



■ ARTÍCULO DE REVISIÓN

Estrategias farmacoterapéuticas emergentes en cuidados críticos: revisión narrativa

Innovative pharmacological approaches in critical care: a narrative review

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RESUMEN

La unidad de cuidados intensivos (UCI) se caracteriza por una elevada complejidad clínica, la necesidad de intervenciones inmediatas y una monitorización continua, cada vez más impulsadas por terapias innovadoras. Esta revisión sintetiza la literatura actual sobre las principales innovaciones y terapias emergentes con potencial para transformar el manejo farmacológico del paciente críticamente enfermo. Se realizó una búsqueda bibliográfica hasta marzo de 2026 en Medline (PubMed) y la Biblioteca Virtual en Salud (BVS), mediante palabras clave o combinaciones en inglés y/o portugués: "critical care", "innovation" y "drug therapy". Entre las principales innovaciones

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se incluyen la monitorización terapéutica de fármacos integrada con el modelado farmacocinético/farmacodinámico (PK/PD), los biomarcadores para la estratificación del riesgo y las terapias inmunomoduladoras, celulares y dirigidas a dianas moleculares. En la sepsis y el síndrome de distrés respiratorio agudo (SDRA), la investigación avanza hacia subfenotipos definidos biológicamente; en el neurointensivismo, la sedoanalgesia neuroprotectora y los sistemas de liberación dirigida de fármacos adquieren creciente protagonismo; y en la lesión renal aguda (LRA), las estrategias emergentes se centran en dianas inflamatorias y metabólicas, así como en enfoques multiómicos. La farmacogenómica y la inteligencia artificial (IA) sustentan la medicina crítica de precisión. La superación de las barreras operativas permitirá que estas tecnologías optimicen la farmacoterapia, reduzcan los acontecimientos adversos y respalden la toma de decisiones clínicas en tiempo real, siempre que se sustenten en guías basadas en la evidencia, una gobernanza institucional sólida y una formación multidisciplinar continua. En definitiva, unos cuidados intensivos personalizados —guiados por biomarcadores, datos digitales e IA, y sin dejar de ser centrados en el paciente, seguros, eficaces y sostenibles— requieren un abordaje multidisciplinar coordinado que permita trasladar los avances científicos a beneficios clínicos tangibles.

Palabras claves: cuidados críticos, gestión de ciencia, tecnología e innovación en salud, quimioterapia.

ABSTRACT

The intensive care unit (ICU) environment is characterized by high clinical complexity, the need for rapid interventions, and continuous monitoring, increasingly driven by innovative therapies. This review

summarizes current literature on key innovations and emerging therapies with the potential to transform pharmacological management in critically ill patients. A literature search was conducted through March 2026 in Medline (PubMed) and the Virtual Health Library (VHL/BVS), using keywords or combinations in English and/or Portuguese: “critical care,” “innovation,” and “drug therapy.” Key innovations include therapeutic drug monitoring integrated with pharmacokinetic/pharmacodynamic (PK/PD) modeling, biomarkers for risk stratification, and immunomodulatory, cellular, and molecular-targeted therapies. In sepsis and ARDS, research is advancing toward biologically defined subphenotypes; in neurocritical care, neuroprotective sedoanalgesia and targeted drug delivery systems are gaining prominence; and in acute kidney injury (AKI), emerging strategies focus on inflammatory/metabolic targets and multi-omics approaches. Pharmacogenomics and artificial intelligence (AI) underpin precision critical care. Addressing operational barriers will enable these technologies to optimize pharmacotherapy, reduce adverse events, and support real-time clinical decision-making, contingent upon evidence-based guidelines, institutional governance, and continuous multidisciplinary training. Ultimately, personalized ICU care, guided by biomarkers, digital data, and AI, while remaining patient-centered, safe, effective, and sustainable, requires a coordinated multidisciplinary approach to translate scientific advances into tangible clinical benefits.

Keywords: critical care, health sciences, technology, and innovation management, drug therapy.

INTRODUCTION

Patients admitted to ICUs present complex clinical presentations, in which multiple etiological and pathophysiological factors coexist and interact dynamically. Conditions such as sepsis, shock, organ dysfunction, systemic inflammation, and metabolic disturbances constitute the main triggers of acute dysfunction, decisively influencing the response to pharmacological treatments and clinical prognosis ⁽¹⁾.

The scientific literature shows a predominance of cardiovascular, respiratory, renal, and neurological diseases, sepsis, and neoplasms as causes of ICU admission, clinical worsening, and mortality. ICU mortality varies substantially across settings and patient populations, reflecting differences in case mix, ICU type, admission criteria, severity of illness, and healthcare system characteristics. In middle- and high-income countries, reported ICU mortality commonly ranges from approximately 10% to 30%, although substantially higher rates may occur in specific populations, particularly among patients with severe sepsis, septic shock, acute respiratory failure, or multiple organ dysfunction. In the context of severe sepsis and septic shock, these rates can exceed 40%, particularly among individuals who progress to Multiple Organ Dysfunction Syndrome (MODS).^(2,3)

Among the main pathophysiological mechanisms in critically ill patients, an exacerbated inflammatory response, associated with endothelial dysfunction and immunometabolic alterations, plays a determining role in the progression of clinical severity. Particularly in sepsis, these alterations promote hemodynamic instability, impaired tissue perfusion, and profound changes in drug pharmacokinetics and pharmacodynamics, requiring individualized therapeutic approaches. Consequently, pathophysiological

syndromes are frequent in these settings, such as delirium, acute respiratory failure, and acquired weakness.⁽⁴⁾

A thorough understanding of the pathophysiological mechanisms underlying acute syndromes is important to stratify prognostic risk, anticipate potential complications, and guide personalized therapeutic interventions, with the goal of optimizing clinical outcomes and improving the quality of life of patients admitted to ICUs.

Patient management in this context has undergone profound transformations in recent decades, driven by biotechnological innovations, the discovery of new therapeutic targets, and the expanding use of digital methods, such as artificial intelligence (AI) and clinical decision support tools.

Thus, this review aims to present the main innovations and emerging therapies with the potential to transform the pharmacological management of critically ill patients, particularly in cases of sepsis, shock, respiratory failure, acute kidney injury, and neurological disorders.

METHODS

This study is a narrative literature review aimed at providing a broad overview of recent and emerging pharmacological innovations in critical care. As a narrative review, no formal protocol, risk-of-bias assessment, or quantitative synthesis was undertaken. To guide the study, the following research question was formulated: "What is the scientific evidence on the main innovations and emerging therapies with the potential to transform the pharmacological management of critically ill patients?"

A non-systematic search of articles indexed in the Medline (via PubMed) and Virtual

Health Library (VHL) databases was conducted through March 2026. The search was performed using the MeSH and DeCS controlled vocabularies, keywords or combinations of terms related to critical care, innovation, and pharmacotherapy, in English and Portuguese, using the Boolean operators AND and OR. No restrictions were imposed regarding publication year or language.

The identification and selection of publications were not based on a predefined systematic search, screening, or eligibility protocol. Articles were selected according to their relevance to the scope of the review, recency, and clinical or translational relevance, assessed arbitrarily by the authors. References cited in relevant publications were also considered when appropriate to identify additional studies pertinent to the topics discussed. When specific clinical trial findings, quantitative results, developmental phases, or other study-specific information were presented, primary studies were preferentially considered when available, whereas reviews and other secondary sources were used primarily to provide broader contextual synthesis.

The literature was organized into the main thematic areas addressed in the review: sepsis and septic shock, acute respiratory distress syndrome (ARDS), neurological disorders, acute kidney injury, pharmacogenomics, and artificial intelligence (AI).

RESULTS AND DISCUSSION

The following results highlight the main innovative therapeutic approaches, particularly in the management of sepsis, shock, respiratory failure, acute kidney injury, and neurological disorders. Additionally, this section presents the emerging integration of pharmacogenomics

and artificial intelligence into intensive care practice. The main findings are described in Table 1.

Sepsis and Septic Shock

Sepsis and septic shock represent complex therapeutic challenges in intensive care units, marked by multifactorial pathophysiology and interindividual variability in drug response. Advances in sepsis pharmacotherapy stem from a deeper understanding of the inflammatory, immunometabolic, and pharmacokinetic-pharmacodynamic alterations in critically ill patients, enabling personalized approaches based on biological stratification, inflammatory biomarkers, and individual pharmacological parameters.^(1,5)

Pharmacological treatment of sepsis in the ICU is fundamentally based on early, individualized antibiotic therapy, judicious use of vasopressors and corticosteroids, and fluid management strategies. In parallel, investigations into immunomodulation, molecular-targeted therapies, and nanotechnology are advancing, although most remain in preclinical stages or early experimental trials.⁽⁵⁻⁷⁾

Pathophysiological changes common in critically ill patients, such as expansion of the volume of distribution, multiple organ dysfunction, hypoalbuminemia, and marked variability in renal function, substantially compromise antimicrobial pharmacokinetics, resulting in unpredictable systemic exposure. In this scenario, therapeutic drug monitoring (TDM) integrated with pharmacokinetic-pharmacodynamic models becomes a potentially useful approach to ensure adequate therapeutic levels and optimize clinical outcomes. In parallel, progress continues in optimizing antimicrobial use through targeted de-escalation, infusion strategies (prolonged infusion of β -lactams), and continuous reassessment

based on clinical response and available laboratory markers, directly impacting the reduction of adverse events and the containment of antimicrobial resistance.⁽⁶⁾ As example, nebulized antimicrobials have been investigated as adjuvant therapy in ventilator-associated pneumonia (VAP), with the potential to achieve high local pulmonary exposure while limiting systemic exposure. However, evidence regarding their impact on clinical outcomes and multidrug-resistant pathogen burden remains heterogeneous.⁽⁶⁾ The AMIKINHAL trial demonstrated a reduction in the incidence of VAP with the use of inhaled amikacin during 28 days of follow-up.⁽⁷⁾

In the hemodynamic support of septic shock, the pharmacological approach is evolving toward more personalized strategies. Norepinephrine remains the first-line vasopressor,^(5,8) however, studies with non-catecholaminergic agents, such as methylene blue (a nitric oxide pathway inhibitor) as adjunct therapy, has shown hemodynamic and vasopressor-sparing effects in small randomized studies, although evidence for patient-centered outcomes remains limited.⁽⁹⁻¹¹⁾ In parallel, hydrocortisone (200 mg/day) is suggested for adults with septic shock who have an ongoing requirement for vasopressors despite adequate fluid resuscitation, typically administered as 50 mg intravenously every 6 hours or as a continuous infusion.⁽⁵⁾ Fluid management constitutes a complementary pillar of this strategy. After initial resuscitation, randomized trials such as CLASSIC and CLOVERS have evaluated restrictive versus more liberal or standard fluid strategies in patients with sepsis and septic shock. Although restrictive strategies reduced subsequent intravenous fluid administration, neither trial demonstrated a significant mortality benefit, supporting an individualized approach based on ongoing assessment of hemodynamic status, fluid responsiveness, and signs of fluid overload,

while avoiding unnecessary fluid accumulation.^(12,13)

Immunomodulation and molecular-targeted therapies represent emerging frontiers in sepsis management, with recent investigations into recombinant cytokines, hematopoietic growth factors, immune checkpoint inhibitors, and cellular therapies. A recent systematic review with meta-analysis demonstrated that these adjuvant immunomodulators are associated with a statistically significant, though clinically modest, reduction in short-term mortality among adults with sepsis, with a favorable safety profile. These findings reinforce the need for larger future clinical trials that assess long-term outcomes.⁽¹⁴⁾

Acute Respiratory Distress Syndrome (ARDS)

ARDS is characterized by diffuse pulmonary inflammation, endothelial and alveolar epithelial injury, increased permeability of the alveolar-capillary membrane, and accumulation of protein-rich fluid in the alveolar space.⁽³⁾ In recent years, the understanding of ARDS has evolved from a uniform syndromic model to a biologically heterogeneous entity, composed of different inflammatory, metabolic, and immunological subphenotypes. This conceptual shift has driven new therapeutic approaches, particularly in the field of pharmacology applied to the ICU, aligning with the precision medicine paradigm.⁽¹⁵⁾

Although protective mechanical ventilation remains the cornerstone of ARDS treatment, several approaches are being investigated, including anti-inflammatory strategies, immunomodulatory therapies, the development of cellular therapies, and the repurposing of existing drugs.^(15,16)

The role of corticosteroids in ARDS was reassessed in light of evidence generated during the COVID-19 pandemic. The

RECOVERY trial demonstrated a reduction in 28-day mortality with dexamethasone 6 mg/day for up to 10 days among hospitalized patients with COVID-19 requiring respiratory support, particularly those receiving oxygen or invasive mechanical ventilation.¹⁷ However, it is essential to recognize that COVID-19 presents pathophysiological particularities that may not apply to other etiologies. In non-COVID-19 ARDS patients, systematic reviews with metanalysis showed that corticosteroids probably reduce mortality, albeit with a modest magnitude and heterogeneity across studies, whereas in severe influenza viral pneumonia, data suggest no benefit or even potential harm.^(18,19) Thus, the indication for corticosteroids in ARDS should be individualized, considering the underlying etiology, the timing of intervention, and the risk-benefit balance. Additionally, neuromuscular blocking agents may be considered in selected patients with moderate-to-severe ARDS to facilitate lung-protective mechanical ventilation and improve patient-ventilator synchrony. Although the ACURASYS trial suggested a mortality benefit with early continuous neuromuscular blockade, the subsequent ROSE trial did not demonstrate a significant mortality benefit with routine early continuous neuromuscular blockade. Current evidence therefore supports a selective rather than routine approach, with careful consideration of clinical context, early use when indicated, and avoidance of unnecessary prolonged exposure.^(20,21)

Immune modulation has shown therapeutic potential in selected subgroups of ARDS with a hyperinflammatory phenotype, particularly in the early phase of COVID-19-associated ARDS.^(15,16) Among the immunomodulatory strategies investigated, the JAK inhibitor baricitinib has demonstrated benefits in clinical outcomes, including faster recovery, in patients with severe COVID-19.⁽²²⁾ Similarly, the anti-IL-6 receptor monoclonal antibody tocilizumab

has shown benefits in selected patients with severe COVID-19, particularly when administered in combination with corticosteroids.⁽²³⁾ Bevacizumab (an anti-VEGF monoclonal antibody) has been investigated experimentally in ARDS, but available evidence remains limited and has not established a clinical benefit.^(15,16) Anti-GM-CSF strategies, including lenzilumab and mavrilimumab, have also been investigated in patients with severe COVID-19 and hyperinflammatory phenotypes; however, current evidence remains insufficient to support their routine use in ARDS.^(24,25) In addition, pyrazolidinone carboxamide derivatives have been investigated as selective inhibitors of FPR1-mediated neutrophil activation in experimental models, with preliminary evidence of reduced pulmonary inflammation in an LPS-induced ARDS mouse model, although their clinical relevance remains to be established.²⁶

In the field of regenerative therapies, mesenchymal stem cells (MSCs) have emerged as an emerging approach to ARDS, with potential to modulate the inflammatory response and repair the pulmonary endothelium.⁽¹⁵⁾ A systematic review and meta-analysis highlighted the potential benefits of MSC therapy while also emphasizing substantial methodological heterogeneity across studies, which limits the generalizability of the findings. Therefore, adequately powered phase 3 randomized controlled trials with standardized protocols, clinically relevant outcomes, and, potentially, stratification according to inflammatory phenotype are needed before MSC therapy can be considered for routine clinical practice.⁽²⁷⁾

It is important to highlight that several drug repurposing strategies investigated in ARDS have not demonstrated consistent clinical benefit in phase 3 trials. Statins, β_2 -agonists (such as albuterol), and antiplatelet-dose aspirin³¹ failed to reduce mortality or duration of mechanical

ventilation in unselected populations.⁽²⁸⁻³¹⁾ Hydroxychloroquine and azithromycin, widely tested during the COVID-19 pandemic, showed no efficacy in SARS-CoV-2-related ARDS and are not considered therapeutic options for ARDS of other etiologies.^(32,33) These results reinforce that drug repurposing requires not only biological plausibility but also validation in trials with adequate design, phenotypic stratification, and clinically relevant outcomes.

Neurological Disorders

Neurological disorders represent one of the main causes of high clinical and therapeutic complexity in the ICU, encompassing conditions such as delirium, sepsis-associated encephalopathy, seizures, traumatic brain injury, and neurological dysfunction secondary to multiple organ dysfunction.⁽¹⁾

Among the innovations targeting neurological disorders in the ICU, three strategic axes stand out: i) individualized sedation and analgesia protocols, prioritizing appropriate analgesia, avoidance of excessive sedation, use of short-acting agents when clinically appropriate, and continuous assessment of the level of consciousness; ii) neuroprotective interventions based on modulation of the neuroinflammatory response and preservation of blood-brain barrier integrity; and iii) advanced drug delivery systems that enable targeted delivery of neuroactive agents to the central nervous system with reduced systemic toxicity.⁽³⁴⁻³⁶⁾

Optimization of sedation and analgesia strategies has been associated with lower delirium incidence and may facilitate preservation of cognitive function in critically ill patients. In this context, systematic reviews with metaanalysis showed that the use of dexmedetomidine in comparison of benzodiazepines, and

continuous monitoring of the level of consciousness are associated with reduced duration of mechanical ventilation, lower incidence of delirium, and shorter ICU length of stay.^(37,38) In patients with acute brain injury, sedation may serve a specific neuroprotective role, including facilitating control of intracranial pressure, maintaining adequate cerebral perfusion, and suppressing seizure activity when clinically indicated. Short-acting agents such as propofol and remifentanyl may be preferred in selected patients because their pharmacokinetic profiles facilitate rapid titration and neurological assessment.⁽³⁹⁾ Ketamine has also been investigated in patients with acute brain injury, particularly because of its analgesic properties and potential hemodynamic advantages; however, evidence supporting its routine use as a first-line sedative in the general ICU remains limited. Its use may be particularly considered in selected clinical situations, including hemodynamic instability and severe bronchospasm.⁽⁴⁰⁾

For seizures, available evidence suggests that several intravenous second-line antiseizure medications may be effective in terminating nonconvulsive epileptic activity; however, direct comparative evidence specifically in nonconvulsive status epilepticus remains limited.^(41,42)

Nanotechnology and advanced drug delivery systems are emerging as emerging approach to improve drug delivery across the blood-brain barrier in acute and chronic neurological conditions. Nanocarriers, including liposomes, polymeric nanoparticles, dendrimers, and extracellular vesicles, as well as alternative administration routes such as intranasal and intrathecal delivery, have demonstrated enhanced brain drug exposure and therapeutic effects in experimental models of stroke, neurodegenerative diseases, and brain tumors. However, most of these approaches remain at the preclinical stage,

and their clinical translation remains limited.⁽⁴³⁾ A systematic review described that several nanoparticle- and liposome-based drug delivery systems have progressed to early-phase clinical trials, primarily phase 1/2 studies, providing preliminary evidence of clinical feasibility but not yet establishing their therapeutic efficacy. Therefore, their potential application in critically ill patients remains largely translational and requires validation in clinical studies.⁽⁴⁴⁾

Acute Kidney Injury

Acute kidney injury (AKI) is defined as a sudden deterioration of renal function, operationalized by the KDIGO criteria through an increase in serum creatinine (≥ 0.3 mg/dL within 48 hours or ≥ 1.5 times baseline) and/or a reduction in urine output (< 0.5 mL/kg/h for ≥ 6 hours).⁽⁴⁵⁾ The 2026 KDIGO update retains established functional criteria based on changes in serum creatinine and urine output while incorporating additional functional and structural criteria, including changes in serum cystatin C and validated biomarkers of kidney damage.⁽⁴⁶⁾ It represents one of the most prevalent complications in intensive care units, affecting 30% to 50% of critically ill patients, and constitutes an independent prognostic factor for hospital mortality, prolonged hospitalization, increased risk of progression to chronic kidney disease, and increased therapeutic complexity, especially regarding the pharmacokinetics of antimicrobials and nephrotoxic agents.⁽¹⁾

To date, no pharmacological therapy has been approved specifically for the prevention or treatment of AKI in intensive care, and management remains centered on supportive measures, such as optimization of renal perfusion, minimization of nephrotoxic agents, and renal replacement therapy when indicated. Advances in elucidating the multifactorial pathophysiology of AKI, including tubular

necroptosis, mitochondrial dysfunction, and impaired epithelial regeneration, have driven the development of strategies targeting specific molecular pathways. Among these targets, modulation of inflammatory responses and cellular metabolism, hemodynamic regulation, and enhancement of cellular repair mechanisms have emerged as investigational approach.⁽⁴⁷⁾ In addition, research involving interventions based on 'omics' technologies and nanotechnology is also being investigated.^(48,49)

Renal hypoperfusion secondary to systemic hypotension constitutes an important precipitating mechanism of acute kidney injury (AKI) in intensive care. In this context, pharmacological strategies targeting intrarenal hemodynamic modulation have been investigated, albeit with heterogeneous results.⁽⁴⁸⁾ Angiotensin II exerts predominantly systemic vasoconstriction rather than selective constriction of the renal efferent arteriole. In an exploratory subanalysis of the ATHOS-3 trial, its use was associated with a lower need for renal replacement therapy (RRT) and reduced mortality in patients with grade 2–3 AKI.⁽⁵⁰⁾ However, given the exploratory nature of this analysis, these findings do not prove nephroprotection and require validation in dedicated prospective trials. Levosimendan, an inodilator with vasodilatory effects that may increase renal blood flow, has been investigated as a potential strategy for preventing AKI after cardiac surgery. Although earlier meta-analyses suggested a reduction in postoperative AKI,⁽⁵¹⁾ more recent evidence has not confirmed a consistent renal benefit. Subsequent large randomized controlled trials, including LEVO-CTS and CHEETAH, and a recent network meta-analysis of randomized controlled trials found no significant difference in postoperative creatinine levels with levosimendan compared with other inotropic strategies, suggesting that its role in renal protection after cardiac surgery

remains uncertain.⁽⁵²⁻⁵⁴⁾ Given the lack of solid evidence for preventive use, emerging investigations are exploring its therapeutic potential application in established AKI, with an emphasis on modulating tubular mitochondrial function, although clinical data remain preliminary.^(48,49)

Inflammatory pathways are activated in intensive care by multiple triggers that engage innate immune system receptors, triggering a cascade of pro-inflammatory cytokines with the potential to cause secondary organ injury, including AKI. In this scenario, immunomodulation strategies targeting different phases of the immune response have been investigated, albeit with heterogeneous results due to the phenotypic diversity of septic patients.^(47,48) RBT-1 are being studied to evaluate their efficacy in reducing AKI in patients following cardiac procedures.⁽⁴⁸⁾ In a randomized placebo-controlled trial (NCT05524051), TIN816 did not demonstrate an apparent renal benefit based on changes in serum creatinine or the incidence of AKI, and the study was subsequently terminated.⁽⁵⁵⁾ These findings illustrate the uncertainty surrounding emerging immunomodulatory approaches for AKI prevention.

Recent evidence demonstrates that mitochondrial dysfunction and impaired cellular energy metabolism are central mechanisms in the pathogenesis of AKI, particularly in the context of sepsis and ischemia-reperfusion.⁽⁴⁸⁾ Intracellular nicotinamide adenine dinucleotide (NAD⁺) depletion and impaired NAD⁺ biosynthesis has been implicated in the pathophysiology of AKI, particularly in settings of ischemia-reperfusion and critical illness. In this context, NAD⁺ precursors, including nicotinamide, nicotinamide riboside, and nicotinamide mononucleotide, are being investigated as potential metabolic therapies.⁽⁴⁸⁾ In a phase 1 placebo-controlled pilot study of patients undergoing cardiac surgery, oral

nicotinamide increased circulating NAD⁺-related metabolites, was well tolerated, and was associated with a lower incidence of AKI, although the study was not powered to establish efficacy.⁽⁵⁶⁾ Clinical trials are currently evaluating NAD⁺ augmentation strategies for the prevention of cardiac surgery-associated AKI and for kidney injury in septic shock, but their clinical efficacy remains to be established.^(47,48)

Complement system activation contributes significantly to tubular injury in the context of rhabdomyolysis and hemolysis. Ravulizumab, a monoclonal antibody targeting complement component C5, has been investigated as a potential nephroprotective strategy in COVID-19-associated acute kidney injury. A randomized, double-blind, placebo-controlled pilot study reported a lower need for renal replacement therapy at day 10 and a numerical trend toward greater renal recovery at day 30 with ravulizumab.⁽⁵⁷⁾ However, these preliminary findings require cautious interpretation because of the small sample size and lack of confirmation of sustained renal benefit. A phase 3 trial specifically designed to evaluate ravulizumab in COVID-19-associated acute kidney injury was subsequently initiated, while a separate phase 3 trial in severe COVID-19 requiring mechanical ventilation was terminated for futility, highlighting the uncertainty surrounding the clinical efficacy of complement inhibition in this setting.⁽⁵⁸⁾

'Omics' approaches (genomics, transcriptomics, proteomics, metabolomics, lipidomics, and epigenomics) enable integrated molecular analysis, revealing complex pathophysiological mechanisms involved in acute kidney injury and repair. These platforms have contributed significantly to the identification of risk biomarkers and early diagnosis, phenotypic stratification of patients based on distinct molecular profiles, and the discovery of new therapeutic targets. Integrative proteome

and transcriptome studies have identified genes and proteins associated with AKI risk, such as NCF1, TNFRSF1B, ACADSB, and ADD1, suggesting pathways amenable to pharmacological intervention or repurposing of existing drugs.^(48,49) In the metabolomics field, preclinical studies have investigated metabolic alterations and potential therapeutic targets in sepsis-associated AKI. For example, in a murine model of LPS-induced AKI, oleic acid administration was associated with improved renal function and reduced inflammation and oxidative stress, accompanied by changes in metabolic pathways involving phenylalanine, purine, sphingolipid, and taurine/hypotaurine metabolism.⁽⁵⁹⁾ These findings suggest a potential link between metabolic modulation and renal protection; however, the evidence remains preclinical and requires validation in clinically relevant models and human studies. The main challenges for clinical application in the ICU include the heterogeneity of AKI (sepsis, ischemia, drugs, surgery), the short window for intervention, and the need for rapid omics biomarker panels to guide ICU therapies.^(48,49)

Pharmacogenomics

Pharmacogenomics constitutes an important component of precision medicine in intensive care, enabling the individualization of pharmacotherapy based on genetic variants that modulate the pharmacokinetics and pharmacodynamics of medications⁽¹⁾. Several drugs routinely used in the ICU have therapeutic responses that may be influenced by polymorphisms in genes encoding drug-metabolizing enzymes, particularly cytochrome P450 isoenzymes such as CYP2D6 and CYP2C19, membrane transporters such as P-glycoprotein (ABCB1), and pharmacological targets such as OPRM1 for opioids.⁽⁶⁰⁾ Pharmacogenomic information may therefore contribute to individualized drug selection and dosing, particularly for

medications with a narrow therapeutic window or high risk of toxicity. However, despite its potential to reduce variability in drug response and prevent adverse drug reactions, the clinical utility and impact of pharmacogenomic-guided therapy in critically ill patients remain to be established.⁽⁶¹⁾

An operational feasibility study in patients undergoing cardiovascular surgery with planned ICU admission demonstrated that 98% had actionable pharmacogenomic variants (that is, with the potential to guide therapeutic adjustments), predominantly related to warfarin, clopidogrel, metoprolol, tramadol, codeine/oxycodone, and proton pump inhibitors. However, the median turnaround time for the report was approximately 52 hours, which may render it unsuitable for immediate therapeutic decisions⁽⁶²⁾.

Despite its potential, the implementation of pharmacogenomics in intensive care faces several structural and operational barriers, including: i) the cost and turnaround time of conventional genetic testing, which may delay the availability of results relative to the urgency of therapeutic decisions in the acute phase; ii) the complexity of interpreting genetic variants in the context of the multifactorial physiological instability of critically ill patients; and iii) challenges in integrating pharmacogenomic results with electronic health records and clinical decision-support systems, limiting the availability of actionable recommendations at the point of prescribing. These barriers highlight the need for rapid testing platforms, standardized interpretation frameworks, and interoperable clinical decision-support systems.⁽⁶³⁻⁶⁵⁾ Despite these challenges, emerging developments may facilitate the broader implementation of pharmacogenomics in critical care. These include the increasing use of next-generation sequencing approaches, including whole-exome and whole-genome sequencing, which may enable the

identification of a broader range of pharmacogenomic variants beyond those included in targeted panels, although targeted genotyping remains widely used and the clinical interpretation of rare and complex variants continues to limit the routine replacement of targeted approaches by whole-exome or whole-genome sequencing.⁽⁶⁶⁾ Rapid point-of-care platforms are also being developed for clinically actionable pharmacogenes; for example, rapid CYP2C19 genotyping platforms have demonstrated concordance with conventional laboratory methods while providing results within approximately 1 hour, potentially facilitating genotype-guided decisions in acute clinical settings.⁽⁶⁷⁾ Finally, pharmacogenomic research is increasingly incorporating pharmacodynamic determinants of drug response, including OPRM1 variants in opioid therapy, thereby complementing the traditionally pharmacokinetic focus of pharmacogenomics. Recent clinical studies and meta-analyses continue to investigate associations between OPRM1 variants and opioid response; however, the clinical utility of OPRM1-guided opioid prescribing remains insufficiently established.^(68,69)

AI-Integrated Therapies

The increasing complexity of patients admitted to ICUs, coupled with variability in clinical outcomes and pressure for greater efficiency in resource use, has driven the incorporation of digital technologies into clinical practice. In this context, AI-based systems stand out as tools capable of integrating multiple data sources, generating clinical predictions, and supporting real-time clinical decisions.^(70,71)

AI-integrated therapies in the ICU refer to the incorporation of predictive algorithms, machine learning models, and clinical decision support systems that interact with clinical workflows with the goal of optimizing and enhancing diagnosis, prognosis, and treatment planning. This

integration enhances the ability to personalize intensive care, reduces variability in medical practice, and facilitates the prioritization of interventions in contexts of high complexity, high demand, and shortage of specialized professionals.^(70,71)

AI is a field of science and technology focused on developing systems capable of performing tasks that normally require human intelligence, such as reasoning, learning, perception, decision-making, and problem-solving. In the healthcare context, machine learning and deep learning techniques are particularly relevant. These approaches enable the construction of models that learn patterns from clinical data to perform tasks such as: i) prediction of clinical outcomes; ii) classification of physiological signals; iii) recommendation of therapies based on probability of benefit; and iv) identification of temporal patterns in physiological data series.^(71,72)

AI applications in the ICU can be classified according to their stage of development and level of clinical evidence. Model development involves training algorithms using retrospective datasets to identify associations or generate predictions, whereas internal validation evaluates model performance using data derived from the same underlying population. External validation assesses whether model performance is maintained in independent populations or clinical settings, whereas prospective validation evaluates model performance under real-world clinical conditions. These stages establish predictive validity and transportability but do not, by themselves, demonstrate that implementation of an AI system improves clinical management or patient outcomes.^(73,74)

Scientific organizations have recognized the importance of digital technologies, including AI-based systems, in improving patient safety and supporting clinical

workflows in the ICU. These guidelines emphasize the need for rigorous evaluation of AI system performance prior to implementation, its integration with evidence-based practices, and post-implementation monitoring of impacts on clinical outcomes.^(70,71)

AI-based models have been investigated for early prediction of sepsis, optimization of mechanical ventilation, and hemodynamic decision support, although evidence demonstrating improvements in patient-centered outcomes remains limited. Recent systematic and umbrella reviews suggest that some AI models may demonstrate discrimination comparable to or better than traditional severity scores such as APACHE II and SOFA; however, superior predictive performance does not necessarily translate into improved clinical outcomes.^(70,71)

It is important to emphasize that the potentially effective integration of AI into clinical practice requires not only robust models but also clinical understanding of the underlying pathophysiological mechanisms so that AI recommendations can be interpreted and applied rigorously. In addition, the use of AI in clinical contexts raises ethical questions, such as algorithm transparency, data privacy and security, and accountability for decisions. Regulation of these systems, including independent validation and certification by regulatory agencies, is still under development in many countries.^(70,71)

Limitations

This review has some limitations. First, its narrative and non-systematic design may have introduced selection bias, as the identification and prioritization of publications were based on their relevance and clinical or translational contribution rather than on predefined systematic eligibility criteria. Second, the literature encompasses heterogeneous levels of

evidence, ranging from established clinical interventions to early-phase human studies and preclinical investigations, which limits direct comparison across therapeutic approaches. Finally, the rapidly evolving nature of several fields discussed, particularly pharmacogenomics, AI, cellular therapies, and emerging molecular targets, means that new evidence may rapidly modify the current assessment of these approaches.

Table 1. Pharmacological and technological strategies in intensive care according to clinical application and stage of evidence.

Clinical condition	Strategy/Intervention	Main evidence/Potential clinical role	Key limitations and considerations	Stage of Evidence
Sepsis and Septic Shock	TDM and PK/PD-guided antimicrobial dosing	TDM and PK/PD approaches can improve attainment of pharmacokinetic/pharmacodynamic targets and support individualized antimicrobial dosing.	Improvement in target attainment does not necessarily translate into improved mortality or other patient-centered outcomes	Established clinical evidence for selected applications
	Prolonged β -lactam infusion and antimicrobial de-escalation	Prolonged infusion can increase the probability of achieving pharmacodynamic targets, while targeted de-escalation may reduce unnecessary antimicrobial exposure and support antimicrobial stewardship.	Benefits depend on the pathogen, MIC, dosing strategy, organ function, and clinical context.	Established clinical practice
	Nebulized antimicrobials as adjunctive therapy	May achieve substantially higher pulmonary concentrations and potentially reduce systemic exposure in selected VAP patients with multidrug-resistant pathogens.	Optimal dose, formulation, delivery device, and ventilator settings remain important; evidence for patient-centered outcomes is limited.	Clinical investigational
	Norepinephrine	Remains the first-line vasopressor for hemodynamic support in septic shock.	Requires individualized titration according to hemodynamic response and clinical context.	Established clinical evidence
	Hydrocortisone	May improve shock reversal and is recommended in selected patients with persistent vasopressor-dependent shock despite adequate initial resuscitation.	Magnitude of benefit varies according to patient selection, timing, and clinical context.	Established clinical evidence
	Methylene blue	Inhibition of the nitric oxide pathway represents a potential adjunctive strategy in catecholamine-refractory vasoplegia.	Evidence is limited and derived from selected populations	Clinical investigational
	Fluid restriction after initial resuscitation	Restrictive and de-escalation strategies may reduce cumulative fluid exposure in patients with persistent or recurrent fluid overload. The CLOVERS trial did not demonstrate a mortality advantage of a restrictive strategy over a liberal strategy during initial resuscitation.	Fluid management should be individualized according to perfusion, responsiveness, and signs of fluid overload	Established clinical evidence for selected applications
Clinical condition	Strategy/Intervention	Main evidence/Potential clinical role	Key limitations and considerations	Stage of Evidence
ARDS	Immunomodulatory therapies	Cytokines, hematopoietic growth factors, immune checkpoint modulators, and cellular therapies have demonstrated potential signals of benefit in selected populations.	Biological heterogeneity and modest effects on short-term mortality limit clinical applicability; larger trials are required.	Clinical investigational
	Corticosteroids	May reduce mortality and/or duration of mechanical ventilation in selected patients with ARDS, with evidence varying according to etiology, timing, dose, and disease severity. Evidence from COVID-19-associated ARDS supports their use in specific clinical contexts, while studies in non-COVID ARDS suggest heterogeneous but potentially relevant benefits.	Optimal regimen and patient selection remain debated; effects may differ across ARDS etiologies, particularly viral infections.	Established clinical evidence for selected applications
	Neuromuscular blocking agents	Early, short-duration use may improve patient-ventilator synchrony and may be beneficial in selected patients with moderate-to-severe ARDS.	Evidence is heterogeneous and does not support routine prolonged use	Established clinical evidence for selected applications
	Baricitinib and tocilizumab	Targeted immunomodulation has demonstrated clinical benefit in selected patients with severe COVID-19, including effects on recovery and mortality in appropriate populations.	Evidence is primarily derived from COVID-19 populations and should not be generalized to ARDS of other etiologies.	Established clinical evidence for selected applications
	Anti-GM-CSF therapies	Lenzilumab and mavrilimumab have been investigated as strategies to modulate inflammatory responses.	Clinical evidence remains insufficient to support routine clinical use.	Clinical investigational
	FPR1 inhibition / pyrazolidinone carboxamide derivatives	Experimental compounds may selectively inhibit activated neutrophils and represent potential targets for neutrophil-mediated inflammation.	Evidence remains predominantly experimental.	Preclinical evidence
	Mesenchymal stem cells	Preclinical studies and early clinical suggest potential effects on inflammation and respiratory function, with a generally favorable preliminary safety profile.	Small studies, methodological heterogeneity, and lack of definitive phase 3 evidence limit clinical extrapolation.	Preclinical evidence/Early-clinical evidence
	Statins, β_2 -agonists, aspirin, and systemic anticoagulation	Large clinical studies have generally failed to demonstrate consistent benefits in unselected ARDS populations.	Potential effects in clinically defined subgroups remain uncertain.	No established clinical evidence

Clinical condition	Strategy/Intervention	Main evidence/Potential clinical role	Key limitations and considerations	Stage of Evidence
Neurological Disorders	Hydroxychloroquine and azithromycin	Clinical trials did not demonstrate meaningful efficacy for COVID-19 and these agents are not recommended as therapies for ARDS.	Lack of demonstrated benefit and potential for adverse effects.	No established clinical evidence
	Sedation minimization and individualized sedoanalgesia	Strategies emphasizing adequate analgesia, lighter sedation, and continuous assessment may reduce delirium, duration of mechanical ventilation, and ICU length of stay.	Implementation must consider neurological status, mechanical ventilation requirements, pain, agitation, and hemodynamic stability.	Established clinical evidence
	Dexmedetomidine-based sedation	May facilitate lighter sedation and is associated with reduced delirium compared with benzodiazepine-based strategies in selected ICU populations.	Bradycardia and hypotension may limit use; effects depend on the clinical context.	Established clinical evidence for selected applications
	Propofol and remifentanyl	Provide predictable titration and may facilitate control of sedation, intracranial pressure, and neurological assessment in acute brain injury	Requires individualized dosing and close hemodynamic and neurological monitoring.	Established clinical evidence
	Ketamine	May provide analgesia and hemodynamic advantages and may be useful in selected situations of acute brain injury such as refractory shock or severe bronchospasm.	Evidence remains insufficient to establish ketamine as a first-line sedative for the general ICU population.	Clinical investigational
	Levetiracetam, valproate, lacosamide and fosphenytoin	Available observational evidence suggests comparable efficacy among intravenous second-line antiepileptic agents for nonconvulsive status epilepticus	Evidence is limited and much of the evidence is extrapolated from studies predominantly involving convulsive status epilepticus.	Limited clinical evidence
	Nanocarriers and advanced drug-delivery systems	Liposomes, polymeric nanoparticles, dendrimers, exosomes, and intranasal/intrathecal approaches may increase cerebral delivery of therapeutic agents in experimental models.	Most evidence remains preclinical; safety, biodistribution, scalability, and clinical effectiveness require further evaluation.	Preclinical evidence/Early-clinical evidence
AKI	Angiotensin II	Exploratory analyses suggest potential effects on renal replacement therapy requirements and outcomes in severe AKI associated with vasodilatory shock.	Findings require confirmation in studies specifically designed to evaluate renal outcomes.	Clinical investigational
Clinical condition	Strategy/Intervention	Main evidence/Potential clinical role	Key limitations and considerations	Stage of Evidence
	Levosimendan	Early studies suggested potential nephroprotective effects, whereas subsequent evidence, including meta-analytic data, did not demonstrate a consistent reduction in AKI or mortality.	Current evidence does not support routine use for AKI prevention.	No established clinical evidence
	NAD ⁺ precursors, particularly nicotinamide	Early clinical studies suggest increased NAD ⁺ availability and changes in biomarkers of tubular injury for sepsis/ischemia-associated AKI	Evidence regarding clinically relevant renal outcomes remains preliminary.	Early-clinical evidence
	Ravulizumab/complement inhibition	A small pilot study suggested potential renal benefits in severe COVID-19-associated renal dysfunction, but findings were not conclusive.	Renal outcomes warrant confirmation in larger trials.	Early-clinical evidence
	Omics-based approaches	Genomic, transcriptomic, proteomic, metabolomic, lipidomic, and epigenomic approaches may facilitate early risk identification, molecular phenotyping, and discovery of therapeutic targets.	Clinical translation requires rapid assays, validated biomarkers, and evidence that biomarker-guided strategies improve patient outcomes.	Preclinical evidence
Pharmacogenomics	CYP2D6, CYP2C19, ABCB1 and other pharmacogenes	Genetic variants can influence drug metabolism, transport, or pharmacodynamic response and may contribute to interindividual variability in drug exposure or response.	Demonstration of a pharmacogenetic association does not establish that genotype-guided therapy improves outcomes in critically ill patients; critical illness may also modify genetic effects.	Clinical utility investigational
	Rapid/point-of-care pharmacogenomic testing	Rapid testing could facilitate incorporation of actionable pharmacogenomic information into time-sensitive prescribing decisions.	Clinical utility, cost-effectiveness, turnaround time, and integration with electronic prescribing systems require further validation in ICU populations.	Clinical utility investigational
	Whole-exome/whole-genome sequencing	May expand the identification of pharmacogenomic variants beyond predefined gene panels in complex clinical scenarios.	Interpretation of rare variants, turnaround time, cost, and demonstrated clinical utility remain limitations.	Clinical utility investigational

Clinical condition	Strategy/Intervention	Main evidence/Potential clinical role	Key limitations and considerations	Stage of Evidence
AI	OPRM1 and opioid response	OPRM1 variants have been investigated as potential contributors to interindividual variability in opioid response and requirements.	Associations remain heterogeneous, and evidence is insufficient to support routine OPRM1-guided opioid therapy in the ICU.	Clinical utility investigational
	Prediction of sepsis, deterioration, or mortality	AI models can integrate multiple clinical and physiological variables and may demonstrate promising discrimination and calibration, sometimes exceeding conventional scores in specific datasets.	Predictive performance does not demonstrate that implementation improves treatment or patient-centered outcomes.	Model development/internal or external validation
	AI-guided fluid and vasopressor therapy	Algorithms have been evaluated for predicting hemodynamic responses and generating treatment recommendations using retrospective or computational approaches.	Retrospective or simulated recommendations do not establish clinical effectiveness or safety when implemented at the bedside.	Clinical investigational
	AI-assisted mechanical ventilation	AI models are being investigated to predict physiological responses and support ventilator-setting decisions.	Clinical benefit, safety, clinician adherence, and effects on patient-centered outcomes remain insufficiently established.	Clinical investigational
	Integrated AI-based clinical decision support	AI may support risk stratification, diagnosis, prognosis, and therapeutic decision-making by integrating large and heterogeneous datasets.	Requires external and prospective validation, workflow integration, interoperability, transparency, monitoring for performance drift, and evidence of clinical impact.	Internal or external validation

Abbreviations: AI, artificial intelligence; AKI, acute kidney injury; ARDS, acute respiratory distress syndrome; ICU, intensive care unit; PK/PD, pharmacokinetics/pharmacodynamics; TDM, therapeutic drug monitoring; VAP, ventilator-associated pneumonia.

CONCLUSION

Intensive care is undergoing a transformation driven by scientific and technological advances and the need for greater precision in the care of critically ill patients. This evolution has given rise to personalized approaches capable of integrating clinical, physiological, and increasingly molecular characteristics into therapeutic decision-making.

The evidence synthesized in this narrative review indicates that this transition is still incomplete. Several individualized strategies, including therapeutic drug monitoring, PK/PD-guided antimicrobial dosing, tailored sedation, and etiology- and severity-based pharmacological interventions, are already incorporated into selected areas of current intensive care practice. In contrast, many emerging approaches remain at different stages of experimental or clinical development. Biomarker-guided therapies, immunomodulatory and regenerative strategies, novel pharmacological interventions for acute kidney injury,

pharmacogenomic-guided prescribing, advanced drug-delivery systems, and AI-based therapeutic decision support have shown promising biological or predictive results, but their clinical effectiveness and impact on patient-centered outcomes remain insufficiently established for routine implementation in most ICU settings.

Therefore, precision critical care is not a replacement for conventional intensive care, but an evolving approach that complements and refines current practice. Its successful integration will depend on translating biological and technological advances into meaningful clinical benefits, ensuring safety, feasibility, and broad applicability across diverse critically ill populations. Crucially, the responsible adoption of these innovations requires multidisciplinary collaboration among physicians, pharmacists, nurses, and other healthcare professionals to ultimately improve patient outcomes.

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Statement on the Use of Generative AI in Writing

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