Sodium-Glucose Cotransporter-2 Inhibitors in Critically Ill Patients and Acute Kidney Injury: Clinical Considerations

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Abstract

Acute kidney injury (AKI) is a severe complication, affecting up to 50% of critically ill patients. The advent of sodium-glucose cotransporter-2 (SGLT2) inhibitors has challenged traditional paradigms of renoprotection. Their mechanisms include restoration of tubuloglomerular feedback, metabolic reprogramming toward ketone utilization, anti-inflammatory actions, and modulation of the sympathetic nervous system. Emerging evidence suggests a complex risk–benefit profile for SGLT2 inhibitors in critical illness. Observational studies consistently show associations with reduced ICU admissions, lower infection rates, and improved survival. However, interventional studies indicate nuanced effects, including potential increases in vasopressor requirements in septic patients. The ongoing PREVENTS-AKI trial, specifically designed for ICU patients, will provide definitive evidence to guide clinical practice. The use of SGLT2 inhibitors in this vulnerable population requires careful consideration of unique safety concerns, including euglycemic diabetic ketoacidosis, increased vasopressor requirements, electrolyte disturbances, volume depletion, and genitourinary infections. Implementation should follow structured protocols with a thorough baseline assessment, daily monitoring, and clear discontinuation criteria. Until more robust evidence emerges, SGLT2 inhibitors represent a promising but cautiously applied option for AKI prevention in selected critically ill patients.

Keywords: sodium-glucose cotransporter-2 (SGLT2) inhibitors; acute kidney injury; critical illness

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Sodium-glucose cotransporter-2 Inhibitors ในผู้ป่วยวิกฤตและภาวะไตวายเฉียบพลัน: ข้อควรพิจารณาทางคลินิก

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แผนกโรคไต กองอายุรกรรม โรงพยาบาลพระมงกุฎเกล้า และวิทยาลัยแพทยศาสตร์พระมงกุฎเกล้า

บทคัดย่อ

ภาวะไตวายเฉียบพลันเป็นภาวะแทรกซ้อนรุนแรงที่พบได้มากถึงร้อยละ 50 ของผู้ป่วยวิกฤต ยากลุ่ม sodium-glucose cotransporter-2 (SGLT2) inhibitors ได้เข้ามาท้าทายแนวคิดเดิมในการปกป้องไต กลไกสำคัญที่ช่วยลดความเสี่ยงของภาวะไตวาย ได้แก่ การฟื้นฟู tubuloglomerular feedback การปรับการเผาผลาญไปสู่การใช้คีโตนเป็นพลังงาน การลดการอักเสบ และการควบคุมสมดุลของระบบประสาทซิมพาเทติก ปัจจุบันมีหลักฐานเกี่ยวกับการใช้ SGLT2 inhibitors ในผู้ป่วยวิกฤตที่สะท้อนทั้งประโยชน์และความเสี่ยง งานวิจัยเชิงสังเกตพบว่า SGLT2 inhibitors อาจช่วยลดอัตราการเข้ารักษาในหอผู้ป่วยวิกฤต ลดอัตราการติดเชื้อ และเพิ่มอัตราการรอดชีวิตได้ ขณะที่การศึกษาแบบสุ่มควบคุมเบื้องต้นพบผลลัพธ์ที่ยังไม่ชัดเจน และอาจต้องเพิ่มการใช้ยากระตุ้นความดันโลหิตในผู้ป่วยภาวะติดเชื้อในกระแสเลือด การศึกษาแบบสุ่มควบคุม PREVENTS-AKI ที่กำลังดำเนินการอยู่จะให้ข้อมูลหลักฐานเพิ่มเติมเพื่อเป็นแนวทางการรักษาที่ชัดเจนขึ้น การใช้ยาในกลุ่มผู้ป่วยนี้จึงควรได้รับการเฝ้าระวังเรื่องความปลอดภัยอย่างใกล้ชิด โดยเฉพาะความเสี่ยงต่อ euglycemic diabetic ketoacidosis, ความจำเป็นในการใช้ยากระตุ้นความดันโลหิตเพิ่มขึ้น ความผิดปกติของเกลือแร่ ภาวะขาดสารน้ำ และการติดเชื้อทางเดินปัสสาวะหรืออวัยวะเพศ การนำยาไปใช้ในทางคลินิกควรมีเกณฑ์การคัดเลือกผู้ป่วย การประเมินเบื้องต้น การติดตามรายวัน และแนวทางการหยุดยาอย่างเป็นระบบ ในระหว่างนี้ SGLT2 inhibitors จึงเป็นทางเลือกที่มีศักยภาพในการป้องกันภาวะไตวายเฉียบพลันในผู้ป่วยวิกฤตที่เหมาะสม ภายใต้การประเมินและดูแลอย่างรอบคอบ

คำสำคัญ: sodium-glucose cotransporter-2 (SGLT2) inhibitors; ภาวะไตวายเฉียบพลัน; ภาวะวิกฤต

Introduction

Acute kidney injury (AKI) is one of the most serious complications in critically ill patients, affecting up to 50% of intensive care unit (ICU) admissions and associated with a mortality rate exceeding 50% when renal replacement therapy is required.[1,2] The pathophysiology of AKI in critical illness is complex and multifactorial, involving hemodynamic instability, inflammatory cascades, oxidative stress, and direct nephrotoxic insults.[3] Despite advances in critical care, therapeutic options for preventing and treating AKI remain limited, with management largely restricted to supportive care and renal replacement therapy.[4] This therapeutic gap has driven research into novel nephroprotective strategies aimed at modifying the course of this high-risk complication.

The emergence of sodium-glucose co-transporter-2 (SGLT2) inhibitors has redefined paradigms in cardiovascular and renal medicine. Initially developed as glucose-lowering agents for type 2 diabetes mellitus, these drugs have demonstrated unexpected and robust

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organ-protective effects that extend well beyond glycemic control.[5] Landmark cardiovascular outcome trials—EMPA-REG OUTCOME, CANVAS, and DECLARE-TIMI 58—showed significant reductions in major adverse cardiovascular events, heart failure hospitalizations, and, importantly, renal endpoints.[6-8] Subsequent dedicated renal outcome trials, including CREDENCE, DAPA-CKD, and EMPA-KIDNEY, have firmly established SGLT2 inhibitors as cornerstone therapy for chronic kidney disease (CKD), regardless of diabetes status.[9-11] Reflecting this evidence, the KDIGO guidelines now recommend SGLT2 inhibitors as first-line therapy alongside renin-angiotensin system blockade in patients with CKD.[12]

This narrative review aims to critically assess the current evidence on SGLT2 inhibitor use in critically ill patients, with a particular focus on AKI prevention and treatment. We examine the mechanistic rationale for nephroprotection, review the available clinical data in ICU populations, discuss key safety considerations—including the risk of euglycemic diabetic ketoacidosis (DKA)—and provide practical recommendations for clinicians. While we await results from definitive trials such as PREVENTS-AKI (NCT05468203), this review seeks to bridge the gap between established benefits in stable patients and the complexities of critical care practice.

Mechanisms of Kidney Protection of SGLT2 inhibitors

The nephroprotective effects of SGLT2 inhibitors are mediated through multiple, interrelated pathways that extend well beyond their primary action of inhibiting glucose reabsorption. Understanding these mechanisms is crucial to appreciating their potential benefits in critically ill patients, in whom diverse pathophysiological insults converge to cause AKI. This section outlines the principal mechanisms by which SGLT2 inhibitors may confer renal protection, with a focus on their relevance in the ICU setting. An overview of these mechanisms in critical illness is illustrated in **Figure 1**.

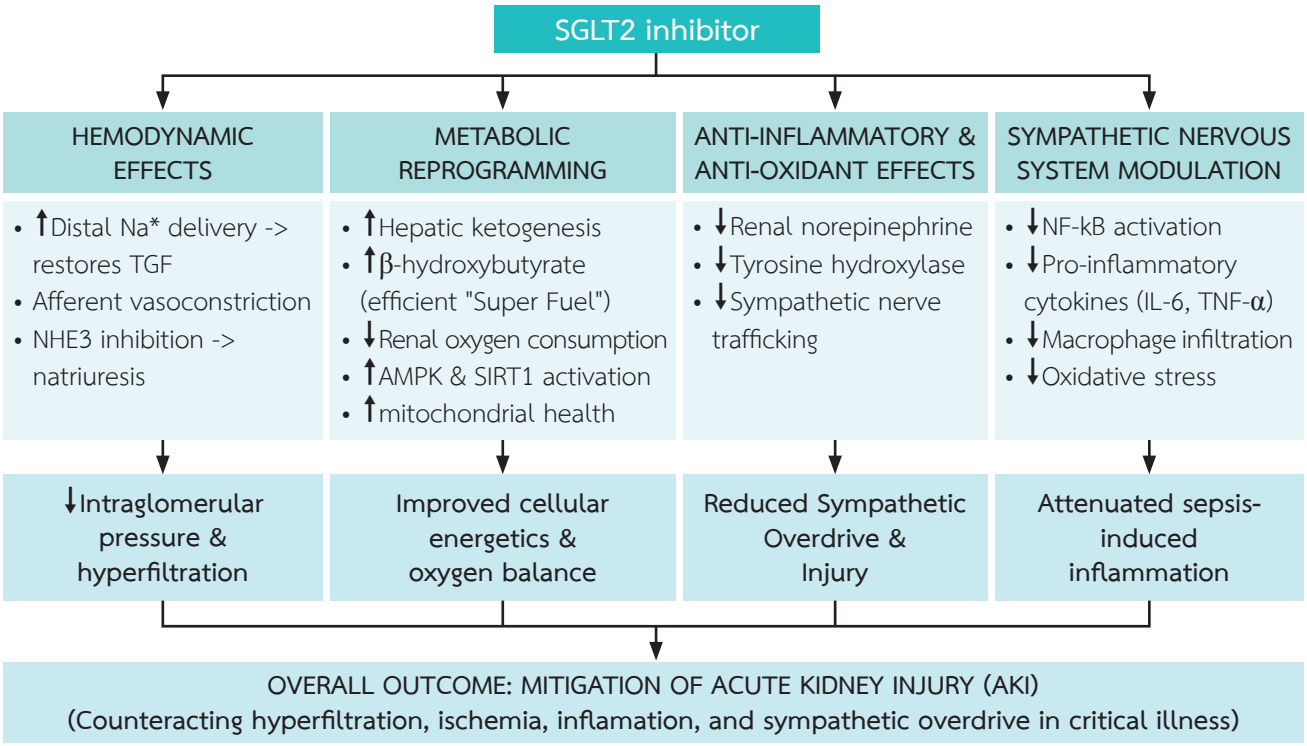

Figure 1 Proposed Mechanisms of SGLT2 Inhibitor–Mediated Kidney Protection in Critical Illness
AKI, acute kidney injury; AMPK, AMP-activated protein kinase; IL-6, interleukin-6; NADPH oxidase, nicotinamide adenine dinucleotide phosphate oxidase; NF-κB, nuclear factor-κB; NHE3, sodium–hydrogen exchanger 3; SGLT2, sodium–glucose cotransporter 2; SIRT1, sirtuin-1; TGF, tubuloglomerular feedback; TNF-α, tumor necrosis factor-α

Hemodynamic Effects

A key hemodynamic action of SGLT2 inhibitors is the restoration of tubuloglomerular feedback—a fundamental autoregulatory mechanism that protects the kidney from hyperfiltration injury.[13] Under normal physiology, macula densa cells in the distal tubule detect sodium chloride delivery and modulate afferent arteriolar tone accordingly. In diabetes and other states of hyperfiltration, excessive proximal tubular sodium-glucose reabsorption via SGLT2 reduces distal sodium delivery, leading to afferent arteriolar vasodilation and glomerular hyperfiltration.[14]

SGLT2 inhibitors counteract this maladaptive response by blocking proximal sodium reabsorption, thereby increasing distal sodium delivery to the macula densa. This stimulates the release of adenosine and induces afferent arteriolar vasoconstriction, thereby lowering intraglomerular pressure.[15] Renal hemodynamic studies have shown that SGLT2 inhibitors can reduce glomerular hyperfiltration by approximately 5–10 mL/min/1.73 m^2, primarily by increasing afferent arteriolar resistance without significantly affecting efferent arteriolar tone.[16] This selective hemodynamic modulation contrasts with the action of renin-angiotensin system inhibitors, which predominantly dilate the efferent arteriole.

Additionally, SGLT2 inhibitors inhibit sodium-hydrogen exchanger 3 (NHE3) in the proximal tubule, enhancing natriuresis and contributing to intravascular volume regulation.[17] This dual inhibition of SGLT2 and NHE3 may be especially relevant in patients with heart failure or fluid overload—conditions commonly encountered in critical care. The resulting natriuresis and osmotic diuresis reduce plasma volume, lower cardiac preload, and improve overall cardiovascular hemodynamics.[18]

Metabolic Reprogramming and Cellular Energetics

SGLT2 inhibitors also induce a shift in cellular metabolism that may mitigate ischemic and inflammatory injury. By promoting glucosuria and lowering the insulin-to-glucagon ratio, these agents stimulate hepatic ketogenesis, resulting in a 30–50% increase in circulating β-hydroxybutyrate levels.[19] Ketone bodies serve as highly efficient fuels for the heart and kidneys, producing more ATP per unit of oxygen consumed than glucose or fatty acids.[20] This metabolic advantage becomes critical in the setting of critical illness, where tissue hypoxia and mitochondrial dysfunction are common.

Beyond ketone production, SGLT2 inhibitors reduce renal cortical oxygen consumption by lowering the energy demand for glucose reabsorption. Blood oxygen level-dependent MRI studies have shown improved renal cortical oxygenation following SGLT2 inhibition.[21] This reduced oxygen demand, combined with improved supply-demand matching via ketone metabolism, creates a protective balance that may help prevent ischemic AKI.

Moreover, SGLT2 inhibitors activate AMP-activated protein kinase (AMPK) and sirtuin-1 (SIRT1)—key regulators of cellular energy homeostasis.[22] These pathways enhance mitochondrial biogenesis, stimulate autophagy, and bolster cellular stress resistance. This nutrient deprivation signaling mimics the beneficial effects of caloric restriction, potentially explaining the broad organ-protective effects of these agents.[23]

Anti-inflammatory and Antioxidant Properties

Inflammation is central to the pathogenesis of AKI, especially in sepsis and other forms of critical illness. SGLT2 inhibitors exert significant anti-inflammatory effects via multiple pathways. They suppress nuclear factor-κB (NF-κB) activation, reduce production of pro-inflammatory cytokines such as interleukin-6, tumor necrosis factor-α, and monocyte chemoattractant protein-1, and limit macrophage infiltration in renal tissue.[24, 25]

Real-world data support these actions, with large observational studies reporting 37–48% reductions in the risk of pneumonia and sepsis among SGLT2 inhibitor users.[26] These benefits likely reflect both direct anti-inflammatory effects and indirect improvements via better glycemic control and reduced glucotoxicity. Additionally, SGLT2 inhibitors decrease oxidative stress by downregulating NADPH oxidase activity and upregulating antioxidant defenses, including superoxide dismutase and catalase.[27]

Modulation of the Sympathetic Nervous System

Emerging evidence suggests that SGLT2 inhibitors attenuate sympathetic nervous system activity—an effect particularly relevant in critically ill patients, who often

exhibit heightened sympathetic tone. Preclinical studies have demonstrated reductions in renal norepinephrine content, lower expression of tyrosine hydroxylase (the rate-limiting enzyme in catecholamine synthesis), and decreased sympathetic nerve activity following SGLT2 inhibition.[28,29]

This sympathoinhibition appears to be bidirectional: sympathetic activation upregulates SGLT2 expression, while SGLT2 inhibition feeds back to suppress sympathetic drive.[30] Clinically, this may translate to lower blood pressure without reflex tachycardia, improved heart rate variability, and potentially reduced arrhythmogenic risk. In the ICU, where excessive sympathetic activation contributes to hemodynamic instability and organ dysfunction, this mechanism may offer additional renoprotection.

Rational Use of SGLT2 Inhibitors in Critical Illness

The multiple mechanisms of SGLT2 inhibitors align remarkably well with the pathophysiology of AKI in critical illness. Their hemodynamic modulation addresses hyperfiltration injury, while metabolic reprogramming enhances cellular resilience to ischemia. Anti-inflammatory effects may help attenuate sepsis-induced kidney injury, and modulation of the sympathetic nervous system could reduce catecholamine-mediated organ damage. However, these theoretical benefits must be balanced against potential risks, including volume depletion in hemodynamically unstable patients and metabolic effects that could precipitate ketoacidosis during physiologic stress.

Clinical Evidence of SGLT2 Inhibitors in Critically Ill Patients

Translating the benefits of SGLT2 inhibitors from stable outpatients to critically ill patients represent a significant knowledge gap in current practice. While robust evidence supports their use in chronic conditions, data specific to intensive care settings remain limited but are rapidly evolving. This section critically examines the available evidence from observational studies, pilot interventional trials, experimental models, and perioperative investigations to provide a comprehensive understanding of SGLT2 inhibitor use in critical illness. A summary of clinical studies in critically ill patients is presented in **Table 1**.

Table 1 Clinical Studies of SGLT2 Inhibitors in Critically Ill Patients

Study	Design	Population	N	Intervention	Key Outcomes	Safety Profile
Mårtensson et al. 2023	Pilot case–control	ICU patients with T2DM	18 vs 72	Empagliflozin 10 mg daily	• Reduced insulin requirements (–15 units/day) • Increased sodium (median 149 mmol/L) • No difference in mortality (16.7% vs 18.1%)	• No DKA episodes • No worsening of kidney function • Stable acid–base parameters
Park et al. 2023	Retrospective cohort	Septic shock with T2DM	36 vs 62	Pre-admission SGLT2i	• Trend toward reduced vasopressor needs • Shorter ICU stay (NS) • Similar APACHE III scores	• No increase in adverse events • No DKA observed
Ng et al. 2023	Territory-wide cohort	Patients with T2DM	10,308 vs 17,664	SGLT2i vs DPP-4i	• Reduced ICU admissions (HR 0.79, 95% CI 0.69–0.91) • Lower all-cause mortality (HR 0.44, 95% CI 0.38–0.50) • 40% reduction in sepsis-related ICU admissions	• Lower UTI rates • Reduced infection-related mortality

Table 1 Clinical Studies of SGLT2 Inhibitors in Critically Ill Patients (continued)

Study	Design	Population	N	Intervention	Key Outcomes	Safety Profile
DARE-19 (Kosiborod et al. 2021)	Randomized controlled trial	Hospitalized patients with COVID-19	1,250	Dapagliflozin 10 mg daily	• Primary outcome not significant (HR 0.80, 95% CI 0.58–1.10) • Numerically fewer AKI events (4.2% vs 5.8%)	• Well tolerated • No excess serious adverse events
DEFENDER secondary analysis (Cutuli et al. 2024)	Post-hoc analysis	Patients with acute organ dysfunction	401	Dapagliflozin 10 mg daily	• Increased urine output (+157 mL/day by day 5) • Improved fluid balance (–290 mL/day) • Increased norepinephrine needs in sepsis	• Minimal electrolyte changes • Mild metabolic acidosis • 97% probability of increased vasopressor use in sepsis
Miller et al. 2023	Nationwide cohort	Surgical patients with T2DM	7,448 continued vs discontinued	Perioperative SGLT2i	• Reduced AKI risk (OR 0.69, 95% CI 0.62–0.78) • Reduced 30-day mortality (OR 0.70, 95% CI 0.55–0.88)	• Increased euglycemic DKA risk (OR 1.11, 95% CI 1.05–1.17) • Median 3-day increase in LOS with DKA

T2DM, type 2 diabetes mellitus; DKA, diabetic ketoacidosis; ICU, intensive care unit; HR, hazard ratio; OR, odds ratio; CI, confidence interval; NS, not significant; UTI, urinary tract infection; AKI, acute kidney injury; LOS, length of stay; APACHE, Acute Physiology and Chronic Health Evaluation; RCT, randomized controlled trial; DPP-4i, dipeptidyl peptidase-4 inhibitor.

Observational Studies in Critical Care

Real-world evidence provides valuable insights into the effects of SGLT2 inhibitors in critically ill populations, although selection bias remains a concern. A landmark territory-wide cohort study from Hong Kong examined 27,972 propensity-matched patients with type 2 diabetes, comparing those using SGLT2 inhibitors with those using dipeptidyl peptidase-4 (DPP-4) inhibitors.[31] Over a median follow-up of 2.9 years, SGLT2 inhibitor use was associated with a 21% reduction in ICU admissions (2.8% vs. 3.7%; HR 0.79, 95% CI 0.69–0.91) and a striking 56% reduction in all-cause mortality (3.1% vs. 7.5%; HR 0.44, 95% CI 0.38–0.50). Subgroup analyses showed that the benefit was most pronounced in patients with CKD, with the protective effect increasing with declining renal function—a finding that challenges conventional concerns about their use in kidney impairment.

The mechanisms underlying the reduced ICU admissions appear to be multifactorial. Analysis by admission category showed a 40% reduction in sepsis-related ICU admissions among SGLT2 inhibitor users, supporting the anti-inflammatory effects discussed previously.[31] Another analysis of 28,987 patients found that SGLT2 inhibitor users had lower rates of pneumonia (incidence rate 11.38 vs. 20.45 per 1,000 person-years) and sepsis (6.00 vs. 12.88 per 1,000 person-years) compared to DPP-4 inhibitor users.[32] When infections did occur, they were associated with lower mortality rates in the SGLT2 inhibitor group, suggesting both preventive and protective benefits.

A Veterans Affairs database study specifically examined patients with septic shock, comparing 36 patients on pre-admission SGLT2 inhibitors with 62 matched controls.[33] Despite similar baseline characteristics and illness severity scores, SGLT2 inhibitor users showed trends toward improved outcomes, including reduced vasopressor requirements and shorter ICU stays, though statistical significance was limited by small sample size. Importantly, no increase in adverse events, including diabetic ketoacidosis, was observed in this high-risk population.

The impact of continuation versus discontinuation during hospitalization has also been evaluated. A nationwide cohort study of 36,505 admissions found that among 5,936 SGLT2 inhibitor users who continued therapy, there was a 45% reduction in mortality (IRR 0.55, 95% CI 0.42–0.73; P < 0.01) and shorter length of stay (LOS: 4.7 vs. 4.9 days; IRR 0.95, 95% CI 0.93–0.98; P < 0.01) compared to those who discontinued therapy.[34] These findings suggest that the protective effects of SGLT2 inhibitors may be particularly relevant during periods of physiological stress.

Interventional Studies in ICU Settings

Direct interventional evidence in critically ill patients remains limited but provides valuable mechanistic insights. The most comprehensive pilot study to date, conducted in Swedish ICUs, compared 18 patients with type 2 diabetes receiving empagliflozin 10 mg daily with 72 matched controls.[35] Under a liberal glucose control protocol (target 180–250 mg/dL), several key findings emerged:

Empagliflozin use was associated with significant increases in serum sodium (median increase 4 mmol/L) and chloride levels, with median maximum sodium levels reaching 149 mEq/L. Although this raised concerns about hypernatremia, no adverse clinical outcomes were observed. Acid-base parameters remained stable, with no significant differences in pH, bicarbonate, or lactate levels. Notably, despite theoretical risks, no episodes of diabetic ketoacidosis occurred, even with beta-hydroxybutyrate monitoring. Glycemic control improved significantly with empagliflozin, including a reduction in insulin requirements (median reduction of 15 units/day) and lower glucose variability. Renal function, assessed by creatinine and urine output, showed no deterioration, and there was a trend toward lower positive fluid balance in the empagliflozin group. Hospital mortality did not differ significantly between groups (17% vs. 19%), although the study was underpowered to detect differences in clinical outcomes.

The DARE-19 trial, although not exclusively an ICU study, provides relevant insights for acutely ill patients.[36] This randomized controlled trial examined dapagliflozin versus placebo in 1,250 patients hospitalized with COVID-19 and cardiometabolic risk factors. While the primary composite outcome of organ dysfunction or death was not significantly different (HR 0.80, 95% CI 0.58–1.10), there were numerically fewer AKI events in the dapagliflozin group (4.2% vs. 5.8%). These neutral overall results may reflect a heterogeneous population and variable timing of intervention, as greater benefit was seen in patients enrolled earlier in their illness.

A secondary analysis of the DEFENDER trial raised concerns about hemodynamic effects.[37] In this post hoc analysis of 401 critically ill patients with acute organ dysfunction, dapagliflozin progressively increased urine output (day 5: +157 mL/day) and improved fluid balance (day 5: –290 mL/day). However, these benefits were accompanied by time-dependent increases in norepinephrine requirements, with a dose difference reaching 0.034 mcg/kg/min by day 5. Subgroup analysis suggested that patients with sepsis or mechanical ventilation were most susceptible, with a 97% probability of increased vasopressor requirements in septic patients

Perioperative and Acute Care Evidence

The perioperative period offers a controlled model of acute physiological stress relevant to critical care. A large Veterans Affairs study of 462,968 surgical patients found that continued SGLT2 inhibitor use was associated with a reduced risk of postoperative AKI but a slight increase in euglycemic ketoacidosis risk (OR 1.11, 95% CI 1.05–1.17).[38] Patients who developed ketoacidosis had a median hospital stay prolonged by three days, highlighting the need for vigilant monitoring.

The EMPACT-MI trial investigated empagliflozin in

acute myocardial infarction, demonstrating a reduction in first hospitalization for heart failure or death from any cause (8.2% vs. 9.1%; P = 0.02) and a trend toward a lower incidence of AKI (0.8% vs. 1.3%).[39] Early initiation studies in acute heart failure further bridge the gap between stable and critically ill populations. The EMPULSE trial demonstrated that in-hospital initiation of empagliflozin in patients with acute heart failure was safe and associated with clinical benefits, including reduced readmission rates.[40] Similarly, the SOLOIST-WHF trial demonstrated that sotagliflozin initiated before or shortly after discharge reduced cardiovascular events without excess safety concerns.[41]

Clinical Implications of SGLT2 inhibitors in Critical illness

The emerging evidence highlights a complex risk–benefit profile for SGLT2 inhibitors in critical illness. Observational data consistently demonstrate associations with reduced ICU admissions, lower infection rates, and improved survival. However, interventional studies indicate nuanced effects, including potential increases in vasopressor requirements in patients with sepsis. Timing appears crucial, with preventive or early use showing greater promise than late initiation in established organ dysfunction.

Careful patient selection is critical. Patients with cardiorenal syndrome, fluid overload, or high infection risk may benefit most, whereas hemodynamically unstable septic patients may be at increased risk of requiring higher vasopressor doses. The ongoing PREVENTS-AKI trial (NCT05468203), specifically designed for ICU patients, will provide essential evidence to guide future clinical practice.

Safety of SGLT2 Inhibitors in Critically Ill Patients

While the potential benefits of SGLT2 inhibitors in critically ill patients are compelling, their use in this vulnerable population demands careful consideration of unique safety concerns. The physiological stress of critical illness, altered pharmacokinetics, and complex drug interactions create an environment where adverse effects may be amplified or present atypically. This section reviews major safety considerations, with emphasis on recognition, prevention, and management strategies relevant to intensive care.

Euglycemic Diabetic Ketoacidosis (eDKA)

Euglycemic diabetic ketoacidosis (eDKA) is the most serious metabolic complication associated with SGLT2 inhibitor use and is particularly relevant in critically ill patients. Unlike classic DKA, eDKA presents with relatively normal blood glucose levels (<250 mg/dL), which can delay recognition and treatment.[42] The incidence in stable outpatients ranges from 0.16 to 0.76 events per 1,000 patient-years, but this likely underestimates the risk during critical illness.[43]

The pathophysiology involves multiple mechanisms that may be exacerbated in critical illness. By promoting renal glucose excretion, SGLT2 inhibitors lower plasma glucose and insulin levels while increasing glucagon secretion, thereby creating a hormonal environment that favors ketogenesis.[44] The resulting increase in lipolysis and hepatic ketone production can progress to ketoacidosis, especially when combined with common ICU precipitants such as sepsis, surgical stress, fasting, or reduced carbohydrate intake.

Critical illness creates a “perfect storm” for eDKA development. The stress response activates counter-regulatory hormones (cortisol, catecholamines, growth hormone) that further promote lipolysis and ketogenesis. Concurrent corticosteroid use, common in ICU patients, compounds this risk. Additionally, many critically ill patients have reduced oral intake or receive inadequate carbohydrate through enteral or parenteral nutrition, removing the substrate needed to suppress ketone production.[45]

Recognizing eDKA in the ICU requires high vigilance, as presenting symptoms (nausea, vomiting, abdominal pain) may be misattributed to underlying disease or medications. Key diagnostic features include the following: (1) anion gap metabolic acidosis (pH <7.3, bicarbonate <18 mmol/L); (2) positive serum or urine ketones; (3) blood glucose <250 mg/dL (often 100–180 mg/dL); (4) exclusion of other causes of metabolic acidosis

Management follows standard DKA protocols with important modifications. Insulin infusion remains the cornerstone of treatment, but higher dextrose concentrations (10–20%) are typically required to prevent hypoglycemia while maintaining sufficient insulin to suppress ketogenesis.[46] The SGLT2 inhibitor must be discontinued immediately; due to its long half-life (12–13 hours), ketosis may persist for 24–72 hours after discontinuation. Current guidelines recommend withholding SGLT2 inhibitors for 3–4 days before elective surgery to reduce eDKA risk.[47] For ICU patients requiring urgent procedures, close metabolic monitoring and appropriate insulin coverage are essential.

Prevention strategies in the ICU include careful patient selection—avoiding use in type 1 diabetes, prior DKA, or low C-peptide states—ensuring adequate carbohydrate intake (>100 g/day), maintaining basal insulin in insulin-dependent patients, daily monitoring of acid–base status and ketones in high-risk patients, and temporary discontinuation during acute illness or procedures requiring prolonged fasting.

Hemodynamic Effects and Vasopressor Requirements

Recent evidence has raised concerns about the hemodynamic effects of SGLT2 inhibitors in critically ill patients, particularly those with septic shock. A secondary analysis of the DEFENDER trial showed time-dependent increases in norepinephrine requirements, with septic patients having a 97% probability of increased vasopressor needs.[37] By day 5, the expected dose difference had reached 0.034 mcg/kg/min—a clinically meaningful increase that may affect organ perfusion and ICU outcomes.

The mechanisms underlying increased vasopressor needs likely involve several factors. SGLT2 inhibitors induce osmotic diuresis and natriuresis, resulting in a reduction of approximately 7% in intravascular volume.[18] While this volume reduction benefits heart failure patients, it may compromise hemodynamic stability in septic shock, where vasodilation and capillary leak already threaten organ perfusion. Additionally, SGLT2 inhibitor–mediated sympathetic inhibition, advantageous in chronic settings, may blunt compensatory responses to hypotension in critically ill patients.[30]

The clinical impact depends on the patient's hemodynamic profile. In cardiogenic shock or fluid-overloaded states, the diuretic and afterload-reducing effects of these medications may be beneficial. However, in distributive shock (e.g., sepsis, anaphylaxis) or hypovolemia, SGLT2 inhibitors may exacerbate instability. Close hemodynamic monitoring and careful fluid balance assessment are essential when considering these agents in the ICU.

Electrolyte Disturbances and Acid–Base Alterations

SGLT2 inhibitors cause predictable electrolyte changes that warrant monitoring in critically ill patients. The Swedish pilot study demonstrated significant increases in serum sodium (median 149 mEq/L) and chloride.[35] Although not associated with adverse outcomes in that small study, hypernatremia in critically ill patients has been independently linked to increased mortality in larger cohorts.[48]

The mechanisms of hypernatremia are diverse. Osmotic diuresis, with free water loss exceeding sodium excretion, contributes to increased serum sodium levels. SGLT2 inhibitors may also increase proximal tubular sodium reabsorption through compensatory pathways, paradoxically limiting natriuresis despite their primary action.[49] In ICU patients with impaired thirst mechanisms or restricted access to water, this can lead to significant hypernatremia.

SGLT2 inhibitors also affect acid–base balance through multiple pathways. By inhibiting proximal tubular bicarbonate reabsorption, they can cause mild metabolic acidosis (typically a 2–3 mmol/L decrease in serum bicarbonate). In patients with pre-existing acid–base disturbances, this effect may complicate management. The DEFENDER analysis revealed progressive, modest decreases in pH over five days of treatment, underscoring the importance of careful monitoring.[37]

Other electrolyte considerations include a mild risk of hyperkalemia, particularly when combined with concurrent RAAS blockade; hypophosphatemia due to increased urinary phosphate excretion; hypomagnesemia resulting from greater urinary magnesium losses; and

potential hypocalcemia associated with increased urinary calcium excretion.

Volume Depletion and Acute Kidney Injury

The relationship between SGLT2 inhibitors and AKI presents an interesting paradox. While large trials demonstrate overall renoprotective effects, the initial hemodynamic changes and volume depletion pose theoretical risks for prerenal AKI, particularly in vulnerable ICU patients. The FDA initially issued a warning about the risk of AKI based on post-marketing reports, which identified 101 cases—58% of which occurred within the first month of treatment.

However, subsequent analyses have largely refuted these concerns. Meta-analyses of randomized trials show a 23–25% reduction in AKI risk with SGLT2 inhibitor use.[50] This discrepancy likely reflects reporting bias in early surveillance and the distinction between transient hemodynamic effects and true tubular injury. The initial decline in eGFR (typically 3–5 mL/min/1.73 m²) represents a functional hemodynamic change, similar to that seen with ACE inhibitors, rather than direct nephrotoxicity.[51]

In critically ill patients, the risk–benefit balance is more complex: those with adequate volume status and stable hemodynamics may derive renoprotective benefits, while hypovolemic or unstable patients may face greater risk. Key factors to assess include baseline volume status and fluid balance, concurrent use of other nephrotoxic medications, the severity of illness with any multi-organ dysfunction, and the patient's ability to maintain adequate enteral or parenteral nutrition.

Infection Risk Considerations

Additional safety concerns in the ICU include genitourinary infections and rare complications. SGLT2 inhibitors increase the risk of genital mycotic infections (2–4 times) and may slightly increase the risk of urinary tract infections due to glucosuria-mediated bacterial growth.[52] In ICU patients with indwelling catheters or immunosuppression, this risk may be amplified. However, large observational studies paradoxically show lower overall infection rates, suggesting that anti-inflammatory benefits may outweigh localized infection risks. This rare but life-threatening necrotizing fasciitis of the perineum (Fournier's gangrene) has been linked to SGLT2 inhibitor use. Although exceedingly rare (1.7 cases per 100,000 person-years), its high mortality (20–30%) warrants awareness in ICU settings.

Risk Mitigation Strategies for SGLT2 Inhibitors in Critically Ill Patients

The safe use of SGLT2 inhibitors in critically ill patients demands a systematic approach to risk assessment, patient selection, and close monitoring. Practical risk mitigation strategies for ICU implementation are summarized in **Table 2** and include careful patient selection by excluding individuals with type 1 diabetes, prior episodes of diabetic ketoacidosis, or severe hepatic dysfunction; comprehensive baseline assessment of volume status, acid–base balance, ketone levels, and electrolytes; and daily monitoring of glucose, ketones, electrolytes, acid–base status, and fluid balance. Maintaining adequate carbohydrate intake (more than 100 g/day) through a structured nutrition protocol, ensuring basal insulin coverage in insulin-dependent patients, and adhering to clear "sick day" rules for temporary discontinuation when necessary are all essential.

Team education, focusing on the early recognition of euglycemic diabetic ketoacidosis and standardized management protocols, further strengthens safety. Because the balance between risks and benefits varies with the clinical context, individualized assessment remains paramount: patients with cardiorenal syndrome and fluid overload may gain net benefit, whereas those with septic shock or significant hypovolemia face higher risk.

Table 2 Risk Mitigation Strategies for SGLT2 Inhibitor Use in the ICU

Risk Factor	Monitoring	Prevention	Management
Euglycemic DKA	• Daily ketone monitoring (in high-risk patients) • Acid–base status every 12–24 h • Anion gap monitoring • Blood glucose every 6 h	• Ensure carbohydrate intake >100 g/day • Maintain basal insulin • Avoid prolonged fasting • Hold SGLT2i for procedures requiring >12 h NPO	• Discontinue SGLT2i immediately • Initiate IV insulin protocol • Administer dextrose 10–20% infusion • Monitor for 24–72 h post-discontinuation
Hemodynamic Instability	• Continuous blood pressure monitoring • Vasopressor requirements every 4 h • Fluid balance assessment • Lactate trends	• Avoid use if norepinephrine requirement >0.1 mcg/kg/min • Ensure adequate intravascular volume • Prefer use in cardiogenic rather than distributive shock	• Optimize intravascular volume • Reassess risk–benefit regularly • Consider discontinuation if vasopressor needs increase >20%
Hypernatremia	• Daily serum sodium • Monitor closely if Na >145 mmol/L • Assess free water deficit	• Ensure adequate free water intake • Monitor if on loop diuretics • Adjust IV fluid composition as needed	• Replace free water as indicated • Consider dose reduction • Discontinue if Na >155 mmol/L
Volume Depletion	• Daily weights • Monitor urine output • Clinical volume assessment • Echocardiography/ hemodynamic monitoring as needed	• Account for increased diuresis (+200–400 mL/day) • Use caution with concurrent diuretics • Monitor closely during CRRT	• Replace fluids as indicated • Reduce diuretic doses if needed • Hold SGLT2i if oliguria develops
Acute Kidney Injury	• Baseline creatinine • Repeat at 1 month • Monitor if increase >30%	• Accept initial eGFR decline up to 30% • Maintain euvolemia • Review concurrent nephrotoxic medications	• Assess volume status • Review for nephrotoxin exposure • Consider holding if AKI progresses
Genitourinary Infections	• Daily perineal assessment • Monitor for UTI symptoms • Obtain urine cultures if indicated	• Provide hygiene education • Implement catheter care protocols • Consider prophylaxis in high-risk patients	• Initiate antifungal or antibiotic therapy as needed • Optimize local care • Discontinue SGLT2i if Fournier's gangrene develops
Drug Interactions	• Review medication list • Monitor for hypoglycemia • Assess for hypotension risk	• Reduce insulin doses by 15–30% if needed • Use caution with diuretics • Monitor closely if using RAAS blockers	• Adjust interacting medications • Increase monitoring frequency • Document significant interactions

DKA, diabetic ketoacidosis; CHO, carbohydrate; NPO, nil per os; IV, intravenous; BP, blood pressure; CRRT, continuous renal replacement therapy; UTI, urinary tract infection; RAS, renin–angiotensin system; PRN, as needed.

Future Directions for SGLT2 Inhibitor Use in Critical Care

The expanding evidence base for SGLT2 inhibitors in critical care highlights promising avenues for research that could reshape the management of acute organ dysfunction. Although current data justify cautious, selective use, substantial knowledge gaps persist. Several pivotal trials are underway that will help clarify optimal use in ICU settings. The PREVENTS-AKI trial (NCT05468203), a landmark multicenter, randomized, placebo-controlled study, is evaluating dapagliflozin for AKI prevention in critically ill patients at high risk.[53] This trial will enroll 1,500 ICU patients, randomized to receive either dapagliflozin 10 mg daily or placebo. The primary endpoint is severe AKI (KDIGO stage 2–3) within 30 days, with key secondary outcomes including mortality, need for renal replacement therapy, and long-term kidney function. Its pragmatic design, broad inclusion criteria, and patient-centered outcomes will provide definitive evidence for routine ICU practice, with results anticipated by 2026.

In addition, several complementary trials are exploring SGLT2 inhibitors in targeted ICU populations. For example, the NCT05360615 trial investigates the initiation of SGLT2 inhibitors after an AKI episode to prevent recurrence and progression to CKD, addressing questions about optimal timing.[54] The RENAL LIFECYCLES trial (NCT05374291) takes an innovative approach by including patients with advanced CKD (eGFR below 25 mL/min/1.73 m²) and those on dialysis with residual urine output—groups historically excluded from prior trials. Its composite endpoint of mortality, kidney failure, and heart failure hospitalization reflects the complex interplay of organ dysfunction in critical illness.[55]

In the perioperative arena, multiple studies are examining whether SGLT2 inhibitors can provide organ protection during high-risk surgery, balancing AKI prevention with the risk of perioperative euglycemic ketoacidosis. These diverse trials, spanning both medical and surgical ICUs and covering septic and non-septic patients, reflect growing interest in the potential of SGLT2 inhibitors to benefit various critical care scenarios.

Although the future of SGLT2 inhibitors in critical care appears promising, it hinges on high-quality evidence to bridge current gaps. As ongoing trials yield results and mechanistic understanding advances, these agents may move from cautious exploration to routine use for preventing and treating acute organ dysfunction. The integration of robust basic science, well-designed clinical trials, and real-world implementation research will ultimately determine whether SGLT2 inhibitors fulfill their promise to improve outcomes for critically ill patients.

Conclusions

SGLT2 inhibitors represent a paradigm shift in nephroprotection, with robust meta-analyses demonstrating a reduction in AKI incidence despite an initial decline in eGFR. This paradoxical benefit challenges conventional assumptions that acute hemodynamic changes are inherently harmful, positioning SGLT2 inhibitors as powerful organ-protective therapies. Successful adoption in critical care will require a systematic approach that encompasses clear patient selection criteria, appropriate timing that favors prevention over treatment, vigilant monitoring, and interdisciplinary collaboration. While significant knowledge gaps remain, the results of ongoing trials—particularly the PREVENTS-AKI study—are expected to provide crucial evidence to guide the safe and effective use of this treatment in the ICU.

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