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Pharmacist in the ICU

Defining Medicines Optimisation in the Intensive Care Unit, *B O'Farrell, L Bosma, R Sloss, C McKenzie*

Critical Care Pharmacists Save Lives, *A Sikora, B Murray, A Most, G Martin*

Clinical Pharmacists in Intensive Care in Europe: From Basement to Bedside, *N Hunfeld, S O'Halloran, A Fischer, C Chapuis, S Guntschnig, I Spriet*

The Multiple Roles of the Critical Care Pharmacist, *S Raj, N Gadher, R Shulman*

Critical Care Pharmacists Contribute to Patient and Economic Outcomes Worldwide, *J Jacobi*

Haemoadsorption in Critically Ill Patients: The New Frontier, *C Ronco*

Corticosteroids in the Intensive Care Unit: Evidence-Based Recommendations *RA Reyes-Monge, LM Méndez-Martínez, S González-Sotelo, S Rayo-Rodríguez, L Soto-Muñoz, C Mendiola-Villalobos, OR Pérez-Nieto, E Deloya-Tomas, TO Mondragón-Labelle*

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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 plas-

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.

mapheresis, 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 improvement 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

<p>CCP Education (United States):</p> <ul style="list-style-type: none"> • 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. <p>CCP Board Certification:</p> <ul style="list-style-type: none"> • 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. <p>Multiprofessional Endorsement: CCPs are essential members of the ICU team.</p> <ul style="list-style-type: none"> • The Society of Critical Care Medicine • American College of Clinical Pharmacy • American Society of Health-System Pharmacists <p>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)</p> <ul style="list-style-type: none"> • 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)

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 pharma-

cists 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 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

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
<i>OR is unadjusted unless otherwise indicated</i> <i>*adjusted OR</i> <i>^hand calculated OR</i> <i>NNT = number needed to treat</i> <i>NNH = number needed to harm</i>			

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

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 decision 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 ramifications 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;

Conservatism Bias (also, Status Quo Bias)	Similar to clinical inertia, conservatism 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

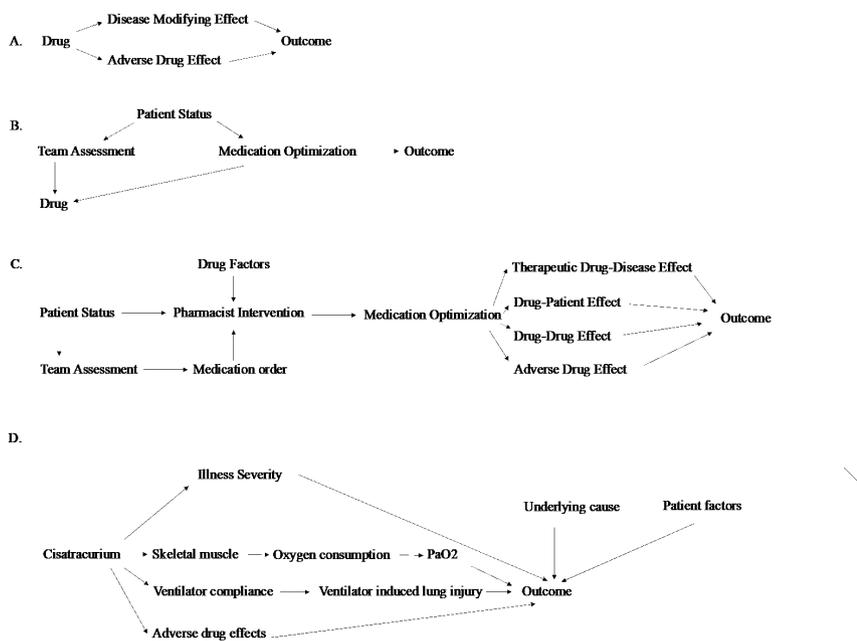


Figure 1. Causal diagrams. Panel A depicts medications conferring both therapeutic and adverse effects that both go on to affect outcomes. Panel B depicts the process by which medication optimisation affects drug choice and outcomes. Panel C depicts the process of retroactive medication intervention 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.

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 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

- 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)

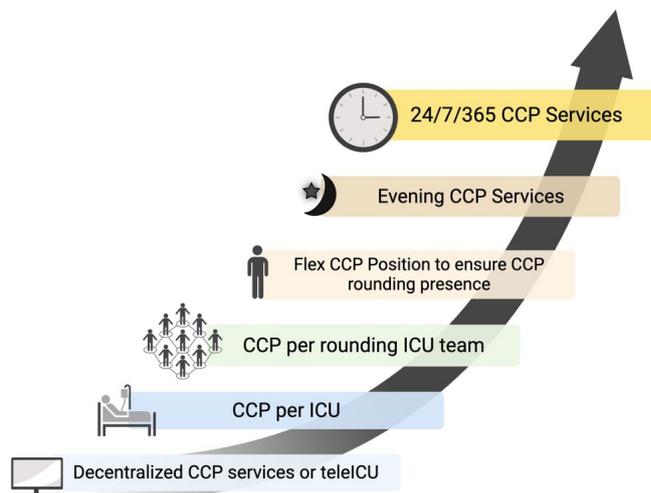


Figure 2. A proposed stepwise approach to expanding critical care pharmacist services.

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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