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Pharmacist in the ICU

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Pharmacists play a crucial role in the ICU, where patients often require complex medication regimens, including multiple medications and intravenous therapies. The role of a critical care pharmacist is multifaceted and vital to ensuring optimal patient care in the critical care setting.

Critical care pharmacists ensure patients receive safe, effective, and appropriate medication therapy. They work with the critical care team to select the most appropriate medications for patients, considering diagnosis, comorbidities, allergies, and potential drug interactions. Critical care pharmacists play a crucial role in dosage optimisation to ensure therapeutic effectiveness while minimising adverse effects. They are involved in monitoring patient response to medications and collaborating with the ICU team to adjust medication regimens as needed. In addition, pharmacists play a key role in antimicrobial stewardship programmes within the ICU, ensuring that antibiotics are prescribed appropriately and with minimal risk. Parenteral nutrition also requires the expertise of critical care pharmacists, as does intravenous fluid therapy.

Pharmacists educate ICU staff on medication use, safety, and best practices. They serve as drug information resources, answering questions and recommending medication-related issues. At the same time, they can educate patients and their families about their medications, including administration, side effects, and medication adherence. They can reconcile medications when patients are admitted to or discharged from the ICU, ensuring continuity of care and minimising the risk of medication errors. They are also a valuable resource because of their expertise in medication-related issues, drug interactions, adverse effects, and alternative therapies. They can advance critical care pharmacy practice by participating in research projects and literature reviews and disseminating evidence-based recommendations. Overall, pharmacists in the ICU play a vital role in optimising medication therapy, promoting patient safety, and improving clinical outcomes.

In this issue, our contributors explore the role of **pharmacists in the ICU** and discuss their responsibilities related to various aspects of pharmaceutical care.

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

Jean-Louis Vincent

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* Pugin, J. et al. Serial Measurement of Pancreatic Stone Protein for the Early Detection of Sepsis in Intensive Care Unit Patients: A Prospective Multicentric Study.

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POINT-OF-VIEW

OTHER FEATURE ARTICLES

Defining Medicines Optimisation in the Intensive Care Unit

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Complex polypharmacy and pathophysiology are common in the intensive care unit (ICU). Medicines optimisation is essential to deliver safe, effective, and individualised pharmacotherapy. This is ideally performed by a specialised ICU pharmacist.

Introduction

Medicines are the most common intervention in healthcare and are a central component of the life-saving treatment offered in the intensive care unit (ICU) (NICE 2015). Safe and effective use of medicines requires three key elements: (1) a comprehensive clinical assessment of the patient; (2) knowledge of treatment options available and supporting evidence base; and (3) the skill to assess potential benefits of pharmacotherapy against toxicity and to tailor dosing in accordance with individual patient need. Without due diligence with respect to these elements, the risk of treatment failure and unintended harm is great (NICE 2015). The aim of this short review article is to describe a selection of the challenges of medicines use in the severely unwell ICU patient and describe how the skills of clinical pharmacists are best utilised, within the multidisciplinary team (MDT) to achieve medicines optimisation.

The ICU Patient

The ICU patient presents with unique pharmacotherapy challenges. These are broadly categorised under the headings of (1) medicines selection, (2) medicines administration and (3) medicines dosing. While there is increasingly more evidence from studies assessing treatments in critical illness, much of our existing knowledge of medicines is derived from phase one studies conducted in healthy adult patients. During critical illness, the ICU patient will develop altered physiology and organ dysfunction and receive many concomitant treatments (Hanks and McKenzie 2016). Furthermore, they present to the ICU with co-morbidities and polypharmacy. Therefore, research studies undertaken in healthy adults should be interpreted with caution. In selecting the optimum medicine, it is crucial to understand the limitations of the evidence, appraise and synthesise the pertinent resources and make an informed judgement as to the expected risks and benefits of treatment. ICU patients are also much more susceptible to adverse drug events than non-intensive care patients, further emphasising the importance of medicines optimisation (Devlin et al. 2010; Kane-Gill et al. 2010).

Medicines Administration

Medicines administration is challenging. The ICU patient is frequently mechanically ventilated and, therefore, cannot swallow; their medicines are typically administered intravenously (IV) or via an enteral feeding tube. The IV route provides rapid treatment and certainty of absorption. Prolonged use of IV formulations that contain adjuvants may, however, lead to increased exposure and toxic effects in some instances (e.g. SBECD with IV voriconazole) (Kiser et al. 2015). IV opioids and sedatives merit particular attention due to the risk of toxicity, physical dependence and iatrogenic withdrawal, which may ensue after as little as 3 to 5 days of treatment (McKenzie et al. 2023). Aside from the attendant toxicity risks, the process of preparing a medicine is also complex. Several steps are involved, including drug calculations, reconstitution, dilution and ensuring the concentration and administration rate are appropriate for the IV access available. In a U.K. study, 10.1% of IV medicine administrations were associated with error (Sutherland et al. 2010). This provides insight into the risks of IV medicines and is a stark reminder of the need for daily medicines review. Medicines are also administered orally

Medicines optimisation actions	Example
Medicines reconciliation at ICU admission	Continuation of long-term psychotropic medicines and/or eye drops for glaucoma
Adjusting the dose and frequency of medicines administration	Reduction of gabapentin and pregabalin dosing in kidney failure
Reviewing the continuing need for medicine if patient clinical status is altered	Discontinuation of prokinetics after ileus is resolved
Evaluating route of administration	Adequate administration of pancreatic enzymes via the nasogastric route
Assuring appropriateness of formulations	Assessing sodium content of injectable medicines
Defining monitoring strategy	Low molecular weight heparin monitoring with antiXa levels
Detecting and avoiding drug interactions	Avoiding combination of valproic acid with meropenem (decreased efficacy of antiseizure medicines)
Rescheduling administration times	Reducing overnight medicine administration in the awake patient
Proposing changes to pharmacotherapy in accordance with evidence	Continuous versus intermittent beta-lactam administration
Switching dosing route	Acetaminophen IV to oral switch whenever feasible
Therapeutic drug monitoring (TDM)	Serum level monitoring for voriconazole.

Table 1. Common examples of actions during medicines optimisation

or via enteral feeding tubes. Challenges in administration via the enteral route include suitability of formulation, interactions with enteral feeding and drug absorption/bioavailability (White 2015; Hanks et al. 2022).

Medicines Dosing

Finally, medicines dosing in the ICU is difficult. The ICU patient has complex pathophysiology; they may be hyperdynamic, hypotensive, fluid-overloaded and have end-organ dysfunction or outright failure. Extracorporeal devices may be required for

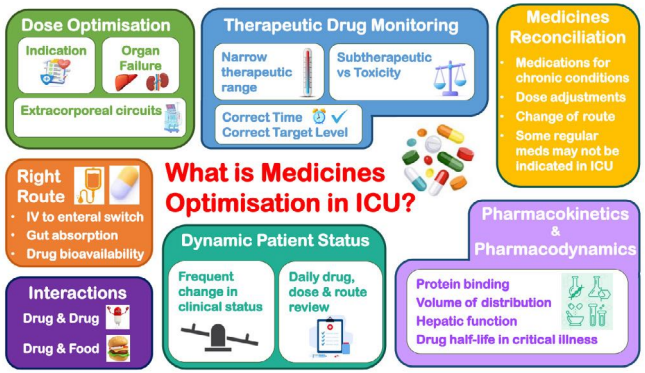

Figure 1. Infographic overview of ICU medicines optimisation process

organ support (e.g. renal replacement therapy, RRT or extracorporeal membrane oxygenation, ECMO). All of this impacts medicine's absorption, distribution, metabolism and excretion, collectively known as pharmacokinetics (Hanks et al. 2022). Medicine or drug action (or pharmacodynamics) is impacted by reduced drug concentration at the receptor site and alteration in drug-receptor binding (Hanks et al. 2022). This requires expert consideration of patient, medicine and pathophysiology as well as awareness of the continually evolving ICU evidence base (McKenzie et al. 2024). It is beyond the scope of this article to describe extensively the impact of critical illness on pharmacodynamics and pharmacokinetics, but it is vital in clinical practice that issues are assessed carefully when deciding medicines dosing. If not, serum and tissue levels may not reach the desired target level, posing a risk of treatment failure. This has been described previously in the landmark beta-lactams study: defining antibiotic levels in intensive care patients (DALI-1) (Roberts et al. 2014). Where pharmacotherapy is concerned, a balance must be reached between maximising efficacy and minimising toxicity from adverse events (Bosma et al. 2018a). This is a core function of the specialist ICU pharmacist and is collectively termed medicines optimisation (McKenzie et al. 2024).

Here we describe the medicines optimisation process, highlight key references in its evolution and describe, with examples, how medicines optimisation occurs in ICU practice.

Structure of ICU Medicines Optimisation (Medicines Review)

In different parts of the world, the term medicines optimisation is interchangeable with other terms, including medicines review (Bosma 2019). For this article, we refer to it as medicines optimisation. Medicines optimisation is defined by the National Institute of Clinical Excellence (NICE) in NG5 2015 as "a person-centred approach to safe and effective medicines use, to ensure people obtain the best possible outcomes from their medicines" (NICE 2015). This involves performing a structured assessment to establish the safety and evaluate efficacy of medicines. The evidence base is applied to guide decisions about the care of the individual patient while assessing their needs, preferences, and values (Greenhalgh et al. 2014; Sackett et al. 1996). In ICU practice, this expert knowledge and skills are applied to interpret a patient's clinical presentation, previous medical history, standard ICU observations (including mean arterial blood pressure, core temperature and urine output), fluid status and interpretation of standard and patient-specific pathology results, (e.g. kidney function and liver enzyme status). After the evaluation of relevant factors, each medicine is then optimised with the aim of maximising efficacy and minimising the risk of toxicity. Medicines optimisation can occur at any point during the ICU patient stay. Due diligence is given to optimisation at ICU admission and discharge. This is known as medicines reconciliation. Evidence shows a higher chance of error with medicines at ICU admission and/or discharge (Bosma et al. 2018b; Bourne et al. 2022). Medicines reconciliation also protects the patient from unintentional (dis)continuation of medication with high certainty of benefit, e.g. statins (Bell et al. 2011).

Frequency of Medicines Optimisation

Medicines optimisation should be delivered by an ICU specialist pharmacist, ideally daily, to account for rapidly changing ICU patient needs individually, although few ICUs have a 7-day clinical pharmacy service (Cheng et al. 2023). In ICUs, where a daily clinical pharmacy service does not exist, the authors recommend that ICU pharmacy professionals use a prioritisation tool to

Medicines Optimisation: Antimicrobial PKPD

Background: 56-year-old male post liver transplant for primary sclerosing cholangitis (PSC). The patient had an intra-abdominal collection. Blood cultures from the drained fluid grew Enterococcus Faecium, which was resistant to teicoplanin and vancomycin. Daptomycin 10mg/Kg IV once daily had been prescribed.

Problem: Daptomycin has a volume of distribution (Vd) of 0.1 L/Kg; thus, achieving adequate tissue concentrations at the target site of infection may be difficult to achieve and risk treatment failure.

Intervention: Multidisciplinary team (MDT) discussion around treatment options. Highlighted the enhanced tissue penetration with linezolid with a Vd of 0.6 L/kg, which could, in theory, be even higher in this patient because of low albumin level and decreased protein binding. Although increased total body clearance may mitigate this (Hanks et al. 2022).

Outcome: Daptomycin was switched to linezolid with advice on dosing, treatment course length and monitoring. Therapeutic drug monitoring (TDM) was recommended as linezolid concentrations greater than 8 mg/L inhibit synthesis of platelet precursor cells by 50%, and high levels are associated with mitochondrial function. (McKenzie et al. 2021).

Medicines Optimisation: Anticoagulation

Background: A 42-year-old male post urgent mechanical aortic and mitral valve replacements. A major haemorrhage occurred during surgery that resulted in acute kidney injury (AKI) needing renal replacement therapy (RRT). Anticoagulation for mechanical valves with heparin infusion was introduced before bridging to warfarin. Platelets began dropping with a positive test for heparin-induced thrombocytopaenia (HIT).

Problem: Argatroban infusion initiated for HIT while bridging onto warfarin. Argatroban increases the INR in a dose-dependent fashion. Determining when therapeutic INR is achieved with warfarin while the patient is being bridged with argatroban infusion is challenging and carries the risk of over- or under-treatment (McKenzie et al. 2021).

Intervention: MDT discussion, including haematology, to agree on the safest and most practical way to ensure adequate anticoagulation. Highlighted the need to stop argatroban for 4-6 hours and then repeat clotting blood tests to determine the true INR on warfarin alone. If sub-therapeutic, argatroban is to be restarted and repeated the following day. To continue warfarin treatment despite inflated INR measurements, which are being caused by the argatroban effect.

Outcome: Therapeutic INR target 2.5-3.5. INR on argatroban plus warfarin with AM blood 4.4. After stopping argatroban for 6 hours, repeat INR 2.1 – sub-therapeutic. Argatroban restarted, warfarin 5mg administered that evening. True INR the following day was 2.5; therefore, argatroban stopped, and warfarin monotherapy continued.

Medicines Optimisation: Sedation

Background: A 56-year-old male ICU admission post thoracic surgery. Past medical history included chronic obstructive pulmonary disease and anxiety, with known alcohol dependency but no consumption in the last six months. Medication history included sertraline and propranolol. Surgery was successful on the post-op pathway with significant pain and agitation.

Problem: Patient intubated for agitation in ICU– sedated with propofol and fentanyl infusions. Two failed extubation due to agitation and respiratory failure; therefore, tracheostomy inserted. Patient was on multiple sedatives, opioids and other psychotropic medicine agents, including propofol, fentanyl, dexmedetomidine, olanzapine, melatonin and lorazepam.

Intervention: MDT discussion to develop strategy to safely wean sedative agents. Interventions included ensuring adequate pain relief with slow weaning of opioid infusions onto enteral formulations, weaning and stopping benzodiazepines known to exacerbate delirium, bridging dexmedetomidine infusion onto enteral clonidine to continue slow weaning (Pandharipande et al. 2006). MDT decisions were led by an ICU specialist pharmacist with an agreed daily plan and clearly documented, including target sedation score, stepwise approach to weaning, consideration of non-pharmacological interventions such as reorientation, communication boards, music and family engagement.

Outcome: Following the pharmacist plan over 10 days following tracheostomy insertion, multiple sedative agents were successfully weaned while patient's agitation and delirium began to resolve. At day 10 post-tracheostomy, patient remained on clonidine 50mcg twice daily, oxycodone 5mg four times daily and melatonin 6mg at night; he did not have delirium (CAM-ICU negative) and was engaging with physiotherapy and other rehabilitation.

focus on patients with more complex medicines, e.g. Medication Related Complexity (MRC)-ICU (Sikora et al. 2022). Moreover, in this field of increasing complexity, the development of technical support through clinical decision support systems (CDSSs) is warranted since it supports the ICU specialist pharmacist and the MDT in medicines optimisation, e.g., in preventing administering high-risk medication combinations (Bakker et al. 2024).

Additional facets of medicines optimisation include exploring methods to deliver pharmacotherapy more effectively (e.g., multimodal analgesia) and supporting nursing colleagues' workload by changing medicines administration (Devlin et al. 2018; Pearce and McKenzie 2023).

Landmark Publications

The introduction of the ICU specialist pharmacist typically begins with a focus on cost-saving and error reductions. The U.S., Australia and the U.K., amongst others, began this development more than 30 years ago (Dasta 1996; McKenzie 1996). In Europe, ICU specialist pharmacy is still very much in its infancy (Bosma et al. 2018a). Yet, in the ICU, there are the same challenges with the increasing complexity of polypharmacy and pathophysiology of the ICU patient.

By the early 2000s, the focus of the ICU specialist pharmacist had evolved from mainly reactive (i.e. reducing error after prescription) into a more proactive involvement in patient care, where medicines were 'optimised'. In some countries (e.g. the U.K.), this resulted in much of the prescribing being delivered by specialist ICU pharmacists, as well as medical doctors, under the leadership of a consultant intensivist (Bourne et al. 2016).

In 2015, the PROTECTED-UK (**P**harmacist's **R**eview and **O**utcomes: **T**reatment-**E**nhancing **C**ontributions **T**allied, **E**valuated, and **D**ocumented) study was conducted in over 21 ICUs in the U.K. and published (Shulman et al. 2015). In this study, the investigators proposed definitions for clinical pharmacy activities as (1) medication error, (2) optimisation, or (3) consult. A medication error was defined as an error in the process of prescribing, dispensing, preparing, administering, monitoring, or providing medicine advice, regardless of whether harm has occurred. Optimisation was defined as a proactive contribution that sought to enhance patient care. A consult was defined as a reactive intervention in response to a request from a member of the MDT for an ICU specialist pharmacist review.

In PROTECTED-UK, the total number of interventions reported (over 2 weeks was 3294, 1693 (51.4%) were optimisations, 1393 (42.3%) were errors, and 208 (6.3%) were consults. Almost three-quarters of these (73.8%) were maximising efficacy and safety (Shulman et al. 2015).

In terms of time spent in ICU, specialist pharmacists spent 3.5 h per day (mean, ±SD 1.7) on direct patient care, reviewed 10.3 patients per day (±SD 4.2) and required 22.5 min (±SD 9.5) per review (Rudall et al. 2017). Intervention rate had a moderate inverse correlation with pharmacist time in the ICU ($P = 0.05$; $r = 0.4$). Optimisation rate had a strong inverse association with total number of prescriptions reviewed per day ($p = 0.001$; $r = 0.7$). A consultant C.P. had a moderate inverse correlation with number of errors identified ($p = 0.008$; $r = 0.6$) (Rudall et al. 2017). In 2023 (Cheng et al. 2023) reported pharmacist intervention over Saturdays and Sundays. Interestingly, out of 346 interventions, 166 (48.0%) were optimisations, 132 (38.2%) errors, and 36 (10.4%) consults. In terms of the overall patient benefit of pharmacist presence in ICU, conducting mainly medicines optimisations, Lee and colleagues reported an analysis of 13 observational and one randomised controlled trial that the inclusion of an ICU pharmacist in an ICU MDT was associated with lower mortality (odds ratio (OR), 0.78; 95% confidence interval (CI) 0.73–0.83) and reduced ICU length of stay (median reduction of 1.33 day; 95% CI −1.75 to −0.90) (Lee et al. 2019). This effect remained significant (OR, 0.79; 95% CI 0.64–0.97) after removing the largest non-randomised trial.

Conclusion

In ICU, polypharmacy is common. ICU patients are prescribed between 20 to 30 medicines per day. Some are essential for long-term co-morbidities encountered frequently in ICU, including type 2 diabetes and cardiovascular diseases. Others are essential ICU lifesaving therapy, e.g. vasopressors and antimicrobials. Adverse effects and drug interactions are common. Optimisation of these complex regimes is essential to protect our patients when they are severely unwell and to enhance their outcome.

Therefore, medicines optimisation performed by a specialist ICU pharmacist, ideally daily, is essential for optimum ICU clinical practice. In this article, we have described an outline of the medicines optimisation process, highlighted key references in its evolution and described, with several examples, how medicines optimisation occurs in ICU clinical practice.

ICU pharmacy professionals (specialist pharmacists and pharmacy technicians) provide patient care by focusing on medicines. They play a continuous and crucial role in medicines optimisation by ensuring the effective use of medicines through interactions with medical colleagues, nurses, allied health professionals, patients, and family members.

Conflict of Interest

Dr McKenzie declares an honorarium for her role as editor-in-chief of Critical Illness (www.medicinescomplete.com), published by Pharmaceutical Press. There are no further conflicts of interest.

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Critical Care Pharmacists Save Lives

The purpose of this review is to discuss the role of critical care pharmacists on the interprofessional healthcare team in the care of critically ill patients and explore current gaps in the provision of comprehensive medication management.

Introduction

"The patient's neurological exam was concerning, new fixed and dilated pupils and an absent cough reflex, so the team wanted to initiate conversations about withdrawal of care, but I remembered that we had used a neuromuscular blocker for a procedure an hour before, and it was probably still hanging around".

"She had come in for toxic epidermal necrolysis secondary to cefepime, and she'd been with us for three months recovering. One day, she had new fever and an increased oxygen requirement concerning for a new pneumonia, and the team ordered cefepime".

"We had acutely managed her antineutrophil cytoplasmic antibody vasculitis with plasmapheresis, steroids, and cyclophosphamide, and she was finally doing better. She was having hypertension that the team wanted to manage, and the intern ordered hydralazine, but her initial vasculitis presentation had been triggered by hydralazine".

"I received an order for 20 mg every 4 hours of intravenous morphine, which didn't seem right. Turns out someone had plugged in numbers incorrectly into an online calculator, and they actually wanted 2 mg morphine".

"The patient was scheduled to receive prothrombin complex concentrate before going to the operating room, but I noticed that it was scheduled to be given more than twelve hours before the surgery and knew it probably wouldn't be effective in that time window".

"I walked by a room and saw methylene blue hanging (it's pretty distinctive, hard to miss). When I asked why the patient was supposed to be receiving it, I found out that the team had actually wanted meropenem".

"A patient with acute acetaminophen overdose was in the ICU for monitoring, receiving intravenous acetylcysteine. I went to discuss the titration with the nurse and found that the line was clamped – the acetylcysteine had been charted but wasn't running".

The story of the critical care pharmacist is one of counterfactuals, the "what ifs" of critical care medicine. Critical care pharmacists do not perform lifesaving procedures, and they do not generally actively hold a patient's life in their hands. Ask any critical care pharmacist, no matter how experienced, and they will struggle to pinpoint an action or a moment in their career that definitively saved someone's life. Yet the stories are there, catalogued as "interventions" and "near-misses," the "but-fors" that speak to negative outcomes prevented. The anecdotes may be jarring, and there is an immediate impulse to push them away as just that: anecdotal, one-off, idiosyncratic, Swiss cheese model, or negligent. Of course, we would never be the ones to have such an error of commission or omission. Yet, it is that same style of thinking, full of cognitive shortcuts, that makes us so quick to add a new medical intervention or technology to practice while still neglecting to consistently wash our hands before entering a patient's room, despite knowing this undoubtedly saves lives (Kahneman et al. 2021; Klotz 2021; Pascale et al. 2010).

Wisdom is knowing how little we know, and humility is knowing we are fallible. Medications have incredible power to heal and

harm (Ely 2021; Sikora 2023). While necessary and lifesaving, they are also complex and dangerous, twin currents for a perfect storm. (Kane-Gill 2012) The intensive care unit (ICU) can be a particularly dangerous place for patients, a setting where a high probability of error meets low tolerance for that error (Cullen 1997; Halpern et al. 2016; Maslove et al. 2017; Practices 2018). Indeed, ICUs are places where cognitive load is high, decisions are frequently made with inadequate information, and risks from incorrect decisions are higher than in other care environments. Medications are stark cases in point for this reality: patients in the ICU receive, on average, twice as many medications as ward patients (Sikora 2023) and that increased volume means patients are more than twice as likely to experience an adverse drug event (ADE) (Maslove et al. 2017; Practices 2018).

As such, the best ICU teams know that 'none of us can know everything.' They leverage multi-professional expertise to make the best decision every time given the circumstances of an information-rich environment under time pressure, incorrect or missing information, and a high cognitive load coupled with decision-making heuristics and cognitive biases we use to lighten that burden. It is this acknowledgement and exploration of our limits that informs international efforts like the "Choosing Wisely in Critical Care" campaign from the Society of Critical Care Medicine and the American Board of Internal Medicine, which advocate for systems of thought that account for the fallibility of human judgement, particularly noting that 'less can be more'. Moreover, the best ICU teams respect that medications are causal agents, for good and bad outcomes alike, and take intentional steps to maximise those benefits while minimising the risks (Sikora 2023). The best available evidence, which included studies conducted across the globe, supports the kernel of truth in those stories: a critical care pharmacist on rounds with the ICU team, performing comprehensive medication management, reduces adverse drug events by nearing 70% and odds of mortality by 20% (Leape et al. 1999; Lee et al. 2019). Pharmacists save lives.

Yet not every critically ill patient has a critical care pharmacist (Borthwick et al. 2018; MacLaren et al. 2021; Newsome 2020a; Pedersen et al. 2019) This is true in at least 30% of ICUs in the United States (U.S.) and the United Kingdom (U.K.), and even in those settings where a pharmacist is present, a high workload can preclude optimal patient care. Weekend rounding services are rare in both U.S. and U.K. studies (Borthwick et al. 2023; Newsome et al. 2021; Sikora 2023; Sikora et al. 2022; Sikora and Martin 2022; Smith et al. 2021). Improving patient access to critical care pharmacists has great potential as a high-yield quality improve-

CCP Education (United States):

- Doctor of Pharmacy (PharmD): 4-year professional doctorate programme (following appropriate years of undergraduate schooling) consisting of didactic and experiential education that meets the standards set by the Accreditation Council for Pharmacy Education.
- Post-Graduate Year One (PGY1) Pharmacy Residency: An accredited programme following completion of a PharmD. PGY1 focuses on enhancing general competencies of optimising medication therapy outcomes in a broad range of disease states.
- Post-Graduate Year Two (PGY2) Pharmacy Residency: An accredited programme following completion of a PGY1 residency. PGY2 focuses on enhancing knowledge, skills, and expertise in a specific area of practice.

CCP Board Certification:

- Board Certified Critical Care Pharmacist (BCCCP): CCPs may obtain board certification through the Board of Pharmaceutical Specialties after completion of a validated examination. BCCCP is accredited by the National Commission for Certifying Agencies (NCCA), the same body as medical accrediting.

Multiprofessional Endorsement: CCPs are essential members of the ICU team.

- The Society of Critical Care Medicine
- American College of Clinical Pharmacy
- American Society of Health-System Pharmacists

CCP Activities: CCPs advance a culture of evidence-based medication use through the Triple Domain of CCP Value: direct patient care, indirect patient care, and professional service. These have been defined as the following. (Sikora 2023)

- Direct Patient Care is defined by the Centers for Disease Control and Prevention as "hands-on, face-to-face contact with patients for the purpose of diagnosis, treatment, and monitoring" (Control) and focuses on the provision of comprehensive medication management (CMM), which is defined as "the standard of care that ensures each patient's medications (whether they are prescription, non-prescription, alternative, traditional, vitamins, or nutritional supplements) are individually assessed to determine that each medication is appropriate for the patient, effective for the medical condition, safe given the comorbidities and other medications being taken, and able to be taken by the patient as intended" (ASHP).
- Indirect Patient Care focuses on the systems and infrastructure surrounding the delivery of Direct Patient Care, with the goal of improving the safety, value, quality, and access to Direct Patient Care provided at the institution (e.g., order set development, medication use evaluations, participation on quality committees)
- Professional service encompasses all other activities undertaken as part of the professional identity of a critical care pharmacist, primarily including but not limited to professional development and ongoing education, education (of trainees, fellow healthcare professionals, the community, etc.), scientific inquiry, and service (including leadership roles at the institutional and organisational level)

Table 1. Fast Facts about Critical Care Pharmacists (CCP)

ment endeavour. Here, we discuss frames of mind that cause us to neglect the vital importance of medication optimisation and those who specialise in this endeavour with the goal to guide discussions for how best to improve patient-centred outcomes.

Standard of Care and Why Pharmacists Are Included

In critical care medicine, a small number of interventions are carried forward as standard of care. These interventions, though frequently unflashy and almost the antithesis of precision medicine, form the backbone of ICU care, the lowest common denominator for all patients. What makes these stand out against the myriad other potential interventions in critical care medicine? First, they represent relatively small changes. Setting a ventilator to deliver a smaller tidal volume or standardising resuscitation practices, while paradigm shifting and requiring education, are not resource intensive (ARDSNet et al. 2000; Rivers et al. 2001). Second, they impact a significant proportion of patients admitted to the ICU. Mechanical ventilation is required by 20-40% of all adult ICU patients (Levy et al. 2018). Sepsis affects nearly 2 million patients annually in the U.S. and is the leading cause of death (SCCM 2024). Third, in the context of the relatively low cost of implementation and broad application (small changes done often), these interventions have an outsize impact on patient outcomes. These interventions revolutionised supportive care practices because they routinely and uniformly reduced mortality when broadly applied to common ICU admission diagnoses that are notoriously recalcitrant to disease-targeted therapy.

Medications are another lowest common denominator in ICU care. Every patient in the ICU receives medications. In fact, ICU patients are prescribed an average of >20 medications, with many deemed high risk by the Institute for Safe Medication Practices (Maslove et al. 2017; Practices 2018). Medication use has taken tremendous strides in the domain of safety over the last 50 years: computerised provider order entry (CPOE), barcoding, dose-checking software, and smart infusion pumps make the operational side of giving drugs to patients safer. Yet, as Peter Drucker quips, "There is nothing so useless as doing efficiently that which should not be done at all". All those technologies make one key assumption: that the medication (including dose, frequency, route, formulation, etc.) currently being administered to the patient was truly the most correct, the safest and most optimal medication for that individual patient and their disease state. Answering this question in a nuanced, evidence-based manner is the domain of the critical care pharmacist.

Indeed, for all the 'standard of care' interventions that come to be codified in the likes of FASTHUGS (Vincent 2005), estimates indicate that unintended ADEs occur in 5% of the over 36 million hospitalised patients per year, and unintended sentinel events occur at a rate of 38.8 events per 100 patient days in the ICU (Cullen et al. 1997; Halpern et al. 2016; Valentin et al. 2006). Each individual ADE doubles patient mortality, and the annual costs of treating ADEs exceeds $1.5 billion in the U.S. alone (Cullen et al. 1997; Halpern et al. 2016; Kane-Gill et al. 2010; Kane-Gill et al. 2012; Kaushal et al. 2007; Maslove et al. 2017; Practices 2018). Similar U.S. estimates show approximately 1.8 million ADEs in hospitalised patients, with estimates of 9,000 patients that die as a direct result of a medication error per year with an expected cost of $40 billion in relation to medication errors (Tariq 2023). In a recent study, two pharmacists identified over 600 medication errors in an eight week study period, despite working in an academic medical centre with safety advents of barcoding, CPOE, etc. (Chase et al. 2023). A large evaluation in the U.K. found that 1 in 6 medication orders required pharmacist intervention (Rudall et al. 2017). This finding has been observed in two other significant studies showing nearly 70% reductions of ADEs by critical care pharmacists on rounds (Leape et al. 1999; Lee et al. 2019). Presence on rounds as part of the team appears important for meaningful impact in studies from the U.S., U.K., and France (Bourne et al. 2022; Bourne et al. 2017; Leguelinel-Blache et al. 2018; Smetana et al. 2023). **Table 1** provides a brief review and associated literature for the profession of critical care pharmacy. Critical care pharmacists promote a culture of evidence-based medication use that supports optimal patient-centred outcomes.

Yet, such cognitive services risk being what Arlene Kaplan Daniels described as 'invisible work' – that which goes unacknowledged and unregulated but no less essential to outcomes. Critical care pharmacists on diverse, multi-professional teams have been repeatedly shown to improve patient-centred outcomes (Pedersen et al. 2018; MacTavish et al. 2019; Stollings et al. 2018). When placing the role of pharmacists in the context of well-known ICU paradigms or other trends of study, this service is essential (as stated by the endorsed Position Statement on Critical Care Pharmacists) (Lat et al. 2020). **Table 2** provides a summary of ICU paradigms.

Pharmacists in the ICU are not revenue generators, and the inability to bill for cognitive services, as well as the awkward pairing of pharmacist salaries and drug costs in pharmacy department budgets, leads to complicated conversations surrounding the implementation of this essential resource. While addressing some of these structural issues in the future could change the conversation around the economics of pharmacy resources, under current systems, adding a pharmacist to an ICU still represents a simple, resource-sparing, and ultimately cost-effective change. When studying the activities and interventions of 215 pharmacists across 85 medical centres in the U.S., the average cost avoidance to salary ratio for a critical care pharmacist was estimated to be between $3.3:1 and $9.6:1 (Rech et al. 2021). Compared to a centralised model, a decentralised model with pharmacists physically present and rounding with the ICU team was associated with over $200,000 in additional cost avoidance (Kopp et al. 2007). With pharmacy charges contributing nearly 20% of total ICU charges and ICU drug costs potentially making up nearly a third of a hospital's overall drug budget, ICU pharmacists (and the medication therapy expertise they bring to the team) represent a resource-conservative intervention (Altawalbeh et al. 2018).

How Cognitive Biases Undervalue Medication Therapy Expertise

Inertia to change has been documented across continents (Borthwick et al. 2023; Muñoz-Pichuante et al. 2024; Sikora 2023). It can be tricky to value medication therapy expertise because such cognitive services have an element of the ephemeral, in contrast to the many "hands-on" skill sets relevant to ICU practice. Reflecting on the type of cognitive biases that can lead to such

Intervention	OR (95% Confidence Interval), p-value	Main endpoint	NNT/NNH
Critical care pharmacist on rounds (Lee et al. ., September 2019)	OR 0.78 (95% CI, 0.73-0.83, p<0.00001)	Pharmacist intervention and ICU mortality	NNT=27
Standard of care			
Early goal-directed therapy for septic shock – meta-analysis (Investigators, 2017-06-08)	OR 0.97 (95% CI, 0.82-1.14)*	90-day mortality (24.9% vs. 25.4%, p=0.68)	NNT=200
Low tidal volume ventilation – ARMA trial (Network, 2000-05-04)	OR 0.68 (95% CI, 0.57-0.82)^	Death before discharge home and breathing without assistance (31.0% vs. 39.8%, p=0.007)	NNT=11
Evaluations under recent study			
Vitamin C sepsis - LOVIT (Lamontagne et al. ., 2022-06-15)	OR 1.28 (95% CI, 0.98-1.68, p=0.07)^	Composite of death or persistent organ dysfunction on day 28 (44.5% vs. 38.5%, p=0.01)	NNH=17
Steroids sepsis - APROCCHSS (Annane et al. ., 2018-02-28)	OR 0.78 (95% CI, 0.62-0.98)^	90-day mortality (43.0% vs. 49.1%, p=0.03)	NNT=16
Fluid resuscitation sepsis - CLOVERS (The National Heart, 2023-01-21)	OR 0.94 (95% CI, 0.71-1.24)^	Death before discharge home by day 90 (14.0% vs. 14.9%, p=0.61)	NNT=100
OR is unadjusted unless otherwise indicated **adjusted OR* *^hand calculated OR* *NNT = number needed to treat* *NNH = number needed to harm*			

Table 2. Odds of benefit for various interventions in critical care

implementation inertia is an important step towards restructuring ICU teams to value the role of this skill set.

Each ICU skill set takes time and practical direct patient care experience to develop. Performing procedures – placing lines, intubating, poking needles and tubes into various spaces – requires skill development. Communicating prognoses and plans of care with patients and family members is a different but no less important skillset. Along those lines, developing a skill set for patient assessment requires years of specialised training, knowledge base development, and direct patient care experience. One must have a mental catalogue of many potential diagnoses augmented by available resources. A mental image or model of each diagnosis needs to be formed, both of characteristic findings as well as elements that would be inconsistent, to inform what to look for or what studies to order to make a particular diagnosis more or less likely. Performing a thorough physical examination is its own observational skill set, from palpating an enlarged liver to listening to lung and heart sounds. But that is only part of the equation; you also must be able to interpret labs, images, and tracings on a screen or a piece of paper. It requires pattern recognition but also an understanding of patient-specific factors that don't fit with the pattern. All the while, you are making mental adjustments to the probability of each differential diagnosis based on new data points being added to the mental model.

Medication expertise is its own unique skill set. It receives only a fraction of dedicated time in medical schools, but true expertise is developed through dedicated education and training. Critical care pharmacists provide that specialised knowledge base and skill set as active members of the ICU team. They are the members of the team best positioned to evaluate the complexities of the patient-medication system and how a drug will interact with not only the disease but also with unique patient factors and other medications the patient is receiving (Sikora 2023). They are the members best able to navigate the balance of the potential benefits of a medication for a given patient against the risks of harm. Their specialised knowledge and training, combined with a wealth of real direct patient care experience and a dedication to evaluation of emerging literature and guidelines, position them to be leaders of a culture of evidence-based medical practice in the ICU. In short, just as you would not want a pharmacist performing your thoracentesis or reading your chest x-ray, you probably would want a pharmacist having a significant say in your medication regimen (or in the medication use culture of an ICU). But if the specialised knowledge and skills that critical care pharmacists bring is so important, why are they underutilised?

When performing a patient assessment, there is no mental calculus occurring as the picture of the patient is formed; we are not adjusting the probability of one diagnosis down by 3% based on the lab value that just resulted and a study that guides that precise valuation. Rather, we utilise heuristics, mental shortcuts that allow us to process information and make decisions quickly (Kahneman 2013). These heuristics, while efficient, are not always optimal and are known to be prone to bias. Recently, there has been greater recognition and acceptance of bias in medical decision-making, and various artificial intelligence-based deci-

sion models are specifically designed to help reduce the impact of bias in human decision-making (Sikora 2023; Webster et al. 2021). Being aware of bias can help reduce the impact. Anchoring bias, for example, occurs when a patient presents looking very much like they fit a particular diagnosis, one that would tie together elements of the story neatly (Tversky and Kahneman 1974); to combat that bias, we can keep our differential broad until more data confirms a diagnosis. Base rate neglect or the availability heuristic can occur when we choose antibiotics that cover vancomycin-resistant enterococcus (VRE) in the absence of risk factors because we recently had a patient with a VRE infection who behaved similarly (Redelmeier and Tversky 1990). If we acknowledge the ubiquitous and unconscious presence of these biases, we can combat their impact on our decision-making.

The impact of bias can also be seen in the slow implementation of pharmacist services in the ICU, a number of which are highlighted in **Table 3.** There are several key themes, including general resistance to changing established systems or a reluctance to relinquish control over some portion of patient care to another profession.

Acknowledging and naming these biases is a key first step in combatting their effects. Reframing critical care pharmacists as care extenders, members of the team that can elevate the level of practice and shift time and energy towards other high-level tasks for which individuals are specially trained may reinforce the essential nature of this resource in the ICU.

Constructs for Re-imagining Medication Use in the ICU

Beyond awareness of the cognitive biases that can cause us to neglect important information, intentionally adopting frameworks of thought regarding medication use has the potential to improve evidence-based use of medications in the ICU.

1. **Medications are causal agents.** We conduct randomised controlled trials with the intention to understand the causal effect of a medication on a disease state and are comfortable with relating the use of antibiotics to the resolution of an infection. Yet, other subtleties abound: what are the rami-

Conservativism Bias (also, Status Quo Bias	Similar to clinical inertia, conservativism bias may lead to a reluctance to alter models, structures, or responsibilities in patient care despite evidence to support change. Even after the establishment of anaesthesia training programmes, surgeons maintained control of anaesthesia in the operating room for many years. (Wunsch, 2023)
Availability Heuristic (also, Selection Bias or Survivorship Bias)	Errors prevented, and near-misses are unlikely to be easily recalled relative to mistakes that reach a patient and cause harm. Do you remember the time when an adverse outcome didn't happen? By their nature, the impact of pharmacist interventions often goes unrecognised.
Effort Justification Bias	An outcome has greater value in our minds if we are the ones responsible. Delegating elements of decision-making ultimately reduces our sense of utility. While having a pharmacist on the team is inherently helpful, it detracts from a sense of responsibility and control.
Confirmation Bias (also Choice-Supportive Bias)	On rounds, you present your plan for the patient in front of the entire ICU team. You look to the pharmacist for their input, and in this case, they have nothing to add. This confirms for you that your medication management is appropriate and that you can perform this element of patient care without pharmacist assistance (even if, on the next patient, the pharmacist has relevant interventions).
Egocentric Bias (also, Illusion of Validity, or Overconfidence Effect)	"Fake it 'til you make it." "Put your nickel down." "Make a plan and say it with confidence." The medical training system encourages physicians to be decisive and to act with confidence, to trust their instincts and their interpretation of data. These are necessary traits for ICU practice but may also lead to the impression that the only one you need to rely on is yourself (and maybe a timely expert consult).
Illusion of Control	The effects of medications are unpredictable in the complex system of a critically ill patient, but assuming knowledge of the unknowable outcomes of decisions is a common logical fallacy.
Base Rate Neglect	Reports detail the high rates of adverse drug events and drug-drug interactions in the ICU. Critically ill patients are at particularly high risk for adverse outcomes. However, it is difficult to imagine that these events could happen at such high rates in your ICU.
Domain Neglect Bias	Medications present their own domain of expertise in the ICU, along with procedural skills, skills of patient assessment, etc. Caring for ICU patients requires interdisciplinary expertise, including physicians, nurses, respiratory therapists, dietitians, and also pharmacists.
Zero-sum Bias	In medicine, if one profession widens its scope of practice, it necessarily narrows the scope of another (or so our biases would lead us to believe). In fact, incorporating more professions and allowing them to practice within the scope of their expertise benefits everyone involved, patients most of all.
Dunning-Kruger Effect	"I know just enough to be dangerous." A little bit of knowledge can inspire a large amount of confidence, and a little bit of experience with medications can form the impression that there isn't really all that much to know.

Table 3. Cognitive biases that undervalue the role of medication expertise

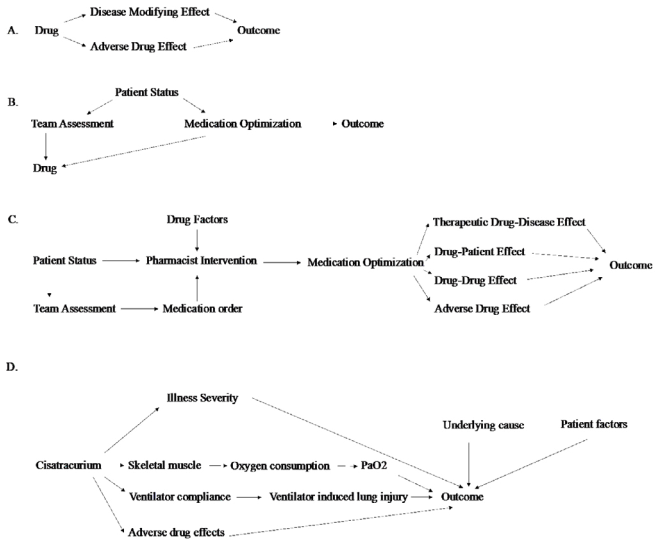

Figure 1. Causal diagrams. Panel A depicts medications conferring both therapeutic and adverse effects that both go on to affect outcomes. Panel B depicts the process by which medication optimisation affects drug choice and outcomes. Panel C depicts the process of retroactive medication intervention and expands upon the possible effects that drugs confer that impact outcomes. Panel D provides a use-case scenario of causal factors for a patient with respiratory failure being treated with neuromuscular blockade.

- A 44-year-old male is admitted to the intensive care unit following fentanyl overdose and aspiration, requiring intubation. He has no known past medical history besides substance abuse. Antibiotics (ceftriaxone and azithromycin) are initiated for community-acquired aspiration pneumonia, and analgesia/sedation is provided with fentanyl and propofol. Respiratory cultures subsequently result with methicillin-resistant *Staphylococcus aureus,* for which linezolid is initiated. He continues to be febrile, and there is some concern for another infectious source versus a withdrawal syndrome or drug fever, possibly serotonin syndrome, considering his medication regimen. Linezolid is switched to vancomycin, fentanyl is converted to hydromorphone, and ceftazidime is added to cover potential gram-negative infection. Over the course of the ensuing days, the patient experiences intermittent fevers, with vancomycin ultimately converted back to linezolid and ceftazidime, often discontinued during periods of defervescence, only to be restarted hours later. He is ultimately extubated a week after presentation, with good mental status but demonstrating opioid-seeking behaviour. An addiction medicine consult is called, and standing oxycodone and methadone are recommended to control pain and manage withdrawal symptoms. The patient remains on linezolid for MRSA and empiric ceftazidime at this time, having received over a week of antibiotic therapy.
- Less than 24 hours later, the patient is found to be obtunded by the bedside nurse. He is responsive but slow to respond when prompted. Given the number of narcotics on his profile, a dose of naloxone is administered, to which the patient has a response but does not return fully to his baseline mental status. The reflex response of the team is to work up and treat for meningitis – an MRI and LP is ordered, ceftazidime is broadened to meropenem, linezolid is converted to vancomycin, and acyclovir is added to cover viral encephalitis. The nurse asks for more naloxone, but the team is worried that he'll be too awake to cooperate with the MRI or the LP if he receives more naloxone, and the decision is made to wait until studies are completed.
- On rounds, the ICU pharmacist questions the decision to work up and treat for meningitis. She reminds the team that the patient has been on broad-spectrum antibiotics for over a week at appropriate doses and points out the absence of fever or leucocytosis to suggest a new infection. She also emphasises the response to naloxone, arguing that he would be unlikely to respond to opioid reversal if he truly had meningitis. Ultimately, the decision is made to hold off on more aggressive intervention and work-up – the patient receives additional doses of naloxone and returns to baseline over the course of the morning. His standing dose of methadone is reduced, and the remainder of his ICU stay is uneventful.

Table 4. A vignette of team-based ICU care optimising medication use and the importance of a diverse, multi-professional presence on care rounds (adapted from real life case)

fications of the choice to go from intravenous to oral? Each time we attach a medication to a patient's IV line, there is risk of infection, fluid overload, unexpected incompatibility, etc. What is the difference between two antibiotics with similar spectrum? The difficulty of parsing these nuances often makes us push them away as irrelevant, yet in the age of Big Data, artificial intelligence, Bayesian analysis, and causal inference, we may finally have the tools to begin to refine (and optimise) our drug selection (Pearl and Mackenzie 2018). It has been previously proposed that there is a Patient – Medication Optimisation – Outcome Pathway and already machine learning methods are showing novel ability to reflect the role of medications on outcomes (Al-Mamun et al. 2021; Rafiei et al. 2023; Sikora 2023; Sikora 2022; Sikora et al. 2023a; Sikora et al. 2023b; Liu 2023). To summarise this causal line of thinking (and the role of those who provide comprehensive medication management), we propose a twist on Mark Twain's adage: The difference between the almost right *medication* and the right *medication* is really a large matter—it's the difference between the lightning bug and the lightning. **Figure 1** provides a series of causal diagrams.

2. **The Goldilocks effect of medication regimen complexity.** Paracelsus stated, "All things are poison, and nothing is without poison; the dosage alone makes it, so a thing is not a poison". Medications obviously conform to this axiom. Thinking about medication use more broadly, the aggressiveness with which medication interventions are provided can be conceptualised in a global sense as medication regimen complexity (encompassing number, type, intensity, and other factors associated with medication intervention). Indeed, a novel metric developed with the precise goal of summarising medication regimen complexity in the intensive care unit (MRC-ICU) has repeatedly shown key relationships with patient-centred outcomes (mortality, length of stay), ICU complications (fluid overload, drug-drug interactions, mechanical ventilation, medication errors), and critical care pharmacist workload (interventions, intervention intensity) (Al-Mamun 2021; Chase 2023; Gwynn et al. 2019; Newsome 2019; Newsome 2020b; Olney 2021; Rafiei

2023; Sikora 2023; Sikora et al. 2022; Sikora 2022; Sikora et al. 2023a-f; Smith et al. 2021; Webb 2021; Webb 2022; Liu 2023;). Given a patient's condition, there is an appropriate level of medication regimen complexity needed to treat them (e.g., a patient with multi-drug resistant infection requiring multiple broad-spectrum antibiotics): to have too little complexity will likely result in death from infection but too much complexity – adding unnecessary antibiotics and aggressive interventions – will likely also lead to poor outcomes. This theoretical line of thinking has begun to be evaluated (Sikora et al. 2023a). There is a correct "dose" of medication complexity, but similar to the trends of pulmonary artery catheters and surgical intervention for necrotising pancreatitis, there is value in caution of wanton usage (Harvey et al. 2005; Mier et al. 1997; NHLBI 2006; van Santvoort et al. 2010).

Practical Application for Improving Evidence-Based Medication Use

Modifications to research infrastructure and ICU team design have potential to improve medication use.

1. **Stepwise improvement of access to critical care pharmacist services.** A proposed vision is that every critical care team that cares for critically ill patients includes critical care pharmacists integrated into the team to provide real-time comprehensive medication management at the bedside. Indeed, an ICU patient would never be without an intensivist and dedicated nurse, and this same patient should never be without a critical care pharmacist. Interprofessional team decision-making would incorporate the specific expertise of each professional to devise a proactive treatment plan, including both medication and non-medication therapy. These recommendations (including those of a critical care pharmacist) would be appropriately documented and appropriately funded through either billable models or as essential services in the same manner as ICU nurses and

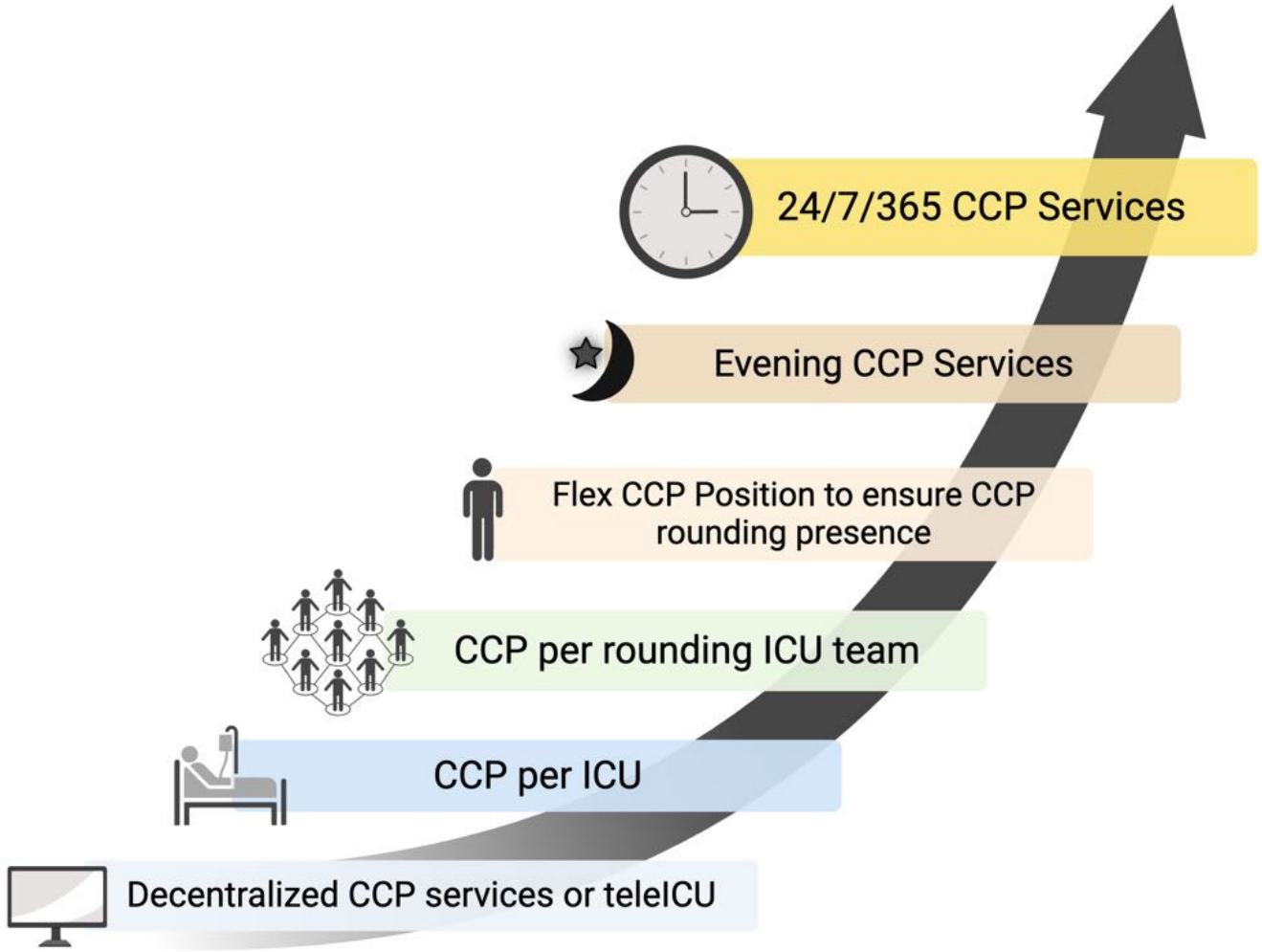

Figure 2. A proposed stepwise approach to expanding critical care pharmacist services.

other healthcare workers. Inherent to this process, critical care pharmacist minimum staffing requirements for ICU patients would be established at institutional levels but also at national accreditation levels, given the importance of healthcare professional workload to patient-centred outcomes. A potential flow for such workload redesign is provided in **Figure 2**, although institutional nuances must be identified such that workload allows for consistent, high-level critical care pharmacist care (Sikora and Martin 2022). Workload redesign considerations include (1) ensuring consistent rounding presence given the strong data to support its benefit to patient outcomes and (2) providing consistency in level of critical care pharmacist care both on weekdays (e.g., minimising cross coverage) and on non-weekday, daytime shift (e.g., rounding on holidays and weekends).

2. **Building research infrastructure that incorporates robust medication data.** To interpret even the most routine medication order, a striking number of factors must be incorporated. These have been previously proposed to fall into three main categories: (1) drug product information (e.g., drug, dose, formulation, route, frequency), (2) clinical information (e.g., mechanism of action, drug-drug interactions), and (3) medication order information, or the specific drug product in the context of that individual patient (e.g., urine output, disease, etc.). An immediate reaction to this type of complexity is to look for shortcuts: lumping drugs by body system they act upon (thus condensing cisatracurium continuous infusion and haloperidol as 'neurology') or to drop formulation information altogether. Yet, the difference between subcutaneous lidocaine and intravenous lidocaine is as big as the lightning bug and the lightning, between getting a cavity filled and treating life-threatening ventricular storm. Though both are technically the same chemical compound, to reduce the high dimensionality of this data is to lose vital information. The result is that very few, if any, prediction-based algorithms incorporate medication data, and nuanced clinical decision support or medication regimen safety checking is lacking. The first steps have been taken towards the development of a common data model and associated ontology for ICU medications and the development of machine learning methods suited to the management and incorporation of this vital data source, though much is yet to be done (Rafiei et al. 2023; Sikora et al. 2023d; Keats et al. 2023).

Conclusion

The complexity of management in the modern care of critically ill patients requires a healthcare team. Comprehensive medication management and those who can provide this cognitive service are essential to this team-based approach. Thoughtfully exploring the biases that can lead us to clinical inertia and ideating on needed steps are important to ensure that all patients receive optimal care.

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Conflict of Interest

None.

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Clinical Pharmacists in Intensive Care in Europe: From Basement to Bedside

Evidence regarding the impact of the ICU pharmacist demonstrates improved outcomes in ICU patients, with a significant impact on the cost of care. This evidence comes from multiple studies performed in different countries. What happens in Europe at the moment? This article describes clinical pharmacy services in a number of Intensive Care Units across Europe.

Historical Perspectives from the U.S. and the U.K.

Patients admitted to Intensive Care Units (ICU) receive multiple medications, mostly by the intravenous route, requiring careful calculation, initiation and follow-up to ensure efficacy and safety. They have rapidly changing medical conditions and organ function, laboratory values and medication. They are more vulnerable to medication errors (ME) and associated adverse drug events (ADE) due to the complexity and intensity of pharmacotherapy (Kane-Gill et al. 2010; Bosma et al. 2021). ME in critically ill patients are most often caused by patient-related factors (e.g. poor physiological reserve, which potentially increases the risks of harm from medication-related errors), medication factors (polypharmacy, including high-risk medications) and dosing- and administration related problems (mainly prescription of continuous infusions, where the doses are calculated according to patient's weight, renal and hepatic functions). Besides these factors, errors are also caused by drug shortages, frequently occurring in the ICU (McKenzie et al. 2024).

Optimising medication is a central and key role expected of hospital pharmacists in all clinical areas, not only in intensive care medicine (Bourne et al. 2022). Ideally, all critically ill patients should have input from a suitably trained critical care pharmacist. Critical care pharmacists add value in a range of different ways, e.g. through direct patient care (pharmacist-driven protocols, medication review and monitoring), involvement in the critical care multidisciplinary ward rounds, and, of course, in the development of clinical guidelines, patient safety initiatives, financial management and quality improvement initiatives (Newsome et al., 2021). **Figure 1** nicely illustrates the key roles of bedside ICU pharmacists.

Pharmacists became involved in critical care in the U.S. starting in the 1960s following the publication of several studies linking their role to improved outcomes and reduced costs (Chant et al. 2015). Leape et al. (1999) published a landmark paper and clearly demonstrated that the presence of pharmacists in a medical ICU reduced medication errors and associated costs. A large survey conducted in U.S. hospitals in 2004 compared costs and clinical outcomes in ICUs with at least a part-time dedicated pharmacist to those without. It showed improved costs and clinical outcomes, i.e. a shorter ICU length of stay and lower hospital mortality, particularly in patients with infections (MacLaren et al. 2008) and thrombo-embolic diseases (MacLaren and Bond 2009).

In the U.K., in the 1960s and 70s, an initiative called "ward pharmacy" was developed in response to concerns regarding errors in the administration of medication to patients in hospitals. Patient-specific drug charts and the deployment of pharmacists to wards were among the early initiatives aimed at streamlining the supply of medication and improving patient safety. Pharma-

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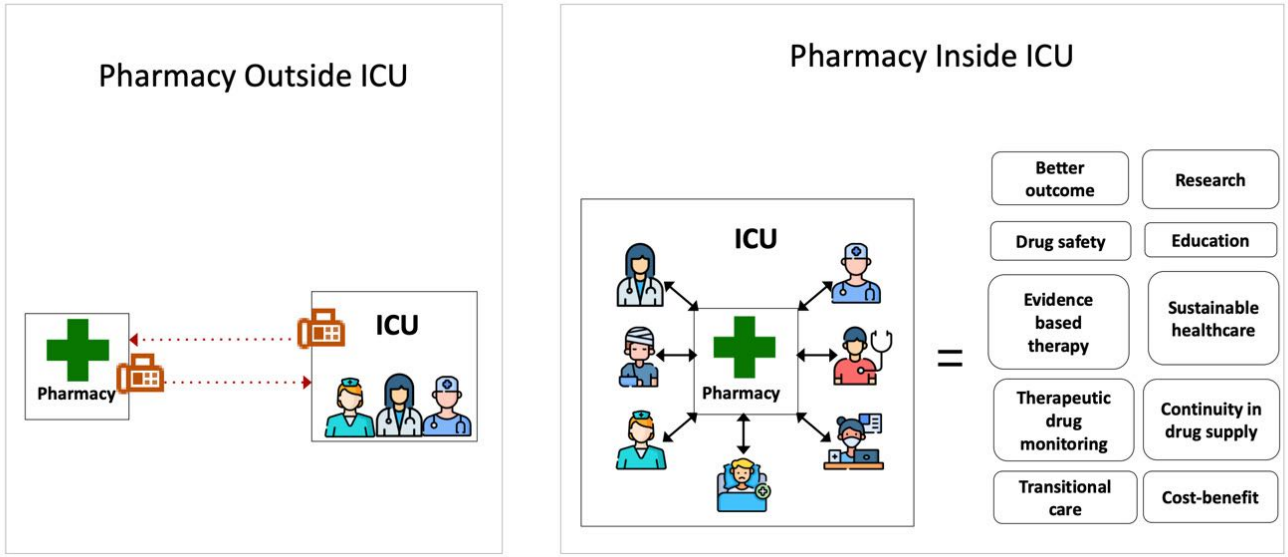

Figure 1. Clinical Pharmacy Services (with copyright permission of Intensive Care Medicine)

cists also started to develop their consultative role and gradually became a source of information for medical and nursing teams. As the 'ward-pharmacist role' expanded over the next 25 years, new services like therapeutic drug monitoring and drug information services developed, and some of these new roles were called "clinical pharmacy services" (Cotter 1995).

This often sporadic involvement in the U.K. health system in the 90s evolved towards a more overt, in-depth role formally described by the NHS Modernisation Agency in 2002 (NHS Modernisation Agency 2002) and 'Adult Critical Care: Specialist Pharmacy Practice' was published by the British Department of Health in 2005 (Department of Health England 2005). The publication of 'Core standards for intensive care units' in 2013 and subsequent incorporation into 'Guidelines for the Provision of Intensive Care Services' in 2016 further established this. The latest update, GPICS v 2.1 (2022), is the definite reference source for planning and delivery of U.K. Critical Care Services and includes specific recommendations related to staffing levels in critical care for pharmacy staff.

In 2020, data was collected regarding ICU pharmacy staffing at U.K. critical care units. Data was obtained for 96% of U.K. critical care units, and it found that 98.2% of U.K. critical care units had specific clinical pharmacist time dedicated to the unit (Borthwick et al. 2023).

But what happens in ICUs throughout Europe? Can pharmacists in European countries achieve what is shown in the U.S. and the U.K., i.e. reduction of medication errors and costs? This paper describes the different pharmacy models used by ICU pharmacists from the U.K. (reference country), Austria, Belgium, France, Germany and the Netherlands. We also show the existing national evidence about ICU pharmacists and finish with future perspectives.

ICU Pharmacist Involvement Throughout Europe

In Europe, different pharmacy models are used in ICUs, ranging from pharmacists providing services from the pharmacy (often "the basement" or "back-office") to full availability at the ICU ward itself (bedside or "front-office"). Information from ICU pharmacists from different countries in Europe and the U.K. (reference country) is provided in **Table 1.** It shows which pharmacy models (pharmacy, ward or mixed) are used, how pharmacists are trained, what their tasks are, how they are involved in research and how their role is covered financially. Furthermore, information about the format, type and size of the ICU is provided, together with evidence about the impact of the ICU pharmacist.

Austria

The implementation of Intensive Care Clinical Pharmacy Services in Austria exhibits considerable heterogeneity not only across

	UK (reference)	Austria	Belgium	France	Germany	The Netherlands
Pharmacy model	Ward-based pharmacy service, 5 days a week, includes pharmacist prescribing role. Limited weekend service. Additional services including guideline development, governance, patient safety etc.	Medicines information and logistical services with the prospect of being able to participate in multidisciplinary ward rounds.	Bedside clinical pharmacy services at the ICU are only present in a few (often large or academic) Belgian hospitals, in a variable way. Pharmacists participate in multidisciplinary case discussions, often focusing on antimicrobial stewardship.	Bedside clinical pharmacy services part- time dedicated to anaesthesiology and ICU Department, present 4 days per week.	Very heterogeneous, ranging from 5-day bedside clinical pharmacy service to once or twice weekly participation in multidisciplinary ward rounds, to medicines information and logistical services only.	Bedside clinical pharmacy service, 5 days per week.
Pharmacist's training ICU	Staff are trained in the Advanced Level Framework in Critical Care Pharmacy and credentialled through the Royal Pharmaceutical Society.	"The Fundamentals of Critical Care Clinical Pharmacy Course" provided by University College London Hospitals National Health Service Foundation Trust, planned to be undertaken in 2024.	Hospital Pharmacists are trained during a 3-year Master's after Master's academic programme, in which an introduction in Clinical Pharmacy is included. Educational programmes specifically focusing on ICU services are not available in Belgium.	Clinical Pharmacy training during internship, clinical internship in ICU in France and in ICU at Sacré-Coeur, Montréal, Canada.	Post-grad education for clinical pharmacy, including introduction to intensive care and hospital pharmacy. Additional post-grad education on infection diseases.	Society of Critical Care Medicine prep course and 2-week internship in the U.S.
Daily tasks	-Daily ward rounds. -Drug history taking and medication review. -TDM -Prescribing. -Guideline development -Medication safety incident review. -Training of junior pharmacists. -Peer review of other ICUs -Financial reporting. -Attendance at governance meetings, MDT* and M and M** meetings.	-General or patient-related medicines information for intensivists -Logistical services	-Ad hoc support on medicines information - Advice on drug administration -Electronic clinical decision support modules -Antimicrobial dosing and TDM advice	-Coordination and supervision of pharmacy students for medication conciliation, prescription analysis; -Optimising drug administration with nurses; -Drug information and protocols -Management of drug dispensing (supervising pharmacy technician) -MDT meetings	Depending on staffing: -Daily to twice weekly ward rounds -Drug history taking and medication review -TDM with major focus on antimicrobials -Guideline development -Medication safety incident review -Training of junior pharmacists -Financial reporting -Attendance at governance meetings, MDT and M and M meetings	-Rounding -Medication verification -Clinical rules/interactions -TDM -Supervision of pharmacy technicians/interns and clinical pharmacologists in training -MDT meetings

	UK (reference)	Austria	Belgium	France	Germany	The Netherlands
Research involvement	Pharmacists hold Associate Principal investigator roles in clinical trials. Also involved in data collection in many ICU clinical trials.	Only small in-house trials, antimicrobial use related.	Academic trials in different domains, mainly focusing on antimicrobial stewardship, PK/PD and dose optimisation.	In-house trials (medication conciliation in ICU, agitation in ICU, antimicrobial dosing in ICU).	Research support for the ICU / hospital via dedicated pharmacy research unit. Own pharmacy research and participation in national/ international research collaboration.	Involved in many ICU trials and own Pharma ICU research line/Green ICU.
Financial coverage	Pharmacy funds some posts, with additional funding from ICU department.	Pharmacy department.	Pharmacy department.	Pharmacy department.	ICU department of pharmacy department.	ICU department.
Number of ICU patients	36	10	96	60	90	30-40
Type of ICU	General ICU, mixed medical and surgical beds.	6 general ICU beds; 4 IMCU (intermediate care unit).	Surgical, medical, neurosurgery, mixed.	1 medical ICU, 1 neurosurgical ICU, 1 polyvalent surgical ICU and 1 cardiovascular and thoracic ICU.	2 Medical ICU 2 Anaesth / Surgical ICU 1 Neuro/Stroke ICU plus IMC for Neuro/ Urology/.	Academic, mixed.
Evidence of pharmacists' role	Borthwick et al. 2023	Stemer et al. 2012	Somers et al. 2019	Chapuis et al. 2010; Chapuis et al. 2019; Chapuis et al. 2019	Waydhas et al. 2023 Hilgarth et al. 2023	Bosma et al. 2018; Bosma et al. 2018; Bosma et al. 2021

Table 1. Different ICU pharmacist models in the U.K. and European countries, based on authors' experience. *MDT= multidisciplinary team, **M and M: morbidity and mortality

different counties but also among individual healthcare trusts. The funding mechanisms for these positions also manifest notable diversity among care providers, predominantly originating from hospital pharmacy departments. The absence of legal regulations governing clinical pharmacy services in Austria grants considerable autonomy to the operational trusts of medical facilities, allowing them to determine the extent and quantity of clinical pharmacists within their employ.

Currently, there is no formal national training programme for ICU clinical pharmacists available in Austria. However, clinical pharmacy training is an integral component of the broader hospital pharmacy specialisation, comprising 80 units out of a total of 240 units in the curriculum (Österreichische Apothekerkammer: Weiterbildungsordnung - Krankenhausfachapotheker (KhFA-WbO 2015 idgF.). Additionally, a postgraduate Master of Science (MSc) degree programme in clinical pharmacy has been implemented at the University of Vienna since autumn 2023 (Klinische Pharmazie 2024). According to a national survey

conducted in 2020, 18.8% of pharmacists employed in Austrian hospitals had successfully completed a postgraduate MSc degree in clinical pharmacy practice, either in the U.K. or elsewhere (Deibl et al. 2020). Anecdotal evidence suggests that some critical care clinical pharmacists have pursued specialised courses, such as the "Fundamentals of Critical Care Clinical Pharmacy Course" provided by University College London (The Fundamentals of Critical Care Clinical Pharmacy 2024).

Notably, not every hospital in Austria that provides critical care maintains a pharmacy department or offers clinical pharmacist positions, as evidenced by the fact that only 15.8% of Austrian hospitals house a Pharmacy Department (Österreichische Apothekerkammer: Apotheke in Zahlen 2020) with even fewer providing clinical pharmacy services. Clinical pharmacists engaged in ICU service delivery in Austria report a spectrum of critical care models, ranging from on-call provision of medication information to the consistent delivery of services, including weekly participation in ward rounds or even more frequent engagement in bedside patient care activities.

The Netherlands

The presence of a pharmacist during the daily multidisciplinary ICU meetings is obligatory based on the Dutch ICU care guidelines (ZorgInstituut 2016). All Dutch pharmacy residents follow a one-day training about ICU pharmacology to be able to join the daily multidisciplinary ICU meetings. In 2012, Hunfeld and colleagues showed in a business case that the addition of a dedicated ICU pharmacist to the medical teams of the ICU resulted in a positive financial outcome. The data used in the business case were published in combination with data from an ICU in a large teaching hospital (Bosma et al. 2018). At the Erasmus Medical Center (MC), the data from the business case resulted in 0.5 FTE ICU pharmacists for (on average) 35 patients. Since there is no specific clinical training for ICU pharmacists in the Netherlands, knowledge and skills are obtained in a " learning by doing" format by sharing information with other ICU pharmacists and through literature from the USA and the UK. It is estimated that 10 out of 80 ICUs in the Netherlands have implemented Intensive Care Clinical Pharmacy Services with a dedicated ICU pharmacist. Funding comes from either the pharmacy or the ICU. With regard to research, many pharmacists are involved in ICU research, mostly focussing on PK/PD trials or medication safety (Wallenburg et al. 2021; Bakker et al. 2024).

Belgium

Clinical pharmacy is a relatively young discipline in Belgium, with the initiation of bedside clinical pharmacy services at different hospital wards, including ICUs, in only a few academic hospitals in 2003. Driven by the favourable results of these first projects, further development of clinical pharmacy services was funded from 2007 onwards in more than 50 acute care hospitals by the Belgian government. Simultaneously, the master's degree in hospital pharmacy was expanded to a 3-year inter-university Master's after Master's programme, in which an educational programme addressing clinical pharmacy fundamentals is embedded, followed by an obligatory internship of 22 weeks at different hospital wards (Somers et al. 2019).

Due to limited national and hospital funding for hospital pharmacy services, clinical pharmacy is typically organised in a three-layered structure in Belgium. First, as all Belgian acute care hospitals are equipped with electronic health records, accurate prescribing is facilitated for hospitalised patients by embedding clinical decision support modules in the electronic prescribing system. These clinical decision support modules include alert systems for drug-drug interactions, maximum dosing, therapeutic duplication, drug allergies, serious adverse drug reactions and the use of teratogenic medication in pregnancy. Clinical pharmacists often contribute to the development and further fine-tuning of these systems, aiming at better performance (Van de Sijpe et al. 2022).

Second, some wards have a bedside clinical pharmacy service. Pharmacists are part of the clinical team and participate in ward rounds and multidisciplinary case discussions, contribute to the effective and safe use of drugs and counsel caregivers and patients. This is typically carried out by highly specialised pharmacists on wards where the risk of drug-related problems is high, i.e. geriatric, oncology, haematology, surgical, transplantation and ICU clinical areas (Somers et al. 2019).

Finally, due to limited funding to expand these bedside clinical pharmacy services, a new back-office service (often referred to as 'Check of Medication Appropriateness') was implemented in most Belgian hospitals. In this hospital-wide service, electronic medical records are screened continuously and in real-time for drug-related problems based on automated clinical rules embedded in the hospital information system. When a drug-related problem is identified by a clinical rule, a clinical pharmacist will review the patient's file and advise the treating physician or the nurse. This service leads to a high acceptance rate (Quintens et al. 2022) and satisfaction, and a significant reduction in the number of inappropriate prescriptions associated with patient harm and is now mandated by Belgian legislation (Quintens et al. 2022; Quintens et al. 2021).

Belgian pharmacists are often involved in academic research at the ICU, focusing on (antimicrobial) pharmacokinetics, optimisation of drug dosing and therapeutic drug monitoring (Dhont et al. 2023; Van Daele et al. 2022).

In general, the involvement of bedside clinical pharmacists in the daily management of patients admitted to the ICU is limited in Belgium. These services are only available in a few Belgian hospitals, and pharmacists are allocated to ward areas for a limited amount of time. A national overview of the Belgian ICU pharmacy professional workforce is not available. Ideally, international standards should mention pharmacy professionals as obligatory members of the ICU management teams. This would encourage hospital directors to reallocate pharmacy resources to the patients who need them the most. In parallel, Belgian clinical pharmacists should be trained in the fundamental knowledge and skills necessary to contribute effectively to the critical care team.

Germany

Clinical pharmacy services for intensive care units have developed steadily over the last ten years. However, considerable variation

remains between the services offered across regions and hospitals. A recent German survey of intensive care departments showed that only 35% of the participants had a pharmacy service. Not surprisingly, intensivists with a clinical pharmacy service rated services such as ward rounds, medication reviews, management of ME, TDM, cost evaluation and management of adverse events alongside medical information and the availability of pharmacy consultation by telephone (24h) as essential. Clinicians without experience in a pharmacy service only rated medical information and the availability (24h) as essential. Core clinical tasks by pharmacists were seen as nice to have (Hilgarth et al. 2023). Therefore, it is not surprising that staffing levels range considerably, from limited or no funding and from providing a weekly ward round only to centres providing comprehensive clinical services.

The recent "Recommendations on the structure, personnel, and organisation of intensive care units", published in 2022 by the German Association of ICU (DIVI), strongly advises providing a clinical pharmacy service during weekdays and out-of-hours. Importance is given to providing a twice-weekly ward round with a dedicated pharmacist (Waydhas et al. 2022). To comply with the recommendation, the DIVI suggests a pharmacist-to-bed ratio of at least 1:30 (0.033 FTE for one intensive care bed). However, robust data on staffing levels is rare. At the University Hospital Dresden, all adult intensive care units now have a clinical pharmacy service in place with dedicated trained pharmacists with a ratio 1:40 (0.025 FTE for one intensive care bed).

Despite the recent demonstration of the economic benefit of clinical pharmacy services in a German intensive care unit (Liebing et al. 2024), funding for dedicated pharmacy services remains one of the main barriers at the moment. However, the recommendation for a pharmacy service will undoubtedly have an impact in the coming years.

The collaborative work between the DIVI and German Hospital Pharmacist Association (ADKA) leads to results. Pharmacists are regular presenters at the yearly DIVI congress, sharing their experience and research. There has been active work in sections of the DIVI. Work on standardising infusion practice has been published (Kraemer et al. 2023), and work on catheter compatibilities and syringe labelling is ongoing.

Where some pharmacy departments, like Dresden, now have dedicated pharmacists with over ten years of experience in critical care, staff training remains a challenging issue for most centres starting new services. There has been recent work in providing additional post-graduate education on pharmaceutical care, including aspects of basics in critical care. The ADKA critical care pharmacy group offers advanced training twice a year. However, this can only be considered a starting point and comprehensive post-graduate training is required. There has been a rising interest and uptake in some courses offered abroad; however, a national/European career path (development) and peer support are required to strengthen the overall provision across centres. Both topics are currently discussed in the ADKA Pharmacy critical care groups.

France

In France, the practice of clinical pharmacy has been developing since the 1980s, with the creation of the French Society of Clinical Pharmacy in 1984, which has developed strong connections with the French Society of Anesthesia and Intensive Care Medicine. Clinical pharmacy was mandated as a core activity for hospital pharmacists in 2016. Clinical pharmacy is practiced in a highly heterogeneous way across the country. In intensive care, very few pharmacists have time allocated to clinical pharmacy as part of their job plan. There is no data on the number of pharmacists working in intensive care nor on the ratio of pharmacists per number of beds. Some hospitals have funded trials of ICU pharmacists working at the bedside, but these have not been continued owing to a lack of resources (Moch et al. 2014; Maison et al. 2020). Some pharmacists became involved in intensive care through their expertise in medical devices, particularly drug infusions (Négrier et al. 2021), while others are more directly involved in patient care, e.g. on targeted projects such as therapeutic drug monitoring of antibiotics (Correia et al. 2023). A few French teams have published their experience in the ICU based on a range of clinical pharmacy activities (Leguelinel-Blache et al. 2018; Lemtiri et al. 2020; Chapuis et al. 2019), demonstrating clinical and economic benefits for the management of intensive care patients.

Training in clinical pharmacy is developing, thanks to the Association Nationale des Enseignants de Pharmacie Clinique (National Association of Teachers of Clinical Pharmacy), but at present, no French programme specific to the intensive care environment is available. Only a few training modules are included in pharmacy curricula (e.g., the Grenoble-Geneva-Lausanne inter-university diploma in advanced clinical pharmacy practice includes a "critical care" day). Most of the few pharmacists working in intensive care (notably in the hospitals of Grenoble, Caen, Valenciennes, Saint-Etienne, Lille, Nîmes, Annecy and Montélimar) have been trained in general clinical pharmacy, and then specifically on-the-job while working in the ICU. Pharmacists can have access to medical intensive care training programmes, but it is not necessarily suitable. There is a need to develop specific training in the French language to further encourage pharmacists to get involved more and more in intensive care units.

Future Perspectives

A recent publication in Intensive Care Medicine (McKenzie et al. 2024) described the ten reasons why pharmacists and pharmacy technicians should be embedded in every ICU team, supported by evidence from multiple studies in different countries (**Figure 1**). The ultimate goal is to equip every ICU in Europe with an ICU pharmacist. This requires support from international societies, especially the International Society of Intensive Care and Emergency Medicine (ISICEM) and the European Society of Intensive Care Medicine (ESICM). Within ESICM, a group of ICU pharmacists are developing a white paper (position paper) which will update current recommendations for critical care pharmacy practice and make recommendations for the future.

Furthermore, ICU pharmacist training and examination (like the European Diploma in Intensive Care Medicine (EDIC)) needs to be developed and implemented over the next few years. Most importantly, the incorporation of the ICU pharmacist in national ICU quality guidelines, together with financial support, is key. These are the necessary conditions to support the ICU pharmacist's transition from basement to bedside in Europe.

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Conflict of Interest

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The Multiple Roles of the Critical Care Pharmacist

Critical care pharmacists use their specialist knowledge to optimise medication for their patients. This article looks at the various roles of the critical care pharmacist within the multidisciplinary team.

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Introduction

The pharmacist's role in critical care is well-developed in the United Kingdom (UK), USA, Australia, New Zealand, Canada and some parts of Europe. In this article, we describe the multiple roles of the critical care pharmacist (CCP), how they collaborate with various members of the critical care team and the role of their supporting pharmacy colleagues.

The CCP plays a key role in optimising pharmacotherapy and clinical outcomes in the intensive care unit (ICU), applying their expert knowledge of drug therapy to the individual patient's needs, and working in conjunction with the multidisciplinary team. CCPs have developed knowledge, skills and experience to become specialists in this field. To enable them along this journey, many pharmacists and pharmacy technicians (PT) attend courses such as our own *The Fundamentals of Critical Care Clinical Pharmacy Course* (Shulman et al. 2024) and achieve curriculum objectives such as those published by the Faculty of the Royal Pharmaceutical Society (new version pending April 2024). A pharmacist's expertise in medicines and pharmacology makes a significant contribution to the goal of safe and effective care of the most vulnerable and unwell patients in the hospital.

CCPs undertake a daily clinical review of each patient's drug therapy, taking into account their acute condition and chronic disorders. Working in conjunction with their PT colleagues, they document a record of the patient's medication history and consider which of these medications are suitable for continued use in the ICU, a process known as medicine reconciliation. Their clinical review will consider laboratory results, clinical observation charts, response and symptoms, and synthesise this information in the context of the appropriateness of the prescribed medications. This review is called medicines optimisation.

Working with the Multidisciplinary Team

CCPs work closely with a range of healthcare professionals in the multidisciplinary team (MDT), bringing their unique focus for the benefit of the patient, analogous to a Formula 1 team (as depicted in **Figure 1**). CCPs contribution working within the MDT has been associated with improved patient mortality (Kim et al. 2010), reduced ICU length of stay (Lee et al. 2019) and a reduced number of preventable and non-preventable adverse drug events (Leape et al. 1999).

Working alongside intensivists, pharmacists use their expert knowledge of drug handling to personalise complex drug therapies for individual patients to optimise the use of medications. For example, they can advise on appropriate doses of drugs or alternative drug options for patients in extremes of body weight, age or organ function (e.g. renal replacement therapy), and they can also interpret therapeutic drug monitoring to ensure there is minimal toxicity and maximal therapeutic benefit.

Critically ill patients are more likely to experience adverse drug effects or interactions due to the large number of medications they are prescribed. Therefore, the pharmacist has an important role in identifying potential adverse effects or highlighting significant drug-drug or drug-condition interactions which may result in adverse outcomes. Encouraging the deprescribing of any unnecessary medications can also help to reduce adverse effects.

Pharmacists work closely with nursing colleagues on critical care and provide support in various ways, including checking the compatibility of multiple intravenous infusions or advising on unusual routes of administration of medications. Discussions explore and can resolve issues around medication tolerability, pain, bowel movements, administration of intravenous medications, sourcing medication, and safe and secure storage of medication.

Dieticians collaborate with pharmacists to formulate feeding plans and decide on the timing of drug administration based on the interactions between enteral feeds and drugs (e.g., levothyroxine should be administered two hours after a feed is stopped).

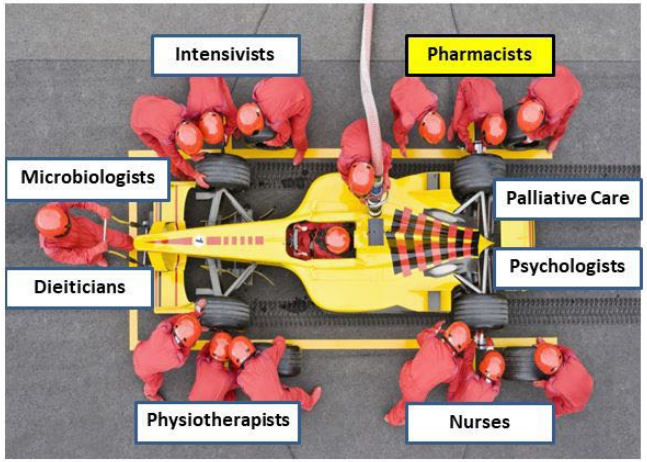

Figure 1 - Members of the Critical Care MDT

They may also produce parenteral nutrition plans based on the patient's requirements. Pharmacists organise the manufacturing or procurement of these bags.

Pharmacists collaborate with physiotherapists to advise on appropriate pharmacological therapy for secretion management. They will also aim to titrate the sedative effects and maximise analgesia to allow for effective rehabilitation.

CCPs and clinical psychologists can work closely to explore both non-pharmacological and pharmacological options for the management of delirium, agitation, anxiety and sleep. They may also work with mental health teams to manage patients with a complex psychiatric history.

Pharmacists participate in the MDT ward round, which brings together contributions to patient care from the various participants to provide shared decision-making, tailoring therapy to the individual patient's needs. Ward rounds are mostly undertaken at the bedside, but the advent of virtual meeting platforms has provided the potential for wider MDT input. In the PROTECT-ED-UK study (Shulman et al. 2015), more than half (59.4%) of pharmacist-led contributions were made during the ward round, demonstrating the importance of pharmacists being present. This study highlighted that many pharmacists' contributions do not arise from a request for input from the MDT but are initiated from the pharmacist's proactive patient review. The study also found that 88% of these pharmacists' contributions were agreed upon and implemented by the MDT.

Additional activities carried out by the specialist CCP include involvement in audit, research, guidelines development, staff education and financial reporting. Larger ICUs will have an ICU pharmacy team consisting of a consultant-level lead pharmacist, senior specialist CCPs and rotational clinical pharmacists, pharmacy technicians and potentially, pharmacy assistant(s) (FICM 2024). In the UK, The Intensive Care Society and the Faculty of Intensive Care Medicine produced the Guidelines for the Provision of Intensive Care Services (GPICS). GPICS states there must be a designated intensive care pharmacist for every critical care unit. There must be one specialist pharmacist for every 10 ICU beds, one for every 20 high-dependency beds for a weekday service, and proportionately more for a 7-day service, which is the target (GPICS 2022). In practice, a larger team is required to cover leave and sickness.

PTs work cohesively with the pharmacist to provide a supporting role. They document the drug history of each patient, forming the first step of the medicine's reconciliation process. This can be complicated given the patient's history, the barriers to communication with the sedated or intubated patient and the need to consult a variety of sources of information. The PTs are also responsible for organising the regular supply of medications in the ICU, responding to urgent requests for critical medications, responding operationally to drug shortages, conducting medication use audits, and liaising closely with the charge nurse. In some hospitals, the role of the PT has extended into areas such as compiling drug expenditure finance reports and staff training.

A pharmacy assistant is an emergent role whose tasks could include fridge temperature documentation, medication expiry checks, medication returns, medicine delivery to the bedside, unpacking medicines deliveries, and organising medication storage in the unit. These roles provide an effective skill mix, freeing up nursing and pharmacist time to focus on their clinical priorities.

Medication Safety and Clinical Governance

ICU patients are prescribed nearly twice as many medications as those in other non-ICU settings. This increases the risk of adverse events, medication errors and drug interactions. (Cullen et al. 1997). Adverse drug events are found to be significantly reduced when ICUs have a pharmacist integrated as part of the MDT (Lee et al. 2019). The pharmacist helps to reduce medication errors and patient harm through clinical chart reviews and medicines reconciliation on an individual patient basis but, in addition, can assist in creating a safer environment via a range of clinical governance measures. An example of this is contributing to regular incident meetings where reported events are investigated by the pharmacist, intensivist and nurse, looking at root cause analyses and ways to prevent reoccurrence. A broader MDT review of medication incidents leads to an enhanced understanding of the contributory factors, leading to more effective solutions. Pharmacists can action system learning and feedback to staff through a variety of means, which also provides a safer environment for patients through continuous improvement (Shulman 2022). CCPs encourage collaboration between the pharmacy department and critical care units, for example, to procure ready-to-administer vials or pre-filled syringes of medications to enhance safety and reduce nursing preparation times.

Wider roles include setting up and maintaining electronic prescribing systems, writing the drug library for medication smart pumps, medication barcoding, and automated dispensing cabinets, which may help improve medicines management and governance around controlled drugs.

Reducing Medication Expenditure

Studies have shown a positive cost-benefit from CCP's contributions. Bosma et al. (2019) estimated a cost–benefit of €119–136

per accepted pharmacist contribution, and one review reported a median cost–benefit of £6.42 per £1 invested in pharmacy services (Crosby et al. 2020). Alongside clinical interventions, other cost-saving activities which pharmacists can undertake include:

- Reviewing drug expenditure reports
- Advising on cheaper but effective switches between drugs within the same class
- Encouraging intravenous to oral switches where clinically appropriate
- Preventing the wastage of medications and managing the stock of medications
- Promoting the deprescribing of medications where not clinically indicated (e.g. anti-infectives, stress ulcer prophylaxis)

Not only do these activities help reduce costs, but they also help the MDT take a more sustainable approach to healthcare. Medications are a large contributor to climate and ecological emergencies, and many of the pharmacy team's actions are consistent with reducing the carbon footprint and environmental risk. This focus will increasingly become more pronounced.

Independent Prescribing Pharmacists

Traditionally, doctors prescribe medication, but at least in the UK, this role has been extended more widely and in critical care, it is standard for the CCP to be an accredited independent prescriber within their area of clinical competence. Up to 72% of critical care units in the UK have a practicing independent prescribing pharmacist on the team (Borthwick et al. 2023). Independent prescribers can prescribe (or deprescribe) medications as part of their clinical review, helping reduce the workload of the MDT and improve efficiency. Prescribing examples include dose adjustments, formulation changes, new medications to initiate as discussed in the ward round, correction of incorrectly prescribed medications, parenteral nutrition, and patients' home medications. Such prescribing decisions can be made immediately without having to contact a medical prescriber, and hence, treatment can be updated without delay.

Antimicrobial Stewardship

Antimicrobial usage in ICUs is high; approximately 70% of critically ill patients receive anti-infectives during their admission (Vincent et al. 2009). Pharmacists play an important role in carrying out antimicrobial stewardship activities. Working closely with physicians, pharmacists can provide advice on appropriate antibiotic choices based on resistance patterns within their area and optimal personalised dosing in relation to organ function and patient characteristics. They can also prompt the medical teams to undertake regular reviews of antimicrobial therapy to prevent unnecessarily prolonged therapy and inadvertently discontinued anti-infectives, which may drive up resistance.

Discharge roles

Patient discharge from the ICU to a non-ICU ward is one of the most challenging and high-risk transitions of care due to the number of medications and the complexity and acuity of the medical conditions that characterise this patient group. (Heselmans et al. 2015).

Bourne et al.'s (2022) systematic review highlighted that frequent medication changes, with many chronic medicines discontinued and acute medication commenced, present a patient safety concern, particularly at the point of transition.

CCPs can advise on the step-down medication plan of patients at the point of transition. This includes highlighting medications that require a medical review, critical care medications that require deprescribing (e.g., antipsychotics for delirium, strong potassium infusions), and continuation of pre-admission medications for chronic conditions. This avoids post-ICU polypharmacy, potential harm and unintentional continuation of medications.

Pharmacists are often best placed to facilitate the safe discharge of complex ICU patients from the ICU to home, as other members of the MDT may not be familiar with the issues around discharge.

Research and Evaluation

Pharmacists have a role in investigating, leading, conducting, and supporting research and evaluation. They frequently collaborate with intensivist teams (for example, Chan et al. 2022) or join pharmacy research teams (for example, Shulman et al. 2015) to investigate gaps in knowledge.

CCPs contribute to writing local and national guidelines and protocols to promote a standardised, equitable approach to pharmacotherapy, considering individual patient characteristics. Both are produced by critically appraising the published data and promoting an evidence-based approach to patient care.

Pharmacists produce medicine management policies, which set out the best practices for safe prescribing, dispensing, pharmacist clinical review, storage and administration of medicines.

Audits and quality improvement projects are developed and implemented by pharmacists, often in collaboration with the nursing, medical or the wider team. This can include conducting monthly audits to monitor the safe and secure storage of medications with the nurses. Regular auditing can measure and improve adherence to standards and lead to continuous improvement and changes in practice.

Education and Training

Pharmacists can provide education and training for nurses and doctors. This could include a 'journal club' literature review as a prelude to practice change, providing prescribing tips for commonly used drugs within critical care, sharing learning outcomes from medication incidents, guidance on the clinical governance process for managing controlled drugs and clinical advice around dosing in organ failure. A team's awareness of

this information will improve medication safety, promote safe prescribing and reduce medication errors from occurring.

Pharmacists also relay information to the MDT about new relevant national guidelines, drug safety alerts, medication shortages and strategies on how these will be managed.

The COVID-19 pandemic highlighted a demand for more critical care trained pharmacists to support the increased number of ICU admissions. To address this training burden, we established an international training course, *'The Fundamentals of Critical Care Clinical Pharmacy Course'* (Shulman and Gadher 2024).

Conclusion

CCPs use their specialist knowledge to perform daily clinical reviews to optimise medication for their patients. Working in close collaboration with the critical care teams, they have become integral members of the MDT, contributing to positive clinical outcomes and safety for patients in the ICU. Their roles also include education and training, research, service improvement, managing drug expenditure and promoting medication safety.

Conflict of Interest

None.

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Critical Care Pharmacists Contribute to Patient and Economic Outcomes Worldwide

Critical care pharmacists have grown in numbers and effectiveness, but their need exceeds availability. Their contributions, role, and benefits are discussed with how to justify adding these highly trained practitioners to your critical care team.

Introduction

I was asked recently what the most important change I had seen during the last four decades of critical care (CC) pharmacy. While there have been amazing advances in technology for monitoring and treatment and important new categories of pharmaceuticals, from my biased perspective, I would suggest that the coalescence of multiple professionals who work together as a CC team to treat patients and apply these advances is a major improvement. Clearly, not one specialty is enough in the complex critical care environment, and the team concept and contributors continue to expand and improve. However, 50 years ago, pharmacists and the pharmacy team were not a consistent part of critical care. Thankfully, the current model of team-based intensive care unit (ICU) care now includes pharmacists as essential members contributing to improved use of medications and monitoring therapeutic effects, development and utilisation of quality improvement processes, education of colleagues, patients and families, and scholarly work that advances knowledge through publication (Haupt et al. 2003). Unfortunately, many places lack these valuable team members for several reasons, including an insufficient number of trained pharmacists, concern with the salary cost of specialty pharmacists, or failure of CC team members to recognise their benefit, as will be discussed.

Clinical Pharmacist Defined

Clinical pharmacists are those individuals who provide direct patient care in a host of different settings. Clinical pharmacy, defined by the American College of Clinical Pharmacy (ACCP), "is a health science discipline in which pharmacists provide patient care that optimizes medication therapy and promotes health, wellness, and disease prevention. The practice of clinical pharmacy embraces the philosophy of pharmaceutical care; it blends a caring orientation with specialized therapeutic knowledge, experience, and judgement for the purpose of ensuring optimal patient outcomes". As a discipline, clinical pharmacy also has an obligation to contribute to the generation of new knowledge that advances health and quality of life (ACCP 2024). Specialised clinical pharmacists follow the medical structure model and are found in a wide spectrum of adult and paediatric practice areas. While the International Pharmacy Federation has outlined a framework for advanced pharmacy specialisation, the definitions and focus vary by country (Galbraith and Bates 2015; Bates et al. 2020). These highly trained individuals can be found worldwide.

Critical care pharmacists have detailed basic clinical duties and defined specific roles and services to be provided for patient care, quality improvement, research/scholarship, training/education, and professional development at a foundational level or a desirable level, depending on the level of CC service (Lat et al. 2020) (**Table 1**). In practice, however, a broad range of clinical and nonclinical services were reported in a 2018-2019 survey of pharmacists and physicians to illustrate how time was allocated and what features were available in medication use systems to support their role (MacLaren et al. 2021). In summary, 50% (Interquartile range (IQR) 40-60%) of time was spent on patient care, 10% (IQR 8-16%) on teaching, 8% (IQR 5-18%) on order processing, 5% (IQR 2-10%) administrative work, 5% (IQR 0-10%) scholarship, and 5% (IQR 0-10%) on non-ICU patient care.

Preparation for these CC specialists is generally accomplished through additional advanced training programmes after meeting general pharmacist licensure criteria. The U.S. pharmacy postgraduate year-1 (PGY-1) is focused on general skills and experiences in a broad range of patient care populations. The PGY-2 specialty residency training programme for critical care has grown substantially (over 205 programmes in 2020) and now includes related programmes in emergency medicine pharmacy. This rigorous 1-year programme encompasses clinical training in various ICU types, research, teaching certification, and quality improvement activities following a specialty standard and CC-specific requirements (ASHP 2023). Successful completion of these intensive programmes prepares a pharmacist to practice at an elevated level in critical care and achieve board certification. How those individuals practice is subject to significant variability and may benefit from greater consistency in job description.

CC Pharmacist activity	Level I	Level II
Patient Care		
Rounds with multi-professional team regularly	Foundational	Foundational
Collaborates with team to prevent inappropriate therapy	Foundational	Foundational
Medication-related consults provided 24hr x 7 days	Foundational	Desirable
Reviews medication history to determine continuation	Foundational	Foundational
Certified in advanced life support and responds to events 24hr x 7 days	Foundational	Foundational
Documents activities to demonstrate impact on cost and care	Foundational	Foundational
Designs and implements new programmes and services	Foundational	Foundational
Patient to Pharmacist ratio is defined by acuity and complexity	Foundational	Foundational
Quality Improvement		
Medication safety leader: ADE identification, management, reporting	Foundational	Foundational
Implements and maintains policies/procedures for safe medication use	Foundational	Foundational
Evaluates the impact of protocols, order sets, care pathways	Foundational	Desirable
Actively serves on committees discussing CC pharmacotherapy	Foundational	Foundational
Collaborates and participates in accreditation preparation	Foundational	Foundational

CC Pharmacist activity	Level I	Level II
Research/Scholarship		
Actively involved in CC Pharmacotherapy research	Desirable	Desirable
Contributes to pharmacy and medical literature	Desirable	Desirable
Participates as a key investigator for CC research	Foundational	Desirable
Serves as a peer reviewer of literature	Desirable	Desirable
Training/Education		
Provides interprofessional experience for multiple levels of trainees	Foundational	Foundational
Supports postgraduate residencies or fellowships	Foundational	Foundational
Develops training programmes for ICU personnel	Foundational	Desirable
Professional Development		
Maintains mastery of knowledge in CC pharmacotherapy	Foundational	Foundational
Seeks board certification	Foundational	Foundational
Provides formal accredited educational sessions at meetings	Foundational	Foundational
Member of pharmacy and professional organisations	Foundational	Foundational
Has protected time for development of non-clinical activities	Foundational	Desirable

Table 1. Selected CC Pharmacy Services for Level I and II Pharmacists(Lat) Level I: complete care for a wide range of disorders, deliver comprehensive services, generally academic centres; Level II: comprehensive care but may exclude some populations and may not have an academic mission; Level III: initial stabilisation but not comprehensive critical care. CC - critical care

Other models for preparation and achievement of required milestones have been developed elsewhere (Choudhary and Newham 2020). The U.K. model for Advanced Level Practice follows several years of structured experiential activities and is now a programme of the Royal Pharmaceutical Society (RPS). It includes a competency framework, syllabus and credentialing but has not been utilised as extensively as desired, based on the volume of care needed, but numbers have improved (Seneviratne et al. 2017). Key components of the development programme include mentorship, organised networks for education and training, supervision of research/projects, integration of trainees into a multi-professional team for experience, education, and skill development and teamwork- both in CC and within the pharmacy with a training ladder and definition of key milestones. Achievement of the highest-level practice, called Consultant/Mastery, gives independent prescribing privileges. A 2020 survey found that 72% of responding advanced care ICUs had a prescribing pharmacist on the team (Borthwick et al. 2023). Some level of

prescriptive authority similarly exists in the U.S. based on local practice agreements or protocols and state law. A survey of CC pharmacists in the U.S. reported dependent prescriptive authority was available to 51.1% and independent authority to 13.4% in 2019 (MacLaren et al. 2021).

Board certification is a tool to demonstrate competency via examination since 2015. At least 4230 pharmacists worldwide are board-certified critical care pharmacists using the title BCCCP. While the majority are in the U.S. (3753), many are elsewhere, including Canada (41), Egypt (21), Saudi Arabia (29), Singapore (18), Taiwan (12), United Arab Emirates (15), Netherlands (8), Hong Kong (4), Qatar (8), and Thailand (4) and more (BPS 2024). It is an important credential for individuals and a tool for screening job candidates. Board certification is a required element for the Society of Critical Care Medicine (SCCM) to consider eligibility for fellowship in the American College of Critical Care Medicine (ACCM).

Pharmacy Team

The continuum of optimal medication use as a component of patient-centred care starts with the identification of all prescribed, non-prescription medications and supplements that are taken by the patient, and to describe those that are not properly utilised, as non-adherence is a frequent contributor to hospital admission. Continuing essential medications also helps avoid withdrawal reactions. Transitions of care warrant re-evaluation of medications to de-escalate treatments and avoid unnecessary, prolonged use. Many members of the pharmacy team (generalist pharmacists and technicians) contribute to accurate medication histories.

Medications must be supplied in a timely manner and in a form that is safe and efficient for the other caregivers. The pharmacy team additionally includes compounding and operational pharmacy specialists who ensure that the medication supply chain is optimised. Ready-to-administer products can increase safety but, importantly, can increase nursing efficiency in the face of greater patient volume, complexity, number of medications, and reduced staffing.

Workforce Development and Expansion

Optimal staffing of CC pharmacists overall is still a dream in many settings, and more fundamental roles for pharmacy staff have yet to be implemented. A growing number of pharmacists are available 24 x 7 (actual or virtual) to meet the rapidly changing needs of critically ill patients (Kruer et al. 2023). The addition of an evening pharmacist in one hospital led to a mean of 9.8 interventions accepted per day with significant cost avoidance (Chase et al. 2023). However, the process of expanding coverage and the number of positions is not clear-cut for pharmacists, as additional nurses, midlevel providers, and physicians are also needed. Many questions remain unanswered regarding the optimal intensity of CC pharmacist staffing, and additional tools are needed to quantify the impact.

The Medication Regimen Complexity score for the ICU (MRC-ICU) has been developed as an indicator of the volume and complexity of medications for a given patient or population of patients, and additional research is ongoing to determine how this information can best be measured and utilised (e.g. to allocate staffing on a given day or as a dependent variable in the measurement of how staffing may affect patient outcome) (Sikora et al. 2022). The feasibility of embedding this scoring tool into the electronic medical record (EMR) has been demonstrated and would expedite the collection of this data (Newsome et al. 2021; Webb et al. 2023).

The best patient-to-pharmacist ratio is undefined and will vary based on the contributions of support staff, such as technicians to collect medication history, additional pharmacists who manage the operations and verification of medication orders, and other responsibilities such as scholarly work, education, and quality improvement. While a ratio of one specialist to approximately 15 patients is often cited as optimal, a median ratio of 17 (IQR 12-26) was reported in a survey of CC pharmacists (MacLaren et al. 2021), and a higher ratio was reported by more than 80% of respondents in an earlier survey- and considered likely unsafe (Newsome et al. 2019). The largest assessment reported a ratio of 26.8 ± 22.1 patients per pharmacist (Rech 2021).

Expanding services to a greater number of patients or needing to cover two service teams was associated with a lower rate of acceptance of interventions compared with coverage of a single service (Smetana et al. 2023). Numerous factors likely contribute to diminishing returns, including communication methods (phone or messaging compared with in-person), lack of team cohesiveness, lack of trust or fear of speaking up.

Excessive workload caused by covering a larger number of patients than is optimal may lead to pharmacist dissatisfaction, turnover and burnout, just as experienced by other members of the care team (Vincent et al. 2019; Ball et al. 2020). A report prior to the initiation of the pandemic suggested that 64% of CC pharmacists surveyed had at least one component of burnout and is likely unchanged in the current CC environment. A higher staffing ratio has led to reduced quantity and intensity of pharmacist interventions and could lower the ability to effectively improve patient outcome (Sikora et al. 2022). Burnout strategies that have been proposed for other professionals, such as reducing the upstream stressors of EMR inefficiency, inadequate technician utilisation, or excessive trainee assignment in a teaching setting, will also be needed for pharmacists.

Metrics

Clinical pharmacists have documented the impact of their interventions in patient care worldwide and summarised in a recent scoping review on papers from nine countries (Crosby et al. 2023). Interventions typically include adverse event avoidance, reduced length of stay (LOS), reduced costs, and intervention acceptance rate. Evaluations have focused on specific aspects of medication use (sedation, analgesia, antimicrobial use, diabetes

regimens, heart failure, and renal replacement therapy, among other topics) as well as overall ICU populations. It is impossible for a pharmacist to take credit for patient-level metrics (morbidity, mortality, LOS, etc.) when care is provided with a team, and there may be reporting bias in the literature. Quantitative measurement of interventions may dilute the impact of high-value activities such as adverse event prevention, individualisation of care, and improved use of resources. Many different methods are used in practice to track productivity, leading to greater difficulties in comparison between sites (Forehand et al. 2022). Economic evaluations of pharmacists have been reported with varying methodologies and often lack robust analysis, but recent studies have improved design.

A Delphi process was used to define important cost-effectiveness interventions for CC teams without assigning responsibility, although pharmacists can be important contributors (Kansal et al. 2023). A report of pharmacist-led quality improvement interventions that included protocolised monitoring of medications, mode of ventilation, antimicrobial stewardship, and reduction of invasive catheters were associated with reductions in ICU and hospital LOS, along with overall drug cost savings of €10,840 per month (95% confidence interval (CI) €10,727 to 10,952) (Leguelinel-Blache et al. 2018). Most reports are more focused on medication utilisation.

The Pharmacist Avoidance or Reductions in Medical costs in CRITically ill adults (PHARM-CRIT) study was a multicentre, prospective, observational study of CC pharmacist interventions in 2018-2019 (Rech et al. 2021). Pharmacist interventions (n=55,926) within 38 categories were reported. The quantity accepted, and potential impact (using a defined cost per intervention) suggested a mean cost avoidance of $418 US per intervention, $845 per patient day, and $7435 per pharmacist shift. The potential return on investment (ROI) was between $3.30 to $9.60 per dollar of salary. While bias in reporting could have influenced these values, prior studies reported ROI values as high as $24 to 1 (Hammond et al. 2019). The most common category of intervention was for individualisation of therapies (52.4%), and these represented 42% of total cost avoidance. Generalisability of this ROI data to other sites is difficult, despite the number of participating pharmacists and practice settings, but this serves as a resource for justification of new positions.

Internationally, pharmacists have also reported economic impact, and a few will be highlighted. Data from the Netherlands, where CC pharmacists have practiced for over a decade, demonstrated cost avoidance, cost savings, a net cost benefit of €64-78 per monitored patient day and a cost: benefit ratio (including salary and benefit costs) of €3.23-3.34, (sensitivity analysis 2.41 – 5.28 to 1) depending on the specific ICU measured (Bosma et al. 2018). Similarly, in Singapore, where pharmacists have practiced in CC for decades, a recent report described total and net cost avoidance from pharmacist intervention for a net ROI of 3.99 to 1 for pharmacist salary (sensitivity analysis 1.07 to 4.29 to 1) (Chan et al. 2021).

Inconsistent patient populations between ICUs make cost impact comparison difficult, and a system to measure medication intensity/complexity is proposed, along with other patient severity-of-illness measures. In a multicentre observational study that included 3908 patients at 28 centres, the MRC-ICU score was significantly associated with higher mortality (odds ratio 1.09, 1.08-1.11), LOS, and the total number of pharmacist interventions (Sikora et al. 2022). Mortality rate tripled from the lowest to highest quartile of the MRC-ICU score (7.8% to 24.8%, $p< 0.01$). Multivariate regression analysis maintained that the MRC-ICU score was significantly associated with mortality and that a higher patient-to-pharmacist ratio was associated with longer LOS and reduced quantity and intensity of interventions. The mean staffing ratio was 26.8 ± 22.1 patients per pharmacist, indicating a significant workload for many pharmacists, although it was not a significant factor for mortality prediction. Thus, it is safe to conclude that CC pharmacists participating actively in bedside care have a valuable impact on drug costs.

Pharmacist intervention patterns may change over time, as other clinicians on the team learn best practices and require less prompting for standard changes such as intravenous to oral therapy or discontinuation of stress ulcer prophylaxis when the need is gone (Leguelinel-Blache et al. 2018). However, in an academic model where team members rotate off service, the dedicated pharmacist has a greater influence in ensuring consistency of practice and continuity of care with new team personnel. Full utilisation of decision support tools with more automated responses in the EMR may also facilitate lower-level task completion with minimal personnel time.

Medication errors remain frequent, can worsen patient outcomes and incur extra costs. A recent report of hospital-wide adverse events found that 39% were medication-related adverse events despite the use of systems and technology to minimise occurrence (Bates et al. 2023). In 2010, prolonged hospitalisation resulted from voluntarily reported ICU medication errors and associated with harm in 12% of cases (Kane-Gill et al. 2010). Underreporting of events is typical. Thus, avoiding medication-related adverse events is a key role for CC pharmacists working at the point of administration and facilitating proper orders. Activities such as individualising medication doses for organ function, appropriately scheduling doses, continuing medications that could result in withdrawal symptoms, and discontinuing duplicative agents are important for optimal patient outcomes. De-escalation of unnecessary therapies (antimicrobials, fluids, sedatives, analgesics, etc.) has a significant potential to avoid unnecessary drug costs and limit adverse effects, but estimating the actual cost of what has been prevented is fraught with potential error. Assumptions must be made about the potential duration without intervention. Ensuring application of protocols for prevention of complications (venous thromboembolism prevention, delirium screening, improved timeliness of stroke thrombolysis or antimicrobial initiation in sepsis, etc.) are other significant roles for pharmacists (Leguelinel-Blache et al. 2018).

Organisational Roles

Critical care pharmacists were not identified specifically when SCCM was formed in 1972, although roles for allied health professionals were predicted, and pharmacist membership has grown to exceed 1800 members of this multi-professional organisation. Pharmacists have served in all leadership roles, including president, chancellor of the ACCM, programme chair, committee chair, journal editorial board member, guideline author, and section and chapter chair. Active participation allows pharmacists to build a network, gain leadership experience and training, become more familiar with best practices and innovative research, and serve as a forum for presentations. Serving alongside other members of the CC team can inform them of this valuable resource and facilitate growth in the profession by creating advocates at other sites.

Other professional organisations foster similar opportunities, and CC pharmacists have participated in CC and pharmacy organisations worldwide. These external forums enhance expertise that translates to similar roles at local practice sites and academia.

Creating Critical Care Pharmacy Roles

Settings without or with inadequate CC pharmacist participation will need a strategic plan to facilitate expansion. Critical care personnel and pharmacy administrators should plan together. A needs assessment of processes that need improvement, which costs could be avoided, or need for programmes to enhance medication safety, education, or optimise medication usage is an important initial step. Pilot projects to collect preliminary data will help build the business plan. Applicable literature should be summarised. Availability of trained CC pharmacists may be a limitation that could require facilitation of training using existing clinical pharmacists.

Creation of a business case for expansion of services and personnel is needed to sell the idea to administrators and describe how expansion of employee numbers (a fixed expense) can reduce other costs. A business plan template has been published and more fully describes the necessary structure and elements, and specific examples have been published (Erstad et al. 2016; Forehand et al. 2023). Medications used in the ICU contributed over 30% of one health-system drug costs in 2012 and had increased by a mean of 5.8% yearly (Altawalbeh et al. 2018). The factors contributing to cost escalation included generic medications (fewer producers, exclusivity), drug shortages, device changes, and expensive new treatments as contributors (Flannery et al. 2017). The ability to keep critically ill patients alive for longer LOS and with more complex treatments is also a potential factor. Mitigation of rising costs is neither simple nor a singular task. The CC team must evaluate drug cost data, evaluate alternatives, and, importantly, take ownership to manage medication utilisation- from prescribing to monitoring and de-escalation. The ROI of a pharmacist has been described as highly beneficial to the organisation relative to cost avoidance, but their input on all aspects of medication optimisation is essential.

The job description should include at least the minimal expectation for the position and should be compatible with the needs assessment and team goals. Metrics for quality and safety outcomes, as well as economic impact and productivity, should be defined along with timelines for initiation and development. Evolution of the role is expected, and the job description should be reassessed frequently in the first year and then annually with revision of duties and goals and elimination of less useful activities as needed.

The addition of a new CC team member may require some change in focus for the entire team, and prospective planning will improve communication and teamwork as roles are redefined. Asking other team members to relinquish some of their tasks may be uncomfortable but can be balanced with the opportunity to add new activities. Defining a format for expanded team-based rounds has the potential to maximise personnel utilisation, participation, patient/family engagement, and teamwork (Real et al. 2020; Lane et al. 2013).

Future

While CC pharmacists have been actively improving patient care in a growing number for over four decades, additional challenges remain, including an inadequate workforce to meet the worldwide needs of critically ill patients. Nevertheless, active CC pharmacists continue to explore new roles and areas for involvement in patient care, initiation, modification, and discontinuation of drug therapy within the context of team-based care (Buckley et al. 2023).

Conclusion

Pharmacists have accomplished a lot in the last four-plus decades and continue to expand roles for optimal CC patient care outcomes and efficient medication utilisation. Structure and important activities have been defined, and metrics to measure impact continue to improve. Although the number of training programmes has expanded, the needs in individual countries may far outstrip the available workforce. Critical care clinicians who do not have a CC pharmacist or do not have consistent coverage will need to work with pharmacy and hospital administrators to advocate for them. Pharmacists in those CC positions are challenged to continue to improve and document their effectiveness and impact to help make the business case for expansion in their setting and others.

Conflict of Interest

None.

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Introduction to Landiolol in Acute Cardiac Care

An overview of landiolol, a potent and cardioselective beta-blocker offering a promising addition to the armamentarium for managing acute cardiac conditions for rapid and effective rate control with minimal adverse effects.

Cardiac emergencies present complex challenges in emergency medical settings, requiring prompt and effective management to improve patient outcomes (Bezati et al. 2023). Beta-blockers have historically played a critical role in the treatment of cardiovascular emergencies (Hindricks et al. 2020; Ibáñez et al. 2015) due to their efficacy in symptom relief and long-term prognosis improvement (Rienstra et al. 2013). However, concerns about their use in acute settings have arisen due to potential negative inotropic effects, especially in patients with compromised cardiac function (Taylor et al. 1981; Waagstein 1993; Yilmaz et al. 2010). In response to these concerns, landiolol, an ultra-short-acting and highly selective beta-1 blocker, has emerged as a promising pharmacologic agent, particularly in Japanese literature, for its favourable safety profile and effectiveness in managing various acute cardiac conditions (Bezati et al. 2023)

History of Landiolol

Landiolol, developed through the chemical modification of esmolol, was designed to be more potent and cardioselective (Iguchi et al. 1992). Early clinical trials demonstrated its efficacy in rapidly controlling cardiac arrhythmias. The first clinical trial on the efficacy for the rapid control of cardiac arrhythmias showed that landiolol reduced heart rate (HR) in all patients without significant adverse effects and, more importantly, without causing any significant reduction in the peripheral blood pressure (BP) (Atarashi et al. 2000).

Pharmacological Profile of Landiolol

Landiolol's pharmacologic profile offers several advantages over other beta-blockers in acute cardiac care. Unlike other beta-blockers, landiolol's metabolism primarily occurs via plasma cholinesterase, resulting in an ultra-short half-life and minimal renal or hepatic involvement, which contributes to its rapid onset and offset of action (Bezati et al. 2023). Its increased cardioselectivity (Iguchi et al. 1992; Nasrollahi-Shirazi et al. 2016) and minimal impact on L-type calcium channels (Bezati et al. 2023) and inward rectifier potassium channels contribute to enhanced haemodynamic stability (Shibata et al. 2012). Moreover, its rapid onset of action and lack of pharmacochaperoning behaviour makes it easier to titrate and discontinue, reducing the risk of cumulative effects or rebound phenomena (Bezati et al. 2023). Additionally, in high doses, landiolol may exert partial agonist effects on beta-1 receptors, potentially conferring cardioprotective and antiarrhythmic properties (Nasrollahi-Shirazi et al. 2016; Patel et al. 2008).

Applications of Landiolol in Acute Cardiac Care

Atrial Tachyarrhythmias Management

In the setting of acute cardiac care, particularly in patients with atrial tachyarrhythmias such as atrial fibrillation (AF) or atrial flutter (AFL), landiolol offers several advantages. Clinical studies have consistently shown its efficacy in achieving rapid rate control while minimising negative inotropic effects, making it particularly suitable for patients with compromised cardiac function or haemodynamic instability (Nagai et al. 1993; Kinugawa et al. 2014). Furthermore, its ultra-short half-life and titratability facilitate precise control of heart rate, allowing for optimisation of atrioventricular synchrony and reduction of symptoms associated with rapid atrial rates.

Management of Acute Heart Failure

Landiolol has emerged as a promising agent for managing acute heart failure (AHF), especially in patients with concomitant atrial tachyarrhythmias. In this population, rapid ventricular response can exacerbate heart failure symptoms and precipitate haemodynamic compromise. By achieving prompt rate control, landiolol helps alleviate symptoms such as dyspnoea and fatigue, thereby improving patient comfort and reducing the need for intensive care interventions. Moreover, its minimal impact on myocardial contractility and relaxation makes it a preferred option over other beta-blockers, which may exacerbate heart failure symptoms by depressing cardiac function (Iwahashi et al. 2019; Matsui et al. 2019).

Management in Patients with Reduced Ejection Fraction

Patients with reduced ejection fraction (EF) represent a challenging subset in acute cardiac care, as they are predisposed to both atrial tachyarrhythmias and haemodynamic instability. Landiolol's selective beta-1 blockade provides effective rate control without compromising cardiac output, making it well-suited for this patient population. Clinical studies have demonstrated its ability to achieve target heart rates while preserving stroke volume and cardiac index, thereby mitigating the risk of hypotension and worsening heart failure symptoms (Shinohara et al. 2020).

Considerations in Severe Renal Impairment

In patients with severe renal impairment, traditional beta-blockers may pose an increased risk of drug accumulation and adverse effects due to impaired drug clearance. Landiolol, with its predominantly hepatic metabolism and minimal renal excretion, offers a safer alternative in this population. By avoiding renal

clearance pathways, landiolol reduces the risk of drug accumulation and associated adverse events, making it a preferred choice for rate control in patients with compromised renal function (Kinugawa et al. 2014).

Management in Septic Cardiomyopathy

Septic cardiomyopathy, characterised by myocardial depression and impaired contractility in the setting of severe sepsis or septic shock, represents a unique challenge in acute cardiac care. Landiolol's beta-1 selective blockade can attenuate excessive adrenergic stimulation, thereby mitigating the risk of tachyarrhythmias and haemodynamic instability (Okajima et al. 2015). While its use in septic shock requires careful consideration alongside standard measures, landiolol may offer additional benefits in improving myocardial oxygen supply-demand balance and reducing the risk of arrhythmias in this critically ill population (Kakihana et al. 2020).

Conclusion

Experts recognise landiolol's potential as a valuable therapeutic option in acute cardiac care, particularly in patients with supraventricular tachyarrhythmias and impaired cardiac function. Its favourable safety profile and reversible adverse effects make it suitable for use even in critically ill patients (Bezati et al. 2023).

"studies have consistently shown the efficacy of landilol in achieving rapid rate control while minimising negative inotropic effects, suitable for patients with compromised cardiac function or haemodynamic instability"

However, dosing adjustments and close haemodynamic monitoring are crucial, especially in patients with severely reduced EF (Wada et al. 2016; Shinohara et al. 2020; Iwahashi et al. 2019) or those with septic shock (Lescroart et al. 2022).

In conclusion, landiolol represents a promising addition to the armamentarium for managing acute cardiac conditions, offering rapid and effective rate control with minimal adverse effects. Its unique pharmacologic properties make it particularly suitable for patients with impaired cardiac function or those at risk of arrhythmias in various clinical scenarios. Continued research and clinical trials are essential to further elucidate landiolol's role in optimising outcomes in acute cardiac care and to establish clear guidelines for its use in different patient populations (Bezati et al. 2023).

Disclaimer

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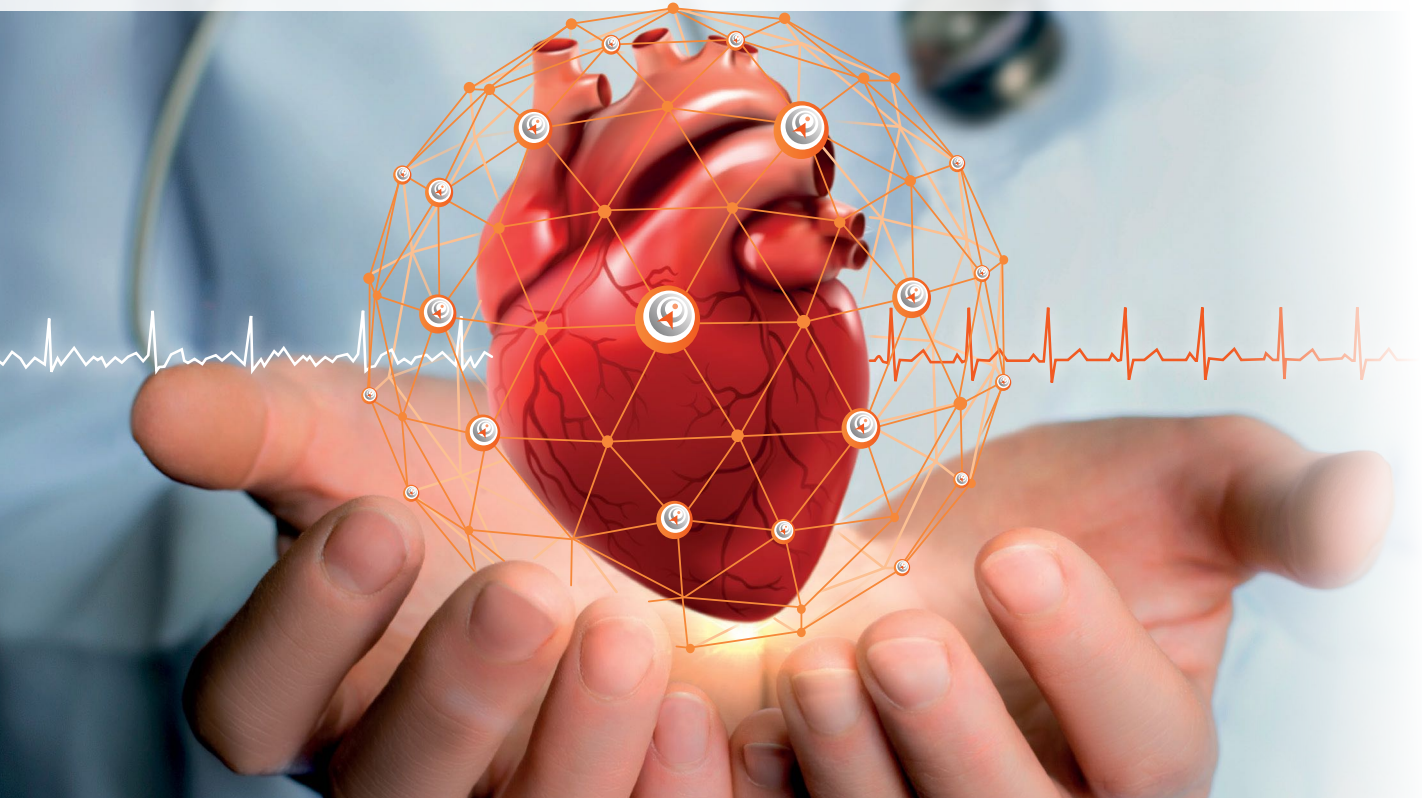
Rapid Rate Control with Myocardial Protection.[1]



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First-line for patients with cardiac dysfunction[2]

- **Limited effect** on blood pressure and inotropy[3]
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Rapibloc® 300 mg: Rapibloc® 300 mg powder for solution for infusion. **Composition:** A vial of 50 mL contains 300 mg landiolol hydrochloride which is equivalent to 280 mg landiolol. After reconstitution each mL contains 6 mg landiolol hydrochloride (6 mg/mL). Excipients with known effect: Mannitol E421, sodium hydroxide (for pH adjustment). **Therapeutic Indication:** Landiolol hydrochloride is indicated for supraventricular tachycardia and for the rapid control of ventricular rate in patients with atrial fibrillation or atrial flutter in perioperative, postoperative, or other circumstances where short-term control of the ventricular rate with a short acting agent is desirable. Landiolol hydrochloride is also indicated for non-compensatory sinus tachycardia where, in the physician's judgment the rapid heart rate requires specific intervention. Landiolol is not intended for use in chronic settings. **Contraindications:** Hypersensitivity to the active substance or to any of the excipients, severe bradycardia (less than 50 beats per minute), sick sinus syndrome, severe atrioventricular (AV) nodal conductance disorders (without pacemaker): 2nd or 3rd degree AV block, cardiogenic shock, severe hypotension, decompensated heart failure when considered not related to the arrhythmia, pulmonary hypertension, non-treated phaeochromocytoma, acute asthmatic attack, severe, uncorrectable metabolic acidosis. For further information on warnings and precautions for use, interaction with other medicinal products and other forms of interaction, fertility, pregnancy, lactation, effects on ability to drive and use machines, unsiderable effects, and habituation effects, please refer to the published SmPC **Prescription only/available only from pharmacy. Date of revision of the text:** 09/2021. **Marketing authorization holder:** Amomed Pharma GmbH, Leopold-Ungar-Platz 2, 1190 Vienna, Austria

1 Summary of Rapibloc® Product Characteristics, current version. – **2** Hindriks G., et al. 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association of Cardio-Thoracic Surgery (EACTS). European Heart Journal (2020) 00, 1-126. – **3** Shibata et al. Direct Effects of Esmolol and Landiolol on Cardiac Function, Coronary Vasoactivity, and Ventricular Electrophysiology in Guinea-Pig Hearts. J Pharmacol Sci 118, 255 – 265 (2012). – **4** Yokoyama H. (2016) Stabilization in Off-Pump Coronary Artety Bypass. Springer Tokyo Heidelberg New York Dordrecht London © Springer Japan. – **5** European Heart Journal Supplements (2018) 20 (Supplement A), A1-A24. – **6** Nasrollahi-Shirazi S et al. Comparison of the b-adrenergic receptor antagonists landiolol and esmolol: receptor selectivity, partial agonism, and pharmacochaperoning actions. J Pharmacol Exp Ther 2016; 359:73–81

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Haemoadsorption in Critically Ill Patients: The New Frontier

Haemoadsorption may represent the new frontier in extracorporeal blood purification. Haemoadsorption has demonstrated effective extraction of a variety of toxins and drugs during episodes of sepsis, acute kidney injury or intoxication. Selective haemoadsorption can be performed by endotoxin-binding polymyxin B functionalised polystyrene fibres. The clinical application of non-selective haemoadsorption in sepsis or other conditions with an evident cytokine release syndrome presents a clear rationale.

Current Challenges

Critically ill patients present several challenges due to multiple organ involvement, complex clinical scenarios, increasing incidence of sepsis, and unmet diagnostic and therapeutic needs (Ronco et al. 2019; Clark et al. 2017). This determines a high demand for innovation and new paradigms. In the areas of sepsis and acute kidney injury (AKI), innovation is mandatory to improve current extracorporeal blood purification techniques (EBP), implement recent advances in technology and biomaterials, and cope with financial constraints. New areas of research include biomaterials, applied nanotechnology, microfluidics, new devices, new membranes and sorbents, transition from diffusion/convection to adsorption. Haemoadsorption (HA) may represent a new frontier in EBP (Ronco and Bellomo 2022). Solute mass separation may occur by barrier (membrane) or by solid agent (sorbent). Diffusion is mainly used in haemodialysis (HD) to remove small solutes, but it becomes inefficient for molecules above 3-5 KDa. Convection is applied in haemofiltration (HF) and haemodiafiltration (HDF) to remove middle molecules up to 10 KDa using ultrafiltration and solvent drag. Still, clearance is limited by the permeability of the membrane (sieving). Even the most modern membranes cannot effectively remove uremic toxins or sepsis mediators with molecular weight above 10-15 KDa. Thus, HA represents a new and interesting option to overcome the limitations of dialysis techniques, providing the required removal of large-middle molecules (Ronco and Bellomo 2023a).

Evolution of Sorbents

Sorbents have been used for two centuries. Natural carbons and allumo-silicates (to exchange ammonium and calcium) were recently substituted by synthetic polymers, chemically modified to become haemocompatible (Ricci et al. 2022). This allowed the clinical application of HA. Sorbents can be natural (zeolites and porous carbons) or synthetic (polymers). They may present high or low-density pores with a macro-, meso- or microporous structure (pore size > 500 Å, 20-500 Å or < 20 Å respectively) (**Figure 1**).

The pore density affects the amount of adsorbate (solute removed by the sorbent), while the pore size distribution affects the spectrum of molecules in the adsorbate. They may come in fibres, granules, beads, spheres, cylindrical pellets, flakes, or powder. They may operate by direct adsorption, anion or cation exchange, or immunoadsorption. Recently, the expanded capacity of adsorption by new polymeric resins has spurred new interest in the use of HA in several clinical conditions in intensive care (**Table 1**) (Copelli et al. 2023).

Rationale for Haemoadsorption

High levels of harmful molecules (solutes) in the blood are observed in the case of kidney or liver failure or in the case of exogenous intoxication and correlate with the severity of disease and mortality. This is the basis of life-saving treatments like EBP. However, the efficiency of toxin removal with current systems may be inadequate to fully replace kidney or liver failure function or to compensate for the dramatic surge in endogenous

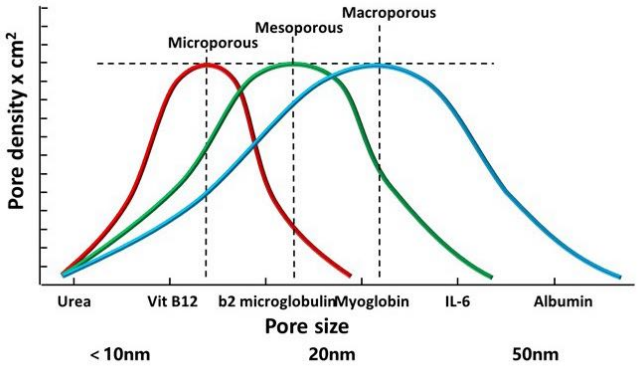

Figure 1. Pore density and pore size distribution in different polymeric resins. Adsorption of different molecular weight solutes depends on the pore size distribution curve that identifies micro-meso- and microporous structures.

Renal	ICU	Liver	Intoxication
• Removal of middle-large & protein-bound uremic toxins • CHD complications: such as CVD, Pruritus, Hypertension • Improvement of life quality • Sepsis-Associated AKI • Renal protection in CRS	• Treatment of critical illness derived from cytokine release syndrome • Removal of inflammatory mediators & cytokines • Hemodynamic stabilization • Organ protections & support	• High bilirubin levels • Severe hepatitis, liver failure and other diseases associated with hepatic encephalopathy • HBV-ACLF • Decompensated cirrhosis	• Accelerate poisons or drug elimination • Kidney and liver protection • Reduce severity of illness • Alleviate organ injury • Shorten hospitalization • Survival improvement

Table 1. Critical illness conditions possibly addressed by HA

pro-inflammatory immune toxins as in the case of cytokine release syndromes (CRS). In those conditions where adequate blood purification cannot be effectively obtained, HA application finds a logical rationale as an alternative or additional therapeutic option (Ronco and Bellomo 2022).

Requirements for Safe and Effective Sorbent Therapy

Modern sorbent therapy requires an effective and haemocompatible sorbent material, a well-designed sorbent cartridge, and easy and simple implementation of related techniques with no or negligible side effects (Ronco and Bellomo 2023b).

Modern sorbents are derived from polymers that create a porous structure with a high surface/volume ratio. Adsorption capacity is measured by experimental isotherms, specific curves that describe the maximal amount of solute that can be adsorbed by a unit of sorbent. Current sorbents demonstrate effective removal of molecules in the range between 10 and 55 KDa, including cytokines, chemokines, and protein-bound solutes, providing a new perspective on EBP. Porosity is regulated by the manufacturer, making it possible to target specific molecules. This results in a tridimensional sponge-like structure that can be analysed by electronic scanning microscopy (**Figure 2**). The forces involved in adsorption are 1) Hydrophobic bonds, generated by the hydrophobic affinity of the sorbent and the target molecules; 2) Ionic bonds, generated by electrostatic attraction between positively charged and negatively charged ions; and 3) Van der Waals forces, the interaction between electrons of one molecule and the nucleus of another molecule (Copelli et al. 2023).

New sorbents are highly haemocompatible, as recently demonstrated in static and dynamic tests performed to detect possible monocyte activation during contact with human blood (Bellomo and Ronco 2023). Biocompatibility characteristics are further improved by a surface coating that improves interparticle blood rheology during treatment. The flow of the fluid phase (blood) inside the sorbent cartridge (divided into inter-particle, extra-particle and intra-particle) is governed by Darcy's law and the Karman-Cozeny equation where the size of the beads, their porosity, the packing density, the length and diameter of the unit, the path tortuosity and Reynold's number are the involved variables (**Figure 3**) (Ronco and Bellomo 2023c). Helical scanning techniques reported in **Figure 4** (Lorenzin et al. 2019) demonstrate a homogeneous distribution of blood flow.

Molecular Targets: Selective and Non-Selective Haemoadsorption

Soluble mediators in the middle-large molecular weight range contribute significantly to organ injury, severity of disease and mortality in septic patients. As in the case of other clinical conditions derived from a cytokine release syndrome (infections, pancreatitis, burns, trauma, etc), sepsis mediators represent logical targets for removal by haemoperfusion. In sepsis, two approaches have been suggested: one based on selective targeting of a key molecule (e.g. endotoxin) and the other based on non-selective, broad molecular spectrum adsorption (Ronco and Bellomo 2022).

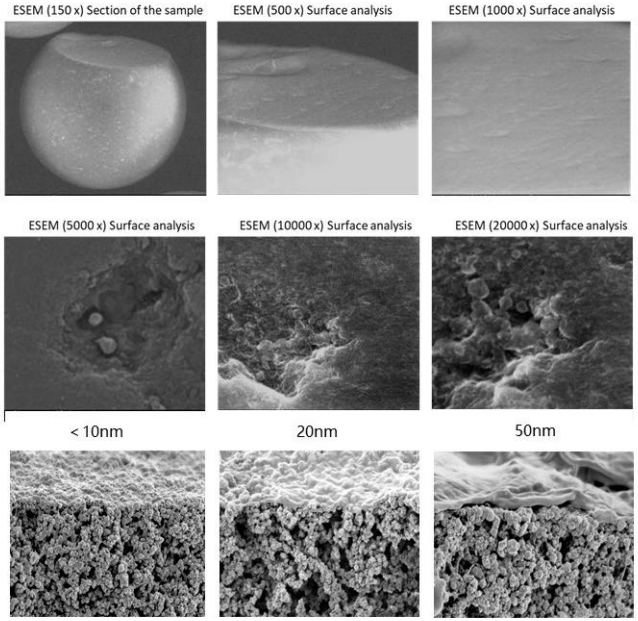

Figure 2. Electron scanning microscopy of sorbent beads at various magnifications. In the lower section, typical micro- meso- and microporous structures can be identified.

In case of the presence of the microbial agent, removal of circulating bacteria or viral particles can be obtained by special affinity binder cartridges. This treatment has been used in combination with special adsorbing membranes such as modified AN69 or adsorbing cartridges (Bellomo et al. 2024). In case of the

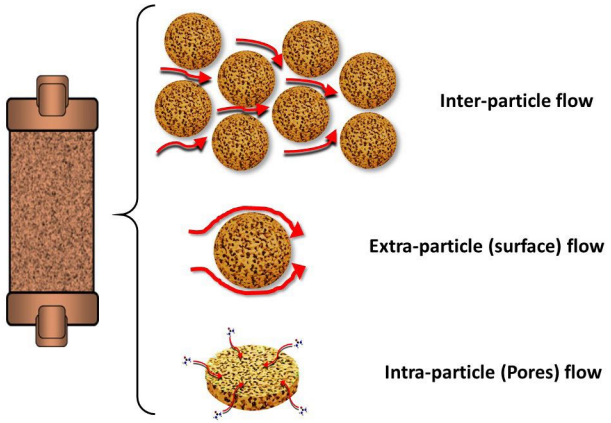

Figure 3. When a liquid mixture is brought into contact with a microporous solid, adsorption of certain components of the mixture takes place on the surface of the solid. The fluid phase flows in the interparticle space, on the surface of the sorbent beads, and finally inside the porous structure. The maximum extent of adsorption occurs when equilibrium is reached, as described by a curve defined "isotherm".

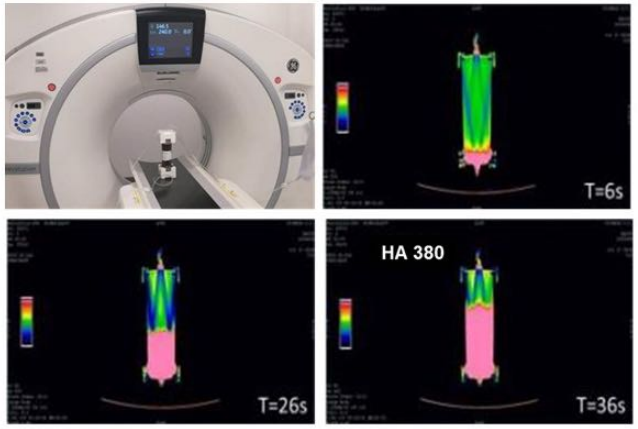

Figure 4. Flow distribution analysis by helical scanning inside a sorbent cartridge HA380. The distribution of the dye injected during blood flow circulation describes a homogeneous pathway with complete exposure of the available sorbent to the fluid phase (blood).

presence of endotoxin in blood, detected by endotoxin activity assay, extracorporeal removal of endotoxin with polymyxin-B cartridge (PMX-HA) can be indicated alone or in conjunction with other adsorption or CRRT techniques (Kellum and Ronco 2023; Cruz et al. 2009; Dellinger et al. 2018; Klein et al. 2018). We should mention that different endotypes may also be a reflection of different conditions of the same patient in different time windows of the ICU stay. In these circumstances, the application of different adsorption and blood purification techniques can be time-sensitive, as suggested in a recent proposal for the sequential application of extracorporeal techniques (Ronco et al., 2023a).

On the other side, from selective potential, are non-selective sorbents capable of removing a broad range of molecules, including mediators and protein-bound solutes. Sepsis induces the expression of a dozen inflammatory mediators where no single molecule is responsible for the entire syndrome. In such circumstances, non-specific removal of the various mediators by haemoadsorption may represent the ideal condition to restore immune homeostasis (Ronco and Bellomo 2022; Ronco et al. 2023b). The cytokine release syndrome (CRS) is a systemic inflammatory response induced by bacteria, viruses, blood exposure to non-biocompatible materials, drugs, and antibody-based therapies or chimeric antigen receptor (CAR)-T cell therapy. Cytokines trigger a cascade with the activation of innate immune cells (macrophages and endothelial cells) with further cytokine release (Cobb and Lee 2021). The presence of a CRS may be demonstrated by biochemical measurements in the presence of the typical clinical picture characterised by hypotension and organ dysfunction. Therefore, it makes no sense to apply a cytokine removal technique if there is no evidence of systemic inflammation or elevated biochemical levels of cytokines. On the other hand, there is a specific time window for this type of intervention, which may prove beneficial in preventing the development of cytokine-mediated organ dysfunction or in protecting the kidney from disease and damage progression. Recently, special cartridges with microporous biocompatible resin have been made available with high capacity of cytokine adsorption (Bellomo and Ronco 2023). According to the peak concentration hypothesis (Ronco et al. 2004; Ronco et al. 2003), higher removal will occur for molecules with the highest concentration in blood and likely with the more impactful action on immuno-dysregulation. In such conditions, patients with impending or overt cytokine storm induced by different causes represent the ideal population for extracorporeal cytokine removal by haemoadsorption (Peng et al. 2008).

Adsorption Techniques and Relevant Indications

Modalities and indications for the clinical use of adsorption are reported in **Figure 5** (Ostermann et al. 2023).

Haemoadsorption (HA): indicated in sepsis and other cytokine-release syndromes, intoxications and poisoning, the technique is generally applied for repeated sessions of 6 to 12 hours each with a blood flow between 100 and 300 ml/min.

Haemoadsorption + CRRT (HA-CRRT): indicated in sepsis-associated AKI for removal of cytokines and uremic toxins, this technique combines a sorbent cartridge in series with a CRRT filter. The complete saturation of the sorbent occurs between 6 and 12 hours.

Plasmafiltration-Adsorption (PFAD): This technique utilises a plasmafilter in the extracorporeal circuit. The filtered plasma, processed through a sorbent cartridge, is subsequently reinfused in the venous bloodline, reconstituting the whole blood. The technique is indicated to remove bilirubin, bile acids and other protein-bound solutes in acute liver failure or decompensated cirrhosis.

Plasmafiltration-Adsorption + CRRT (PFAD-CRRT): This technique combines PFAD with CRRT and is indicated to remove bilirubin, protein-bound solutes and uremic toxins in patients with combined liver and kidney failure.

Double plasmafiltration and molecular adsorption system (DPMAS): This technique utilises a plasmafilter in the extracorporeal circuit. The filtered plasma is processed through two different

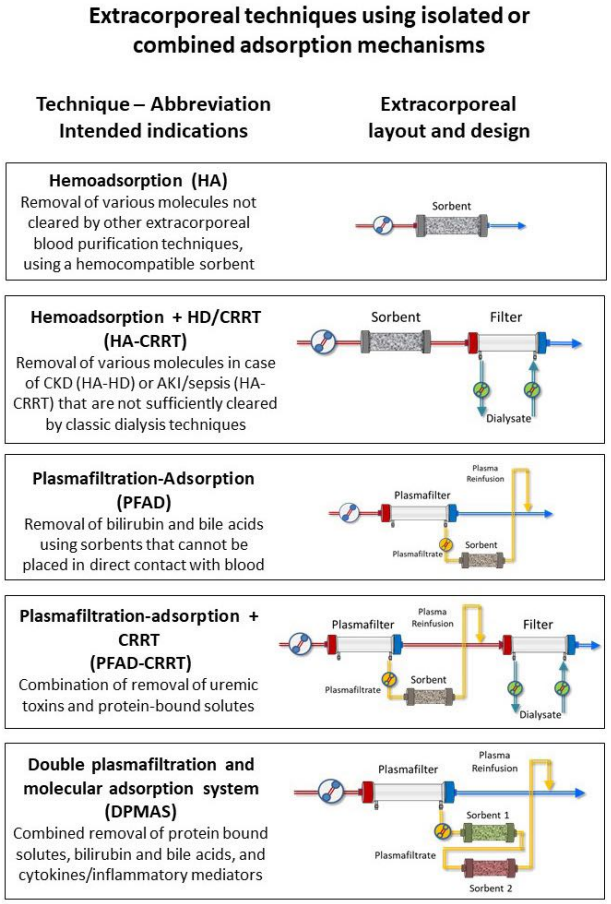

Figure 5. Schematic representation of the sepsis population subdivided into different clinical phenotypes and specific endotypes describing the interaction between the pathophysiological mechanism and the patient response. If an infection is documented, antibiotic therapy is a priority, together with remediation of the infectious focus. When bacteria or viral particles are overwhelmingly high in the bloodstream, extracorporeal removal with affinity binders may be considered (11). If endotoxin activity assay (EAA) shows a value between 0.6 and 0.9 units, extracorporeal removal with polymyxin-B haemoperfusion (PMX-HA) is indicated. If the phenotype is characterised by a cytokine release syndrome (CRS), haemoadsorption with cytokine adsorbers (HA) can be utilised in sequence with PMX-HA or isolated for repeated sessions of minimum 6 hours. In case of the presence of Stage-1 AKI, HA can be indicated to mitigate the severity of the CRS and progression towards stages 2 and 3 AKI. When organ failure (i.e. AKI stage 3 or acute liver failure) is present and due to persistent CRS, HA and extracorporeal organ support (CRRT, TPE or other ECOS therapies) can be combined with HA.

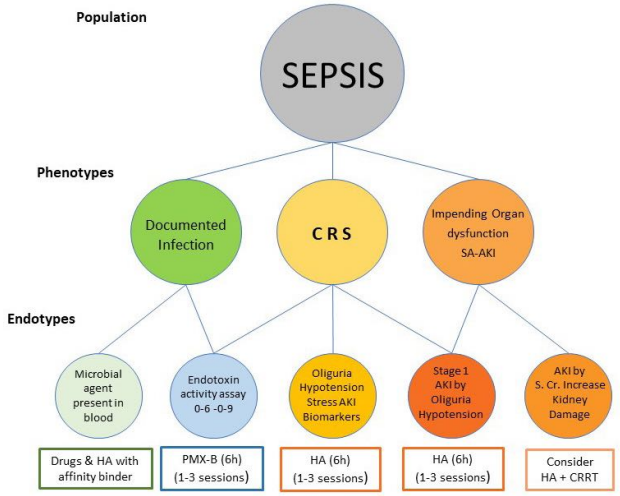

Figure 6. According to the peak concentration hypothesis, the figure suggests the potential role of HA in several clinical conditions. The presence of immune-dysregulation and cytokine release syndrome caused by infections, pancreatitis, burns, trauma, or cardiac surgery (including ECMO or CPB= cardiopulmonary bypass conditions). Non-specific cytokine blockade by HA or HA+CRRT may protect the endothelium and restore a certain degree of immuno-homeostasis with improvement in organ function.

sorbent cartridges in series and is subsequently reinfused in the venous bloodline, reconstituting the whole blood. The technique is indicated in acute liver failure and decompensated cirrhosis to remove bilirubin, bile acids and other protein-bound solutes, together with circulating inflammatory mediators.

Haemoadsorption in ICU: Who is the Ideal Candidate?

Current EBP applied to AKI and septic patients presents important limitations (White et al. 2023). As such, new and more effective techniques are needed. Studies on the application of HA have been limited to small populations, producing sometimes controversial results (Zarbock et al. 2023; Zarbock et al. 2023b; Virág et al. 2021; Houschyar et al. 2017). This is in part due to the heterogeneity of the study patients. HA can, in fact represent an effective treatment for critically ill patients characterised by peculiar phenotypes (**Figure 6**). It is now evident that both sepsis and SA-AKI are a mixture of syndromes in which the cause and the response of the host play an important role in creating specific endotypes with peculiar characteristics and clinical pictures (Kellum and Ronco 2023; Cruz et al. 2009; Dellinger et al. 2018). Among them are haemodynamic instability, variations in temperature and leucocyte/platelet count, microthrombotic/microangiopathic profiles, and oliguria (Klein et al. 2018). In recent years, the possibility of measuring endotoxin activity using a specific assay (EAA) has allowed clinicians to identify a specific patient endotype in which endotoxin is detectable in blood and may represent a target for extracorporeal removal. Polymyxin-B-coated polystyrene fibres have been included in a special adsorption cartridge and are capable of removal of circulating endotoxin up to approximately 20 µg in a two-hour treatment (Cruz et al. 2009; Dellinger et al. 2018). Analyses have demonstrated that positive results are more likely in patients with significant organ failure and in patients with endotoxin activity between 0.6 and 0.9 (Klein et al. 2018). New studies should, therefore, be focused on this specific phenotype (Iba and Klein 2019).

The same approach can be utilised to identify the right population affected by sepsis and/or sepsis-associated AKI. As described in **Figure 7**, sepsis and AKI are multifactorial syndromes, and only when presenting a specific endotype (Oliguria-based Stage 1 with sepsis or CRS-induced hypotension), there is a rationale for application of HA, even in the absence of any other RRT. In other stages, HA can be combined with CRRT if immuno-modulation or cytokine removal beyond renal support is desired (Zarbock et al. 2023b; Ronco and Kellum 2024).

Endpoints for Haemoadsorption Trials?

Once the right population has been identified, the endpoints for clinical trials should be clearly defined with a hierarchy of importance. For extracorporeal therapies such as HA, a progression from biochemical endpoints (removal of molecules) to biological endpoints (cellular effects of molecule removal such as enzymatic

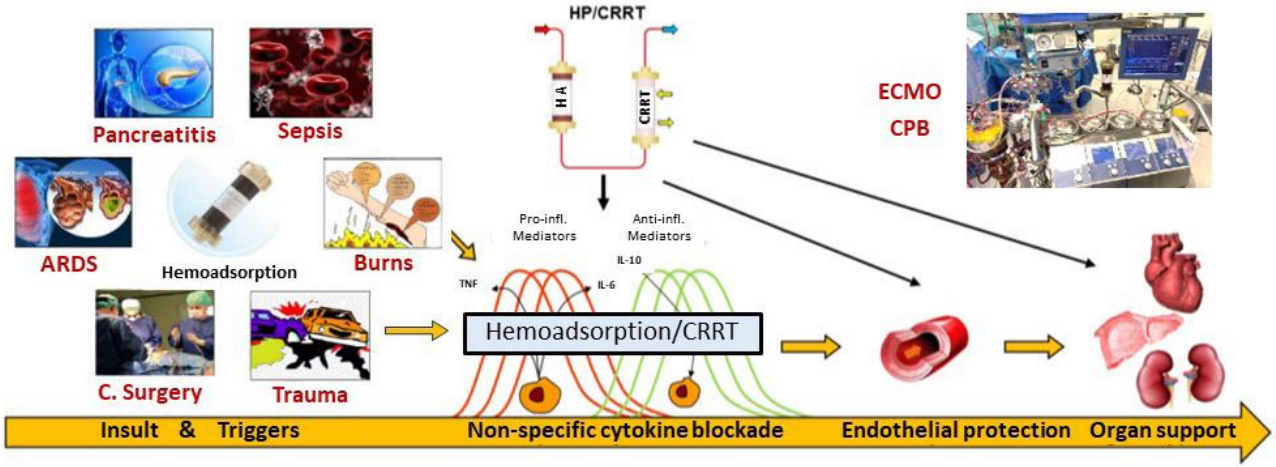

Figure 7. Different pathological conditions may be at the origin of a cytokine release syndrome. In such conditions, a disruption of the host immune-response occurs with peaks of inflammatory and anti-inflammatory humoral mediators present in blood at different times. Since a targeted extracorporeal removal is impossible in the absence of a real-time cytokine measurement, the non-selective nature of haemoadsorption with cytokine adsorber cartridges is indicated to restore immune-homeostasis and produce endothelial and organ protection effects.

reactions, cellular functions, and immunological response) would be appropriate. Furthermore, pathophysiological endpoints (life parameters such as blood pressure, heart rate, PaO2/FiO2, diuresis, cardiac output, etc.) and then clinical endpoints (clinical outcomes including organ function and disease severity, need for dialysis, hospital-free days, mechanical ventilation free days, survival) should be considered. Survival represents the ultimate endpoint, but while trying to achieve sufficient evidence for this measure, it is important to avoid dismissing a treatment as ineffective because the right study has not yet been conducted. Evidence is a wall, and every small brick represents an addition to current knowledge. To advance in the acquisition of new evidence, it is important to share consensus on a structured research agenda (Bellomo et al. 2023) and proceed with collaborative efforts to build registries, well-designed studies, and big data collection.

Available Clinical Data

Several studies have reported the use of HA in the setting of intoxication, poisoning or drug overdose (e.g. paraquat or organophosphates, mushroom-related toxins, pesticides, valproate, carbamazepine and other) (Ghannoum et al. 2014; Kawasaki et al. 2005). Studies report information concerning clearance and mass removal when sorbents are used in isolation or in series with continuous haemodialysis. Extraction rates vary from 20 to 90% (Baylis et al. 2022), and mitigation of severity of the clinical picture has been reported.

There is limited information on the use of HA and plasma-filtration adsorption for severe liver failure, even though there is a robust rationale for targeting ammonia or bilirubin in this setting (Kittanamongkolchai et al. 2017; Santoro et al. 2007). Few studies confirm the utility of the DPMAS in comparison to plasma exchange (Marcello and Ronco 2023; Guo et al. 2020; Wang et al. 2023), and a large study on more than 1400 patients seems to confirm these results (Chen et al. Ongoing trial).

Several trials have addressed the possible effectiveness of PMX-HA for the removal of endotoxin in patients with sepsis. The first trial was reported in 2009 under the name of the EUPHAS (Cruz et al. 2009). This study reported physiological advantages on blood pressure, gas exchange, and use of vasopressors with polymyxin B haemoperfusion. In addition, it found that polymyxin haemoperfusion decreased time to mortality. The second study was a multicentre randomised controlled trial of the early use of polymyxin B haemoperfusion in patients with septic shock due to peritonitis (Payen et al. 2015). A larger study was the EUPHRATES trial (Dellinger et al. 2018). This multicentre randomised controlled trial compared polymyxin B haemoperfusion to conventional therapy in 450 adult critically ill patients with septic shock and an endotoxin assay activity of 0.60 or higher in 55 North American hospitals. This trial found no survival advantage among all participants or in the pre-specified subgroup of patients with a multiorgan dysfunction score > 9, both on intention to treat analysis or pre-protocol analysis.

A subsequent post-hoc assessment of the EUPHRATES study, however, has been conducted with a focus on the specific group of patients without extreme endotoxemia (Klein et al. 2018). In this subgroup of patients, haemoperfusion with polymyxin B appeared to carry a survival advantage on time-to-event analysis. A new study is currently underway in patients with endotoxaemic septic shock called TIGRIS (*Clinical Trials.gov identifier: NCT03901807*). This is a prospective, multicentre, randomised, open-label trial of standard medical care plus the PMX cartridge versus standard medical care alone in subjects with endotoxaemia and septic shock. Subjects in critical care areas will be assessed for septic shock using known or suspected infection, multiple organ failure, fluid resuscitation and hypotension requiring vasopressor support as primary criteria. Subjects will meet all entry criteria for study if endotoxin activity is within the range of ≥ 0.60 to <0.90. This study is scheduled to recruit 150 patients.

HA with non-selective cartridges represents a form of generic anti-inflammatory/immunomodulation HA strategy and has been studied in sepsis in the form of case series and comparative studies (Nassiri et al. 2021; Boss et al. 2021; Paul et al. 2021; Alharthy et al. 2021; Brouwer et al. 2019; Schädler et al. 2017; Supady et al. 2021; Esmaeili Vardanjani et al. 2021; Sazonov et al. 2021; Huang et al. 2010; Huang et al. 2013; Chu et al. 2020; Sánchez-Morán et al. 2023; Lertussavavivat et al. 2023; Becker et al. 2023).

Typical observations in the majority of studies were a remarkable reduction in Interleukin-6, tumour necrosis factor-alpha and other cytokines, significant reduction of inflammatory biomarkers (biochemical endpoints), Improved HLA-DR expression and monocyte function (biological endpoints), improved haemodynamic stability with reduction of vasopressor requirement (physiological endpoint), improvement in SOFA and other severity scores (clinical endpoints) and, in some studies, improvement of survival (ultimate endpoint). Data need to be further confirmed in larger trials and selected populations with homogeneous endotypes (Bellomo et al. 2024).

The Haemoadsorption Research Agenda

The state of research in the field of haemoadsorption resembles that of continuous renal replacement therapy (CRRT) in the 1980s. Studies need to be done to establish the biological, physiological, and clinical effects of sorbent-based techniques. Just like diffusion and convection across semipermeable membranes have been extensively studied over a period of more than 50 years, the third approach of mass separation based on the utilisation of solid agents (sorbents) should be explored to expand the future options provided by EBP. First, such research should first focus on achieving a better understanding of the basic aspects of the adsorption process. We need to understand the basic properties of each sorbent material, the mechanisms of adsorption and the potential side effects, including the unwanted removal of protective solutes such as antibiotics or nutrients (Bellomo et al. 2024; Migliorini et al. 2018; Ronco et al. 2001; Godi et al. 2021). We, therefore, need to establish a well-structured research agenda, in particular, the need to identify patient's endophenotypes that are likely to benefit from HA. We need to establish adequate dose, frequency, and criteria for HA application. We need to identify target molecules and biomarkers and find a way to perform effective biomonitoring; we need to identify adequate endpoints for clinical trials to establish solid evidence, and we need to consider potential side effects and contraindications for this therapy promoting a medical-industry alliance for the development of new and more safe and effective devices. Another area of research will be the thorough analysis of the cost-benefits of HA, possibly moving from a strict budget-oriented approach to a more ethically oriented strategy. All these steps will allow significant progress in the field for the benefit of the patients.

Conflict of Interest

None.

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Corticosteroids in the Intensive Care Unit: Evidence-Based Recommendations

Corticosteroids are commonly used drugs in multiple diseases and conditions of critically ill patients. In this article, we review the pharmacology of corticosteroids and provide recommendations for their use in the ICU based on the best available evidence.

Corticosteroids: Pharmacology and General Aspects

Corticosteroids are hormones synthesised in the adrenal cortex from cholesterol. They are classified into mineralocorticoids and glucocorticoids. Their functions include maintaining water and electrolyte balance, anti-inflammatory effects, regulation of blood pressure, immunosuppression, glycaemic control, and other metabolic pathways (Young and Marsh 2018). Exogenous or synthetic corticosteroids exhibit glucocorticoid and mineralocorticoid properties to varying degrees (**Table 1**). Most circulating steroids bind to plasma proteins such as corticosteroid-binding globulin (CBG), albumin, and alpha-1 acid glycoprotein. In critically ill patients (e.g., sepsis, severe burns, or acute myocardial infarction), CBG rapidly decreases its plasma concentration, increasing the amount of free glucocorticoids that can control the inflammatory response, gluconeogenesis, and stress (Gardill et al. 2012). The effect of cortisol may be insufficient due to adrenal dysfunction and corticosteroid resistance to counteract an exaggerated and prolonged inflammatory response (Keh 2016). Exogenous corticosteroids enter cells by binding to the glucocorticoid receptor, exerting their action in the nucleus, where they bind to DNA, generating down-regulation of the release of inflammatory substances (Barnes 2011). Side effects at moderate or high doses may be associated with an increased infection rate, longer ICU stay, more ventilator days, and a tendency towards higher mortality (Britt et al. 2006), as well as myopathies, gastrointestinal bleeding, fluid retention, and psychotic reactions (Yasir et al. 2023).

In this article, we review the pharmacology of corticosteroids and provide recommendations for their use in the ICU based on the best available evidence.

Septic Shock

Corticosteroids have been under evaluation as adjunctive therapy for septic shock for over 50 years. In the latest meta-analysis, the relative risk (RR) for 90-day mortality in patients with septic shock, comparing hydrocortisone to placebo, was 0.93 (95% CI, 0.82 to 1.04; p=0.22). This value was 0.86 (95% CI, 0.79 to 0.92) for the combination of hydrocortisone and fludrocortisone and 0.96 (95% CI, 0.82 to 1.12) without fludrocortisone (Pirrachio 2023). It is recommended to initiate corticosteroids when a norepinephrine dose of 0.25 mcg/kg/min is reached.

Community-Acquired Pneumonia and *Pneumocystis jirovecii Pneumonia*

A randomised controlled study demonstrated a decrease in mortality among patients with severe community-acquired pneumonia (CAP), defined as the initiation of invasive mechanical ventilation (IMV) or non-invasive mechanical ventilation with at least 5 cm H2O of PEEP, administration of high-flow nasal cannulas, PaO2/FiO2 less than 300, and PORT PSI of at least 130 points. The study found a reduction in mortality in patients who were administered hydrocortisone compared to placebo

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Agent	Potency GC	Potency MC	Dose Equivalent	Length	PB	Metabolism	Indications
Glucocorticoids							
Short action							
Hydrocortisone	1	1	100	8-12 h	>90%	CYP3A4/GP	Septic shock, adrenal crisis, myxoedema coma
Inhaled Budesonide	ND	ND	ND	2-4 h	85-90%	CYP3A4	Asthma exacerbation
Intermediate action							
Methylprednisolone	5	0.25	20	12-36 h	76.8%	CYP3A3	ARDS, postextubation laryngeal oedema
Prednisone	4	0.6	25	12-36 h	70-90%	CYP3A4	COPD exacerbation, alcoholic hepatitis, Pneumocystis jirovecii pneumonia
Long action							
Dexamethasone	25	0	3.75	36-72 h	77%	CYP3A4/GP	COVID-19 pneumonia, bacterial meningitis, CNS tumours
Betamethasone	25	0	3.75	36-72 h	64%	CYP3A4	Foetal lung maturation
Mineralocorticoids							
Fludrocortisone	10	125	ND	12-36 h	70-80%	CYP3A4	Septic shock

Table 1. Drugs dosage, mechanism of action, and indications of corticosteroids
GC: glucocorticoid, MC: mineralocorticoid, GP: glycoprotein P, PB: protein binding, PJP: *Pneumocystis jirovecii pneumonia* *Hydrocortisone equivalent dose

(absolute difference, -5.6%, 95% CI, -9.6 to -1.7; p=0.006), a decrease in intubations (HR, 0.59; 95% CI, 0.40 to 0.86), and a reduction in the use of vasopressors (HR, 0.59; 95% CI, 0.43 to 0.82) (Dequin et al. 2023). A systematic review with meta-analysis demonstrated that the use of corticosteroids reduced the risk of all-cause mortality in CAP (RR: 0.69, 95% CI: 0.53-0.89), especially in younger patients (Cheema et al. 2024; Chaudhuri et al. 2024).

In patients with *pneumocystis jirovecii pneumonia,* a systematic review and meta-analysis showed a decrease in mortality associated with the administration of 40 mg of prednisone twice daily for five consecutive days, followed by 40 mg once daily for the next five days and 20 mg once daily for the remaining 11 days (21 days) (RR 0.59, 95% CI, 0.41 to 0.85) (Hannah et al. 2015).

COVID-19 Pneumonia

In the RECOVERY study on COVID-19, the administration of 6 mg of dexamethasone per day to patients receiving supplementary oxygen or respiratory support was associated with a reduction in 28-day mortality in those undergoing IMV (RR 0.64; 95% CI, 0.51 to 0.81) and those receiving oxygen therapy (RR 0.82; 95% CI, 0.72 to 0.94) (RECOVERY Collaborative Group 2021). A systematic review and meta-analysis on the use of corticosteroids in patients with COVID-19 pneumonia demonstrated a decrease in mortality with the use of corticosteroids (OR 0.72, 95% CI 0.57-0.87). Viral clearance, superinfections, and the use of antibiotics were more common in this cohort (van Paassen et al. 2020).

Acute Respiratory Distress Syndrome

The use of corticosteroids in patients with acute respiratory distress syndrome (ARDS) is reserved for the following causes: CAP, COVID-19, *pneumocystis jirovecii* and diffuse alveolar haemorrhage (lack of evidence). Initiating corticosteroids after 14 days of IMV is not recommended, and adverse effects should be monitored, including immunosuppression, bacterial, fungal, parasitic, or mycobacterial infections (Qadir et al. 2024).

Postextubation Laryngeal Oedema

In patients who have failed the cuff leak test but are otherwise deemed ready for extubation based on other assessments, it is recommended to administer corticosteroid therapy at least four

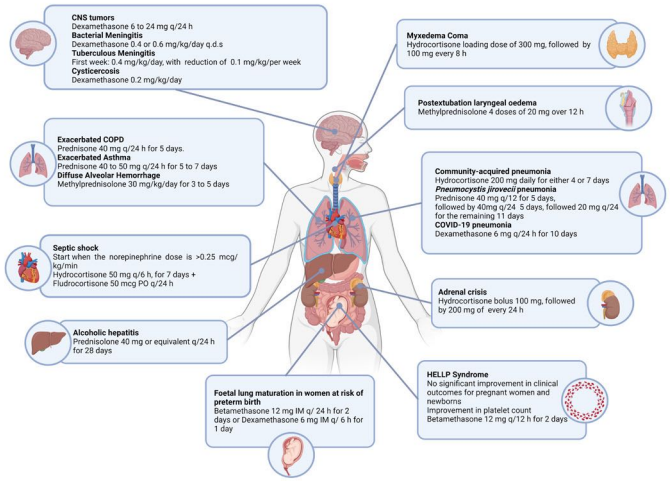

Figure 1. Use of corticosteroids in multiple pathologies

hours before extubation. It is suggested to give four doses of 20 mg of methylprednisolone over 12 hours, which reduces the incidence of postextubation laryngeal oedema (3% vs 22%, $p < 0.0001$), the overall incidence of reintubations (4% vs 8%, $p = 0.02$), and the proportion of reintubations secondary to laryngeal oedema (8% vs 54%, $p = 0.005$) (Francois et al. 2007).

Exacerbated COPD

According to the GOLD 2024 guidelines, the use of systemic corticosteroids is recommended during COPD exacerbations, with a maximum duration of five days and a daily dose of 40 mg of prednisone (or equivalent). This treatment approach is found to be equally effective through enteral or parenteral administration (GOLD 2024). Corticosteroids have been shown to reduce recurrence rates and the need for hospitalisation in patients experiencing COPD exacerbations. There is a significant improvement in lung function test results and a decrease in the risk of treatment failure in both outpatient and hospitalised patients when compared to placebo (OR 0.48; 95% CI 0.35, 0.67), without a significant difference in mortality (Walters et al. 2014).

Exacerbated Asthma

It is recommended to use inhaled corticosteroids for the treatment of exacerbated asthma. The benefits of this approach include acute relief of symptoms, a reduction in the risk of severe asthma attacks, a lower likelihood of hospitalisation, and the avoidance of initiating oral corticosteroids (Global Initiative for Asthma 2023). Oral corticosteroids are recommended for patients who, despite using inhaled corticosteroids for 2-3 days, fail to improve their symptoms during an asthma attack. The recommended dose is 40-50 mg/day of prednisone for 5 to 7 days (Normansell et al. 2016). In patients presenting to the emergency department with asthma exacerbation, the administration of corticosteroids via any route (IV, oral, IM, or inhaled) is recommended within the first hour of admission. This measure has been shown to reduce the probability of requiring hospitalisation by 50% (0.50 95% CI 0.31-0.81 p=0.004) (Rowe et al. 2001).

Adrenal Crisis

Adrenal crisis or insufficiency is defined as an acute deterioration in health associated with absolute hypotension (systolic blood pressure <100 mmHg), with characteristics resolving after the parenteral administration of glucocorticoids (demonstrated by a marked resolution of hypotension within one hour and improvement of clinical symptoms within two hours) (Rushworth et al. 2019). There are no controlled clinical trials regarding the treatment. The use of parenteral hydrocortisone is suggested. It is administered through a bolus injection of 100 mg IV or IM (while awaiting IV access). This bolus should be followed by 200 mg of hydrocortisone every 24 hours, either through continuous IV infusion or, alternatively, in doses of 50 mg of hydrocortisone per IV/IM injection every six hours (Arlt 2016).

Bacterial Meningitis

A systematic review and meta-analysis of randomised controlled trials on bacterial meningitis found that patients administered dexamethasone versus placebo had significantly lower rates of severe hearing loss (RR 0.67; 95% CI: 0.51 to 0.88), a decrease in the incidence of any hearing loss (RR 0.74; 95% CI), and neurological sequelae (RR 0.83; 95% CI: 0.69 to 1.00; p=0.05). An analysis focused on different bacteria causing meningitis demonstrated that patients with *Streptococcus pneumoniae* meningitis treated with corticosteroids had a lower mortality rate (RR 0.84; 95% CI: 0.72 to 0.98). Most studies utilised a four-day regimen of dexamethasone (0.4 or 0.6 mg/kg/day) administered in four daily doses (Brouwer et al. 2015).

Tuberculous Meningitis

A systematic review and meta-analysis of randomised controlled trials on tuberculous meningitis demonstrated that corticosteroids reduce the risk of death by 25% between two months and two years after initiating treatment (RR 0.75; 95% CI 0.65 to 0.87). In most studies, a dexamethasone dose reduction regimen was employed over the course of one month, distributed as follows: in week 1, 0.4 mg/kg/day for 7 days; in week 2, 0.3 mg/kg/day for 7 days; in week 3, 0.3 mg/kg/day for 7 days; and in week 4, 0.1 mg/kg/day for 7 days (Prasad et al. 2016).

Cysticercosis

In cases of viable intraparenchymal neurocysticercosis with multiple enhanced lesions, the use of anti-inflammatory therapy with corticosteroids is suggested to manage diffuse cerebral oedema. This therapy should be administered before initiating treatment with antiparasitic drugs, with a strong-moderate recommendation. In the case of subarachnoid neurocysticercosis, chronic use of high-dose steroids is advised, in addition to requiring intensive antiparasitic therapy and, in some cases, surgical intervention. Although the doses are not fully standardised, the administration of dexamethasone at 0.2 mg/kg/day may be considered, according to the strong-moderate recommendation. For patients with spinal neurocysticercosis and spinal cord dysfunction, such as paraparesis or incontinence, the use of corticosteroids is suggested as part of adjunctive management along with antiparasitic therapy, with a strong-moderate recommendation (White et al. 2017).

Myxoedema Coma and Thyroid Storm

The treatment of myxoedema coma primarily revolves around the use of thyroid hormones (Ylli et al. 2019). The administration of corticosteroids is recommended as part of the initial treatment for myxoedema coma, involving intravenous administration at appropriate stress doses before levothyroxine administration (Jonklaas et al. 2014). It is essential to note that this recommendation lacks support from controlled clinical trials. In cases of thyroid storm, a loading dose of 300 mg of hydrocortisone is suggested, followed by 100 mg every 8 hours (ATA guidelines 2016). However, it is important to acknowledge that the supportive evidence for this recommendation is not derived from large-scale clinical trials (Ross et al. 2016). A nationwide retrospective study indicated that corticosteroids do not improve survival in patients with thyroid storm. Moreover, they also induce glycaemic dysregulation and an increased need for insulin (Senda et al. 2020).

Alcoholic Hepatitis

A systematic review and meta-analysis revealed that corticosteroid monotherapy (prednisolone 40 mg or equivalent for 28 days) significantly reduced mortality compared to placebo (OR=0.58; 95% CI, 0.34-0.98; P=0.04) (Sung-Lee 2017).

Central Nervous System Tumours

Dexamethasone has been used for malignant brain tumours. It is employed to manage peritumoral oedema and alleviate symptoms related to intracranial hypertension. For the treatment of peritumoral oedema, described doses include 4 mg every 6 hours for 8 to 19 days, resulting in an average reduction in oedema volume (26%). Another regimen involves 4 mg every 6 hours for 7 days, followed by a maintenance dose of 4 mg/day until surgical intervention or radiotherapy, leading to an average reduction in oedema volume (56%). The following regimen is proposed based on symptom relief (Ly et al. 2017): initial one-time dose of 10 mg, followed by 4 mg every 6 hours

Diffuse Alveolar Haemorrhage

Diffuse alveolar haemorrhage (DAH) is a severe pulmonary complication that can occur in certain autoimmune diseases such as systemic lupus erythematosus, vasculitis associated with antineutrophil cytoplasmic antibodies (ANCA), antiphospholipid syndrome, and anti-glomerular basement membrane syndrome (Al-Adhoubi and Bystrom 2020). Corticosteroids are recommended in up to 98% of all cases. Their primary goal is to reduce the acute inflammatory response of the alveolar endothelium (Ednalino et al. 2015); however, to date, therapeutic recommendations for corticosteroids are based on retrospective trials and anecdotal reports. Despite the use of high-dose corticosteroids, mortality exceeds 50% (Park 2021).

HELLP Syndrome

A systematic review with meta-analysis (Sun et al. 2023) found no significant improvement in clinical outcomes for pregnant women and newborns with HELLP syndrome. However, the platelet count showed improvement after the administration of betamethasone at a dosage of 12 mg every 24 hours for two days (81.2%, 95% CI [43%, 533%]) compared to a placebo group (94.5%, 95% CI [24%, 627%]); there was no statistically significant difference between the two groups (p=0.23) (Ozer et al. 2009).

Foetal Lung Maturation in Women at Risk of Preterm Birth

Prenatal corticosteroid treatment in women at risk of preterm birth reduces the risk of respiratory distress (OR 0.66; 95% CI 0.54 to 0.82; p<0.001), mortality (OR 0.64; 95% CI 0.50 to 0.81; p<0.001), intraventricular haemorrhage, (OR 0.67; 95% CI 0.54 to 0.83; p<0.001), leukomalacia periventricular (OR 0.65; 95% CI 0.47 to 0.92; p<0.001) and necrotising enterocolitis compared to unexposed premature newborns. Corticosteroids should be initiated when a high risk of preterm birth is anticipated within the next one to seven days to achieve its effectiveness; if administered less than 24 hours before delivery, the effectiveness is incomplete. Betamethasone has shown a greater reduction in intraventricular haemorrhage. A course of therapy consists of intramuscular betamethasone 12 mg doses every 24 hours for two doses, or intramuscular dexamethasone 6 mg doses every 6 hours for four doses. An alternative is intravenous hydrocortisone 500 mg every 6 hours. (Dongkin et al. 2021).

Conclusion

The use of corticosteroids has demonstrated effectiveness in multiple pathologies in the ICU (**Figure 1**); however, clinical trials are needed to establish dosage and treatment duration for autoimmune and endocrine disorders.

Conflict of Interest

None.

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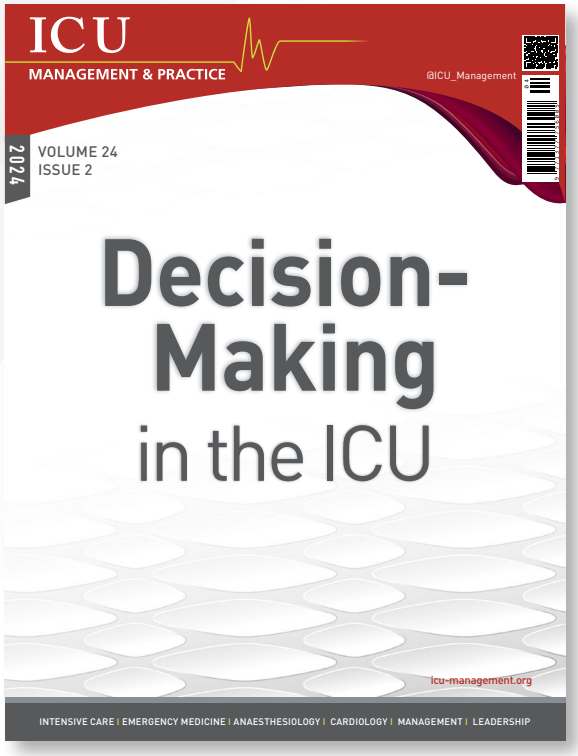

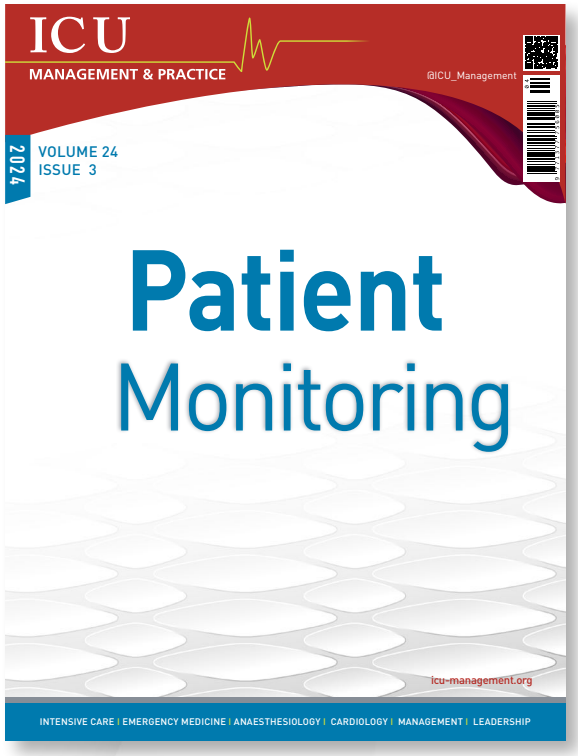

COVER STORY: Decision-Making in the ICU

Critical care practitioners often have to make decisions in high-stress and uncertain situations. Our contributors explore the decision-making process in the ICU, discuss factors that influence decisions related to critical care treatment and highlight the importance of clear guidelines to help clinicians through the complex decisionmaking process in critical care.

COVER STORY: Patient Monitoring

Timely and accurate monitoring is crucial to improving patient outcomes and reducing the risk of complications. In this issue, our contributors discuss how vital signs, cardiac, respiratory, haemodynamic, neurological, temperature, glucose monitoring and other important indicators can help critical care providers make timely and informed decisions in the ICU.

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