Endosymbiotic control: a novel strategy consists of releasing mosquitoes infected with the intracellular endosymbiotic bacterium *Wolbachia*, thereby reducing mosquito lifespan and inhibiting viral replication.

- **Personal protective measures:** A combination of chemically-treated gear and clothing and a strong chemical repellent may be necessary in areas with high concentrations of disease-carrying arthropods.

- **Vaccine:** CYD-TDV is a formulation of four chimeric yellow fever 17D-dengue vaccine viruses. In April 2018 the World Health Organization (WHO) advised that it should be administered only to individuals with a history of previous dengue virus infection or laboratory evidence of previous dengue virus infection. It is administered in three doses at months 0, 6, and 12.




^Colloid is preferable if the patient has already received previous boluses of crystalloid
*Reassess the patient's clinical condition, vital signs, pulse volume, capillary refill time and temperature of extremities.
IV = intravenous; HCT = haematocrit; ↑ = increased; ↓ = decreased

**Figure 5.** Algorithm for fluid management in hypotensive shock



## Conclusion

Dengue, as a mosquito-borne disease, can be prevented by effective mosquito control measures and vaccine development, which is under evaluation. Suspected dengue cases should be assessed carefully and directed to the appropriate care setting. Early recognition of severe dengue infection is essential as it needs prompt initiation of more aggressive therapy. Outpatient management is appropriate for patients without warning signs, with plenty of fluids and advice to watch for signs of dehydration, clinical deterioration or lack of improvement with defervescence or impending shock. Inpatient management is warranted for patients with dengue with warning signs, severe dengue infection or with coexisting conditions. They should be closely watched for signs of bleeding or worsening shock. Thus, high clinical suspicion, appropriate diagnostic measures and treatment at the right time is the key to achieve good outcomes in these patients and reduce morbidity as well as mortality. ■

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# Antifungal treatment in the ICU

## Best practice in managing fungal infections

Invasive candidiasis: Every milligram of antifungal counts! Think Aspergillus!

Invasive fungal infections (IFIs) are a major cause of morbidity and mortality in critically ill patients. Almost 80% of IFIs are due to *Candida spp.*, which are the third most common isolated microorganisms in the intensive care unit (ICU) (Kett et al. 2011; Bassetti et al. 2017). Although the incidence of invasive candidiasis (IC) varies considerably according to different reports and geographic locations, it ranges from 1 to 10 per 1000 ICU admissions. Candidaemia is the most common form of IC, followed by intra-abdominal candidiasis. Both are characterised by a high crude mortality, ranging from 25 to 60%, although strongly affected by underlying conditions and presence of sepsis and septic shock (Cortegiani et al. 2017b). The recently completed *Epidemiological study on incidence of candidemia in European ICUs (EUCANDICU)*, conducted by the European Society of Clinical Microbiology and Infectious Diseases Study Group for Infections in Critically Ill Patients (ESCMID ESGCIP), will soon provide more homogenous and updated data about ICU-related incidence of IC in Europe.

Aspergillus is the second most common cause of IFI in ICU. It is difficult to assess the exact incidence of invasive pulmonary aspergillosis (IA) in non-neutropaenic critically ill patients, due to difficulties in risk stratification and diagnosis. However, it is increasing and it is probably higher than previously thought (Taccone et al. 2015).

Recent data have changed our understanding of and view about the management of both IC and IA in non-neutropaenic patients. The aim of this report is to discuss best practice in management of IFIs in the ICU, according to recent evidence.

> **"early discontinuation of empirical antifungal treatment in high-risk patients, using serial measurement of biomarkers...may be safe and cost-effective"**

### Invasive candidiasis

**"Dilemmas" from the evidence**

The gold standard for the diagnosis of IC remains blood culture, which may miss more than 50% of cases in bloodstream infections and up to 80% in deep-seated candidiasis (Clancy and Nguyen 2018). Moreover, the average turnaround time for identification is 3-5 days, with additional time needed for susceptibility testing. Several retrospective and prospective observational studies found a strict correlation between timing of antifungal treatment initiation and patients' survival, especially in case of sepsis and septic shock. Of note, this association has been found in patients with both candidaemia and intra-abdominal candidiasis (Puig-Asensio et al. 2014; Bassetti et al. 2015). These findings led to a widespread use of antifungals according to "untargeted" treatment strategies, such as prophylaxis (based on risk factors or scores), pre-emptive (based on "surrogate markers") or empiric (signs and symptoms of infections) (Cortegiani et al. 2017b). In a recent cross-sectional 1-day multicentre study in France, 7.5% of all ICU patients received antifungals without proof of IFI in two-thirds of these cases (Azoulay et al. 2012).

At least two negative consequences on fungal ecology may be correlated to the increased use of antifungals. The first is the increasing rate of antifungal resistance, especially in non-albicans *Candida spp* (e.g. *C. glabrata*). Although not homogenous worldwide, reports from North America demonstrated a worrisome trend of bloodstream infections by echinocandin-resistant *C. glabrata* (to around 13%) with a hot-spot mutations in FKS genes, which encode glucan-synthase enzyme (target of echinocandins) (Cortegiani et al. 2018a). Of note, fluconazole and amphotericin B resistance are frequently associated with these mutations. Another issue is the very fast spread worldwide of *Candida auris*, a nosocomial pathogen which frequently presented multidrug or even extended or pan-drug resistance with a crude mortality rate up to 72% (Cortegiani et al. 2018b).

Four major multicentre randomised controlled trials (RCTs) failed to demonstrate a benefit in terms of mortality when comparing azoles or echinocandins versus

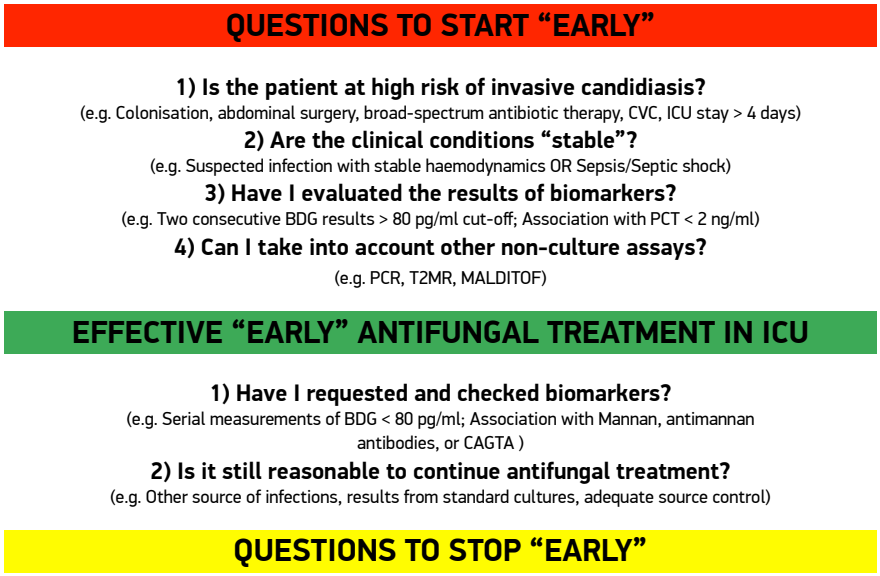


**Figure 1.**

placebo in a wide range of non-neutropaenic critically ill patients (i.e. general non-neutropaenic ICU patients at low or high risk of IFI, emergency abdominal surgery patients, and septic patients with multi-site Candida colonisation) (Schuster et al. 2008; Ostrosky-Zeichner et al. 2014; Knitsch et al. 2015; Timsit et al. 2016; Cortegiani et al. 2017b). However, in two trials enrolling high-risk patients and septic patients with Candida colonisation, there was a significant reduction of proven or probable IFI in patients receiving antifungals (Ostrosky-Zeichner et al. 2014; Timsit et al. 2016).

A recent Cochrane systematic review included 22 RCTs for a total of 2,761 patients (Cortegiani et al. 2016a; 2017a). There was moderate quality evidence that antifungal agents administration before the definitive diagnosis of IC in non-neutropaenic patients ("untargeted" treatment) did not reduce mortality (RR 0.93, 95% CI 0.79 to 1.09, p=0.36). However, there was low-grade evidence that untargeted strategies significantly reduce the incidence of proven IFI (RR 0.57, 95% CI 0.39 to 0.83, p=0.0001). Interestingly, a subsequent trial sequential analysis demonstrated that it is unlikely that further research would change these results (Cortegiani and Giarratano 2018). Lastly, guidelines from the Infectious Disease Society of America strongly recommended empiric antifungal treatment with an echinocandin in patients with risk factors of IC (e.g. abdominal surgery) and no other cause of fever (Pappas et al. 2016). The treatment should be initiated as soon as possible in case of septic shock. The guidelines also underlined the need to support this decision with other means, such as score, surrogate markers or cultures from non-sterile sites.

These results are difficult to interpret (Cortegiani et al. 2016b) and apply in clinics, but they may suggest that classic "untargeted" antifungal strategies should be replaced. However, new strategies for effective "early" antifungal strategies are urgently needed (**Figure 1**). Useful insights came from recent evidence about non-culture diagnostics.

### Non-culture diagnostics: the solution for dilemmas?

1,3-β-d-glucan (BDG) is a fungal cellwall polysaccharide of several pathogenic fungi. Although not specific for *Candida* spp., it is the most studied and used marker. A recent meta-analysis demonstrated a pooled sensitivity of 78% and specificity of 81% for IFI diagnosis and a best cut-off value of 80 pg/ml (He et al. 2015). The diagnostic performance of BDG improved if positivity was confirmed by two tests. Although most studies tested BDG in candidaemia, its usefulness has been proven for intra-abdominal candidiasis (sensitivity 70%, specificity 78%) and to differentiate IC from colonisation (Tissot et al. 2013; Martin-Mazuelos et al. 2015). Moreover, its association with other biomarkers such as procalcitonin (<2.00 ng/mL), could help in early differential diagnosis between candidaemia and bacteraemia (Cortegiani et al. 2014; Giacobbe et al. 2017). However, it is still unclear if BDG can be an effective marker to start antifungal treatment. In a subanalysis of the *Empirical Antifungal Treatment in ICUS (EMPIRICUS)* trial, empiric treatment with micafungin in septic patients did not improve survival in comparison to placebo, regardless of BDG levels (Timsit et al. 2016). The ongoing multicentre *(1,3)-β-D-glucan Based Diagnosis of Invasive Candida Infection in Sepsis (CandiSep)* trial will shed light on the effectiveness of a BDG-based strategy to initiate early antifungal treatment in comparison to standard culture-based strategy in patients with sepsis and high risk for IC (Bloos et al. 2018).

Recent studies evaluated biomarker-based strategies for early discontinuation of antifungal treatment. In a multicentre cohort study enrolling 85 ICU high-risk patients receiving empiric antifungal treatment for suspected candidaemia, two consecutive negative BDG tests permitted stopping anidulafungin at day 4, without missing any recurrent episode of candidaemia until day 30 (very high negative predictive value) (Nucci et al. 2016). Rouzè et al. (2017) performed a single-centre unblinded RCT enrolling 110 patients receiving empirical treatment. They randomised patients to receive treatment according to a biomarker-based strategy guided by the results of BDG, mannan and anti-mannan serum assays at day 0 and 4 after randomisation, in comparison to standard empiric treatment according to guidelines. The cut-offs used were 80 pg/mL for BDG, 125 pg/mL for mannan and 20 UA/mL for anti-mannan. Empirical antifungal treatment was discontinued more frequently in the biomarker-based group than in the control group (54% vs

2%, p < 0.001) with a significantly shorter duration of therapy (median 6 vs 13 days, p < 0.0001). Early discontinuation had no impact on patient outcomes, including the incidence of subsequent proven IC. These data suggest that early discontinuation of empirical antifungal treatment in high-risk patients, using serial measurement of biomarkers (especially more than one), may be safe and cost-effective (**Figure 1**).

T2 magnetic resonance (T2MR) assay is an automated molecular technology which can detect five commonly isolated *Candida* spp., namely *Candida albicans, glabrata, parapsilosis, tropicalis, krusei*. Very interestingly, it works on whole blood specimens (without blood culture) and does not need prior isolation of *Candida spp*. Moreover, T2MR does not need extraction or purification of target molecules, contrary to standard polymerase chain reaction (PCR). The estimated turnaround time is less than 5 hours (Clancy and Nguyen 2018). The limit of detection ranges from 1 to 3 colony-forming units (CFU)/mL compared to the 100-1000 CFU/mL limit of standard PCR. Recently, two large multicentre studies, *Detecting Infections Rapidly and Easily for Candidemia Trial (DIRECT1* and *DIRECT2*), evaluated the clinical performance of T2MR for rapid diagnosis of candidaemia. The overall sensitivity and specificity were 91% and 99%. In patients receiving antifungal drugs, T2MR was able to identify candidaemia episodes missed by blood culture (Clancy et al. 2018). Moreover, the recently published *Serial Therapeutic and Antifungal Monitoring Protocol (STAMP)* multicentre trial, enrolling 31 patients with candidaemia on antifungal treatment, demonstrated that T2MR was superior to blood culture for monitoring clearance of candidaemia (Mylonakis et al. 2018). Although these are promising results, the limited availability and costs may limit T2MR use in clinical algorithms. Further studies should evaluate T2MR performance in IC without candidaemia, in mixed Candida infections, and how to clinically interpret results that are discordant with blood culture.

### "Bayesian" approach to Candida infection in ICU

Although several "dilemmas" remain unsolved, clinicians should apply a "Bayesian" approach to the management of *Candida* infections (Clancy and Nguyen 2018). This means that efforts should be made to estimate (and maximise) the pre-test likelihood of infection, whichever tests are used. Tests should be selected based on which is the most probable form of *Candida* spp. infection in that critically ill patient (e.g. candidaemia, intra-abdominal candidiasis). For example, the prevalence of candidaemia ranges from <1% in general patients in whom blood culture is collected to more than 10% in ICU high-risk patients, such as those in septic shock receiving broad-spectrum antibiotics though central venous catheter and multi-site Candida colonisation. The same is true for intra-abdominal candidiasis, the prevalence of which may range from around 5% to more than 30% in patients with peritonitis for recurrent gastrointestinal anastomotic leaks. After the decision to start antifungal treatment and after performing the appropriate source control (e.g. abdominal surgery, removing catheters) clinicians should focus on how and when to stop the drugs (**Figure 1**).

## Recent evidence on invasive aspergillosis

Prompt administration of an effective treatment for invasive aspergillosis (IA) is pivotal to reduce mortality, which ranges from 60 to 90%. Patient selection is important and should start with considering risk factors. Nowadays, many critically ill patients not belonging to groups with "classic" immunosuppression criteria (e.g. haematologic, HIV, transplant) may develop IA, with general incidence in ICU ranging from 0.5% to 19% (Bassetti et al. 2014). The diagnosis in ICU is challenging due to unspecific radiological findings, difficulty in obtaining histological specimens and the low applicability of standard European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) criteria in this setting. New guidelines specifically addressing IFI in ICU, including aspergillosis, are ongoing (Bassetti et al. 2018). Risk factors to be considered in the general ICU population are chronic heart failure, severe bacterial infection under broad-spectrum antibiotic treatment, surgery, malnutrition, sepsis, acute respiratory distress syndrome (ARDS) and, above the others, chronic obstructive pulmonary disease (COPD) and the cumulative dose of steroids. There is a correlation between the degree of immunocompromise due to the above-mentioned comorbidities and the risk of acquisition of IA. Very recently, a retrospective multicentre cohort study evaluated the association between influenza and IA in non-immunocompromised ICU patients (Schauwvlieghe et al. 2018). Influenza was found to be an independent risk factor for IA (adjusted odds ratio 5.19; 95% CI 2.63–10.26; p=0.0001). The group with both influenza and IA had significantly higher 90-day mortality than without influenza (51% vs 28%; p=0.0001). Moreover, a recent retrospective analysis of the Extracorporeal Life Support Organization registry (ELSO) registry suggested that mortality of patients in extracorporeal membrane oxygenation (ECMO) with Aspergillus involvement was significantly lower than the overall ELSO cohort (35.7% vs 48%) (Cavayas et al. 2018). Based on these data, influenza and severe respiratory failure (even in ECMO) should be considered major risk factors for IA in ICU patients.

Diagnosis of pulmonary IA should be based on clinical, radiological and microbiological (culture and non-culture) results. Galattomannan in broncho-alveolar (BAL) fluid lavage is actually the best non-culture assay for the diagnosis of pulmonary IA, since it is more sensitive than standard culture. The 2017 European Society of Clinical Microbiology and Infectious Diseases-European Confederation of Medical Mycology-European Respiratory Society (ESCMID-ECMM-ERS) guidelines recommend to consider an optical density index (ODI) of 0.5-1, although ODI>1 has higher predicted values (strong recommendation) (Ullmann et al. 2018). BDG may be helpful for specific detection of IA, but in association to BAL galattomannan. Thin-section chest computerised tomography (CT scan) is the imaging of choice, but classic signs are rare in ICU patients, who usually present unspecific radiological findings (Ullmann et al. 2018). Aspergillus PCR from blood and BAL may be of help, especially in combination with galattomannan.

It is still unclear if a prophylactic treat-

ment may be cost-effective in high-risk non-neutropaenic ICU patients. A "diagnosis-driven" approach based on the clinical picture, respiratory culture and BAL galattomannan may be reasonable. Voriconazole is the treatment of choice, with amphotericin-B or echinocandins as suitable alternatives (Ullmann et al. 2018).

## Conclusion

Management of IFIs in ICU still remain a matter of intense debate and a clinical challenge. Uncertainties in diagnostics, high mortality and resistance to antifungals are burning issues. However, "best practice" should include all available information, from simple risk factors analysis to non-culture diagnostics. Early discontinuation is safe and should be applied. Two themes should guide our clinical approach: 1) in IC "Every milligram of antifungals counts!" 2) "Think Aspergillus!"

### Conflict of interest

Andrea Cortegiani declares that he has no conflict of interest. In the past five years Matteo Bassetti has participated in advisory boards and/or received speaker honoraria from Achaogen, Angelini, Astellas, AstraZeneca, Bayer, Basilea, Cidara, Gilead, Melinta, Menarini, MSD, Nabriva, Paratek, Pfizer, Roche, The Medicine Company, Shionogi, Tetraphase, VenatoRX, and Vifor. ■

### Abbreviations

CFU colony-forming unit
CT computerised tomography
IA invasive aspergillosis
IC invasive candidiasis
ICU intensive care unit
IFI invasive fungal infection
ODI optical density index
RCT randomised controlled trial
T2MR T2 magnetic resonance

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# Interprofessional teamwork in the ICU

## Panacea or illusion?

Reflections on key research insights into interprofessional teamwork in the ICU with a critical yet optimistic view for its future.

Over the years, interprofessional teamwork in the intensive care unit (ICU) has been viewed as a panacea to most ills and indeed described as a core value of critical care practice (Parker 2016; Donovan et al. 2018; Lyons 2018). However, my recent conversations with ICU colleagues from the UK, US, Canada, Brazil and Hong Kong reveal that challenges to this way of working still abound. In this article, I reflect on key research insights and experience I developed from studying this issue over a number of years; and seek to provide a critical yet optimistic view for the future.

The interest in interprofessional working in ICU can be traced back to the 1980s, following studies by Knauss and colleagues in the U.S. (Knaus et al. 1986). Analysis of large datasets made the problem clear, which can be summarised in the following conclusion: in units rated better on teamwork 55% more patients survived than were expected to, while in the worst rated units 58% more patients died than were expected to. Let us be clear then, poor interprofessional teamwork costs lives and compromises quality of care. This is no big revelation, as anyone who has ever worked in ICU can attest to. However, it does beg a bigger question—why do we need research to point out and encourage people to practise the obvious?

There are very few ICU clinicians, and there are some, to be sure, who can confidently argue teamwork is not an aspiration worth pursuing. Indeed, being a team player is a requirement that pops up in most interviews for an ICU post. And, at its most basic level, everyone understands what it is about: respect, trust, communication, supportive leadership, coordination, and so on. Yet, after decades of talking about it progress remains slow. Why is interprofessional teamwork so difficult to achieve? As someone who has been fascinated about this topic for years, I have come to the simple conclusion that interprofessional teamwork in ICU, as in much of healthcare, does not come naturally.

Interprofessional teamwork does not take place in a vacuum. There are a number of variables that can affect adoption of this way of working to one extent or another, many of which have been the subject of intense debate, such as staffing, resources, facilities, guidelines, to name a few. Here, I want to explore the issue at a more primal level, and to do so we must acknowledge it as situated in the wider healthcare delivery system in which clinicians operate: the system of professions (Abbott 1988).

> "good leadership is the catalyst to good teamwork"

The social organisation of the different professions making up what we call a healthcare delivery system can be likened to an ecology, a very fragile ecology indeed. Each profession exists, as a distinct grouping, on the basis of exclusive expertise and authority over an area of activity—what sociologists call jurisdictions. Examples include diagnosis, prescribing, mobility and family support. This is a key way in which professions are distinguished from one another. Some jurisdictions can indeed be shared, but others are retained exclusively. Evidence of this way of thinking is found in job descriptions, professional codes of conduct and regulatory bodies. The problem with interprofessional teamwork is that some people see it as challenging some traditional, well-ingrained understandings of who is responsible for and gets to do what.

Of course, in ICU, professionals do not go around contemplating their job descriptions or the pressures of their professional society or regulatory body. They are far too busy to even think about these issues. Agreements about how ICU work is organised and how care is delivered are not set in stone, but are negotiated at the level of everyday practice through discussion, often conflict and ultimately compromise (Xyrichis et al. 2017). One of our challenges, ICU colleagues say to me, is that we do not have time to have such discussions. And, even when we do, the ephemeral nature of ICU teams means these discussions need to be repeated quite a lot.

To be fair, researchers, academics and policy makers have not made the situation any easier. Setting unrealistic expectations without providing people with the tools needed to implement and operationalise change in day-to-day practice is not acceptable. Complex phrases can impress senior management but mean little to people on the shop floor: consider the popular call for 'flattened hierarchies', an oxymoron if ever there was one. Teamwork has never been about working without a leader and I have never met a clinician to say so. The opposite is true—good leadership is the catalyst to good teamwork. A good leader's job is to bring the best out of their team, facilitate discussion and direct decision-making; and, when necessary, cast the deciding vote—but it is never their job to ignore others, put them down and fend off legitimate concern. The discussion above tackles only some of the issues, what I consider to be most critical, misunderstood and under-appreciated. I could go on for pages, but let me now move away from pointing out problems to suggesting solutions.

## How to improve interprofessional teamwork in the ICU

Is there anything we can do to improve interprofessional teamwork in the ICU? Lots of things, but most important is to talk to each other, at all levels, starting from senior leadership. Have an open discussion about perceived, and actual, barriers to teamwork in your unit including the issue of who is responsible for what. Start with a common example known to cause tension in your unit, for example getting a patient out of bed, prescribing a new drug, weaning or withdrawing treatment—these are all issues that demand the attention of different professionals and are a good starting point for discussions.

If you are really serious about improving teamwork in your unit, try a self-assessment exercise using something like the Interprofessional Activity Classification Tool (InterPACT) (Xyrichis et al. 2018). This can help trigger conversations about the different kinds of interprofessional activity, and diagnose weaknesses or areas needing reinforcement. Each ICU is unique, and not one tool or model can apply everywhere—it is up to the team to take ownership of their way of working, but it needs commitment from the top. A senior intensivist said to me once during an interview: 'monkey see, monkey do'—if there is teamwork at the top the rest of the team will follow.

For those of you intrigued by this brief introduction to the many and complex issues surrounding interprofessional team practice in the ICU, and want to learn more, I suggest you take a look at this recent book by Reeves and colleagues: *Collaborative practice in critical care settings: a workbook* (Reeves et al. 2018). Part of the collaborative practice series of the UK-based Centre for the Advancement of Interprofessional Education (CAIPE), this book provides a rich analysis of the main issues and provides practical advice, exercises and templates applicable to different contexts. ■

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**For full references, please email editorial@icu-management.org or visit https://iii.hm/qpc**

# Dr. Theodoros Kyprianou joins Editorial Board

Image credit: Dwight Andrews, UTHealth

**Kyprianou Theodoros**

*ICU Management & Practice* is delighted to announce that Dr. Theodoros Kyprianou, MD, PhD, EDIC, has joined the Editorial Board. Dr. Kyprianou will be Section Editor for the new Informatics & Technology section in the journal, starting in 2019.

Dr. Kyprianou is a consultant physician in Respiratory & Intensive Care Medicine, practising in Cyprus and the UK. He holds the post of Associate Professor at St George's University of London 4-year MBBS Programme, delivered at the Medical School, University of Nicosia since 2013. He was the founding Head of the Department of Intensive Care at Nicosia General Hospital in Cyprus (2006-2018).

He has a long-standing interest in the applications of informatics in medicine and in intensive care medicine in particular. He coordinates the MSc Applied Health Informatics & Telemedicine distance learning programme at the Open University of Cyprus and served as Chair (2015-2017) of the Technology Assessment & Health Informatics Working Group and as deputy chair of the e-Learning Committee (2016-2018) at the European Society of Intensive Care Medicine. His research interests focus on ICU ehealth, bio-signals and big data analytics. He is currently a member of the standing programme committee of EU HORIZON 2020 (SC1-Health, Demographic Change and Wellbeing) based in Brussels.

Prof. Jean-Louis Vincent, Editor-in-Chief, said: "Technology is vital to the ICU, and we want to examine and consider the benefits and challenges of this rapidly changing area. We welcome Dr. Kyprianou's experience and expertise and look forward to bringing this new section to our readers."

## ICU Management & Practice launches Informatics & Technology section

As informatics & technology advances invade health professionals' clinical routine, especially in intensive care medicine, practical advice and clear reviews are needed on topics such as artificial intelligence, big data, clinical information and decision support systems, closed-loop automations and so on. Submissions and ideas for the new section are welcome, and should be sent to the managing editor in the first instance - **editorial@icu-management.org.**

### References


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# Subject index

Issues/ Pages

| | |
|---|---|
| Volume 18, Issue 1 | **1-80 https://iii.hm/i22** |
| Volume 18, Issue 2 | **81-144 https://iii.hm/kee** |
| Volume 18, Issue 3 | **145-224 https://iii.hm/ohn** |
| Volume 18, Issue 4 | **225-288 https://iii.hm/qqe** |

# Author index

# AGENDA

For a full listing of events visit https://iii.hm/aly

## JANUARY

**7-11** Blood Diseases in the ICU: Advanced Training
Paris, France
**https://iii.hm/pz4**

**13-18** 9th Annual Winter Symposium in Intensive Care, Anaesthesia and Emergency Medicine
Vail, USA
**https://iii.hm/pz5**

**30-31** CRITICARE 2019: 25th Annual Conference of Indian Society of Critical Care Medicine
Mumbai, India
**https://iii.hm/pz7**

## FEBRUARY

**1-3** Milan Critical Care Datathon and ESICM's Big Datatalk
Milan, Italy
**https://iii.hm/q1u**

**4-7** Canadian Critical Care Conference 2019
Whistler, Canada
**https://iii.hm/pz8**

**7-8** 24th International Symposium on Infections in the Critically Ill Patient
Seville, Spain
**https://iii.hm/pz9**

**17-20** SCCM 2019-48th Annual Meeting of the Society of Critical Care Medicine
San Diego, USA
**https://iii.hm/pza**

**21-24** 15th WINFOCUS World Congress on Ultrasound in Emergency & Critical Care
Dubai, UAE
**https://iii.hm/pzb**

## MARCH

**19-22** ISICEM 2019-39th International Symposium on Intensive Care and Emergency Medicine
Brussels, Belgium
**https://iii.hm/pzc**

**27-29** 24th Congress of the European Association of Hospital Pharmacists (EAHP) 2019
Barcelona, Spain
**https://iii.hm/pzd**

## APRIL

**4-6** 15th Emirates Critical Care Conference 2019
Dubai, UAE
**https://iii.hm/pze**

**10-13** 8th EuroELSO 2019
Barcelona, Spain
**https://iii.hm/pzf**

**11-12** 16th Annual Critical Care Symposium
Manchester, UK
**https://iii.hm/pzg**

**11-13** ESICM EUROASIA 2019 - European Society of Intensive Care Medicine
Taipei, Taiwan
**https://iii.hm/pzh**

**13-16** 29th European Congress of Clinical Microbiology and Infectious Diseases - ECCMID 2019
Amsterdam, The Netherlands
**https://iii.hm/pzi**

**18-22** 6th SG-ANZICS Asia Pacific Intensive Care
Singapore, Singapore
**https://iii.hm/pzj**

## MAY

**1 – 3** 7th ERAS World Congress
Liverpool, UK
**https://iii.hm/pzk**

**8-10** 30º SMART - Smart Meeting Anesthesia Resuscitation intensive Care
Milan, Italy
**https://iii.hm/pzl**



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