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Advances in Glucocorticoid Therapy for Acute Pancreatitis: A Review

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Background: Acute pancreatitis (AP) is a prevalent gastrointestinal emergency with a substantial risk of severe complications. Evidence indicates that glucocorticoids (GCs) may attenuate organ failure and reduce mortality in AP through their anti-inflammatory and immunomodulatory properties. However, the therapeutic application of GCs in AP remains contentious due to potential adverse effects, such as heightened infection risk and exacerbation of pancreatic injury.

Objective: This review evaluates recent developments in GC therapy for AP, with an emphasis on their mechanisms of action, therapeutic efficacy, and associated risks.

Methods: A review investigates the role of GCs in AP pathophysiology, their impact on inflammatory markers, organ function, survival outcomes, and the ongoing controversies regarding their clinical efficacy and safety.

Results: Current evidence suggests that GCs may attenuate inflammation and enhance survival in animal models and select clinical studies on AP. Yet, findings regarding their impact on disease progression and patient outcomes remain inconclusive. In addition, combination therapies incorporating GCs may be most effective within a multimodal therapeutic approach.

Conclusion: GCs exhibit potential in the management of AP by modulating inflammatory pathways and immune responses. Their use necessitates thorough risk assessment. Large-scale clinical trials are essential to establish standardized protocols, optimal dosing regimens, and patient selection criteria for GCs therapy in AP.

Key Words: glucocorticoids (GCs), acute pancreatitis (AP), inflammation, immunoregulation, therapeutics

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Acute pancreatitis (AP) is a prevalent gastrointestinal emergency with an incidence ranging from 3.4 to 73.4 cases per 100,000 individuals, exhibiting an annual growth rate of 2%–5%.[1] Approximately 20% of cases progress to severe acute pancreatitis (SAP), which is characterized by systemic inflammatory response syndrome (SIRS) and multiple organ dysfunction syndrome (MODS), with a mortality rate of 20%–40%.[2,3] SAP represents a critical clinical challenge due to its high mortality and the complexity of its pathophysiology, which involves uncontrolled inflammation driving pancreatic damage and multiorgan failure.

Recent research indicates that glucocorticoids (GCs) may mitigate organ failure and reduce mortality in SAP by inhibiting the NF-κB signaling pathway, thereby suppressing pro-inflammatory cytokine release and modulating the cytokine storm through the downregulation of T-cell activation.[4,5] These mechanisms suggest that GCs may provide significant immunomodulatory and anti-inflammatory effects in the management of SAP. Figure 1 proposed mechanism of action of GCs in AP. GCs exert their anti-inflammatory effects primarily by binding to the glucocorticoid receptor (GR), leading to the inhibition of NF-κB activation. This prevents the aberrant release of pancreatic enzymes (like trypsinogen to trypsin) and reduces the secretion of key pro-inflammatory cytokines (TNF-α, IL-1β, and potentially IL-6) from pancreatic acinar cells and immune cells such as neutrophils. GCs also directly modulate neutrophil function, reducing NF-κB-dependent inflammatory mediator secretion. This cascade of events helps dampen the SIRS and potentially mitigates organ damage. The therapeutic application of GCs in AP remains contentious due to their potential to induce drug-associated pancreatitis and exacerbate pancreatic injury, necessitating meticulous risk assessment.[6] Furthermore, their immunosuppressive properties heighten the risk of secondary infections, particularly in SAP patients who are predisposed to infection due to immune compromise and intestinal barrier dysfunction.

The pathophysiology of AP is multifactorial, beginning with pancreatic injury—triggered by gallstone obstruction, chronic alcohol consumption, or hyperlipidemia[7]—which leads to premature activation of pancreatic enzymes, particularly the conversion of trypsinogen to trypsin, stimulating other digestive enzymes such as phospholipase A2 and elastase,[8] initiating pancreatic autodigestion, acinar cell necrosis, and a local inflammatory response.[9,10] This injury provokes a robust inflammatory cascade characterized by the release of pro-inflammatory cytokines (TNF-α, IL-1β, IL-6, IL-8),[11] activating macrophages and neutrophils, increasing microvascular permeability, and exacerbating pancreatic edema, ischemia, and necrosis. As inflammation escalates, it progresses to SIRS, marked by a cytokine storm that induces endothelial activation, capillary leak syndrome, hypovolemic shock, and organ ischemia,[12] further amplified by complement system activation and reactive oxygen species (ROS)-mediated damage.[13] Uncontrolled SIRS can lead to MODS, affecting the lungs (ARDS), kidneys (AKI), and liver.[14] To counterbalance

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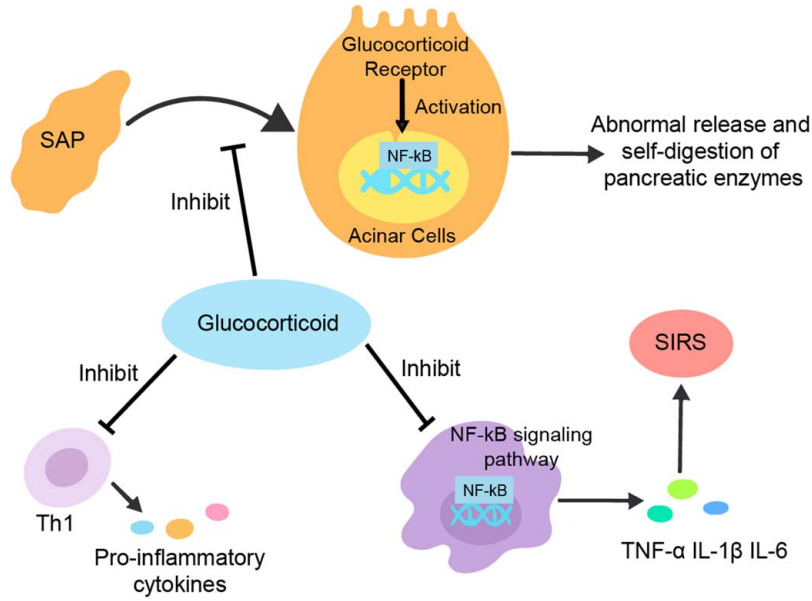

FIGURE 1. Mechanism of glucocorticoid action in acute pancreatitis: inhibition of NF-κB activation and cytokine storm modulation.

SIRS, compensatory anti-inflammatory response syndrome (CARS) may occur, but excessive immunosuppression[15] increases susceptibility to secondary infections, particularly infected pancreatic necrosis due to intestinal barrier disruption and bacterial translocation,[16,17] worsening sepsis and organ failure. Thus, dysregulated inflammation, driven by a cytokine storm, is central to AP progression, necessitating timely intervention to prevent systemic complications and improve outcomes.

In light of these concerns, further exploration of the mechanisms, efficacy, and safety of GCs in the treatment of AP is warranted. This review seeks to synthesize recent advancements in GCs research, evaluating their therapeutic potential and associated challenges to guide more effective treatment strategies for AP management.

THE EFFECTS OF GLUCOCORTICOIDS THERAPY IN ACUTE PANCREATITIS

AP is a multifaceted disease frequently associated with SIRS, MODS, and secondary infections, all of which significantly exacerbate clinical outcomes. By modulating critical inflammatory pathways, GCs may attenuate the systemic complications of AP.

Suppressing Systemic Inflammation/Cytokine Storm, Restoring Immune Balance, and Modulating Systemic Inflammatory Response Syndrome

The primary pathologic mechanism in SAP involves the progression of localized pancreatic inflammation into a systemic pro-inflammatory response, ultimately resulting in multiple organ failure. Pancreatic injury induces the release of pro-inflammatory cytokines, including TNF-α, IL-1β, IL-6, and IL-8, which disseminate through the bloodstream, triggering SIRS. If not effectively controlled, this cytokine storm can progress to MODS, significantly increasing the risk of mortality. GCs have potent anti-inflammatory and immunomodulatory to treat AP.[18]

Animal studies indicate that GCs exert a beneficial influence on inflammatory markers in AP. One study demonstrated that GCs inhibit transcription factors such as NF-κB, thereby suppressing cytokine release and preventing the dissemination of inflammation: 90 SAP rats were randomly divided into a model control group and a DXM-treated group. The rats of treated group were injected with DXM injection through the vena caudalis, 0.5 mg/100 g body weight and single administration 15 minutes after successful preparation of the SAP model while the rats of control group were injected with saline of the same volume after the sham-operation. The content of NF-κB protein lower in the treated group than those in the model control group.[19] Furthermore, another study, the rats (n = 178) allocated to different groups: in group 1, AP induced by retrograde administration of Na-taurocholate into the pancreatic duct (group AP), in groups 2, 3, and 4, the rats given 4 mg/kg body weight (BW) dexamethasone (DEX; group APD), or 20 mg/kg BW hydrocortisone (HYD; group APH), or 5 mg/kg BW RU (group APRU) subcutaneously just before the induction of AP. RU incorporated into multilamellar phospholipid liposomes prepared from phosphatidylcholine and cholesterol, plasma amylase and IL-6 levels were significantly reduced in the DEX (APD) and HYD (APH) treatment groups compared with the untreated AP group. In contrast, administration of the GC antagonist RU-38486 (APRU) intensified the inflammatory response, as evidenced by elevated IL-6 levels.[20] These researches that GCs effectively modulate inflammatory markers and attenuate pancreatic injury in AP, particularly when used in conjunction with other therapeutic agents.

A retrospective single-center cohort study employed propensity score matching, which conducted with the 1: 1 nearest neighbor matching method and the covariates included sex, age, BMI, TGs, APACHE II scores, and SOFA. There are 59 patients from GCs group and NGCs group. In GCs group, the duration of GCs used was 1–6 days, and doses of prednisone or the equivalent doses of other glucocorticoids are usually <80 mg/d. The study

demonstrated that C-reactive protein (CRP) and TNF-α levels were significantly reduced in the GCs group compared with the non-GCs group after 7 days of hospitalization.[21] This decrease in inflammatory markers indicates that GCs therapy may exert beneficial anti-inflammatory effects in patients with AP, further supporting its potential therapeutic role in managing inflammation.

The pathophysiology of SAP is characterized by excessive pro-inflammatory responses and immune dysregulation, leading to tissue injury. GCs exert potent immunomodulatory effects, regulating immune activity and preventing inflammatory imbalance. Specifically, GCs inhibit T-cell activation and proliferation, suppress the Th1-mediated immune response, and reduce the secretion of pro-inflammatory cytokines, thereby alleviating local pancreatic inflammation and limiting its systemic dissemination.[4,22]

Furthermore, GCs play a crucial role in restoring immune homeostasis during the immune phases of SIRS and CARS. By balancing these opposing responses, GCs help prevent both immunosuppression and hyperinflammation, which is critical for avoiding extreme immune dysregulation in SAP patients.[23]

GCs alleviate excessive inflammatory activity to mitigate SIRS in AP. Endotoxemia can cause SIRS. GCs, through their GR, produce suppression of TNF in a GR monomer-dependent way in macrophages and inhibit TNFR1-induced ISG gene expression and necroptotic cell death mediators in IECs in a GR dimer-dependent way.[24] The expression of the GR is correlated with poor outcome from septic shock and downregulate GR signaling genes may cause worse outcome.[25]

Managing Infection, Sepsis, and Microvascular Dysregulation

Glucocorticoids demonstrate significant therapeutic potential in SAP through their multifaceted effects on infection control, sepsis management, and microcirculatory improvement. Secondary infection, particularly infected pancreatic necrosis, represents a critical complication of SAP that frequently progresses to sepsis, septic shock, and elevated mortality. Current evidence indicates GCs improve clinical outcomes in sepsis and severe infections through several key mechanisms.[26–28] These agents modulate the inflammatory response by mitigating excessive inflammatory activity while simultaneously correcting immunosuppression, thereby enhancing host defense capacity against infection and attenuating cytokine storm severity, which collectively improves patient survival. Furthermore, GCs exhibit important anti-shock properties by increasing vascular responsiveness to vasopressors, stabilizing endothelial integrity, and reducing capillary permeability, all of which contribute to hemodynamic stabilization in septic shock. Clinical studies confirm that GCs significantly reduce ICU stays and mortality in sepsis and septic shock patients, primarily through their anti-inflammatory effects, microcirculatory improvement, and hemodynamic stabilization.[27] In the specific context of SAP, GCs demonstrate substantial therapeutic value by controlling excessive inflammation, regulating cytokine storms, and helping manage secondary infections.

The beneficial effects of GCs extend to addressing microcirculatory dysfunction, a critical pathologic feature of SAP and sepsis that contributes to multiple organ failure development. Increased microvascular permeability in SAP leads to tissue edema, hypovolemic shock, and exacerbation of pancreatic necrosis and distant organ damage. Experimental studies provide compelling evidence for these protective effects. In a rat SAP model, intraperitoneal dexamethasone (1 mg/kg) administered 3 hours post-SAP induction markedly attenuated pathologic changes in lungs and pancreas, reducing edema, hemorrhage, and inflammation while decreasing the lung wet/dry weight ratio and increasing hepatic ATP levels.[29] Another study demonstrated that intravenous DEX administered 15 minutes post-SAP induction attenuated multiorgan damage, showing protective effects on pancreatic, pulmonary, hepatic, and renal function. This was evidenced by reduced serum amylase and creatinine levels, suppressed Bax and NF-κB expression (limiting apoptosis and inflammation), and decreased ICAM-1 expression in lungs that reduced inflammatory cell infiltration.[30] Additional research in a murine SAP model showed that DEX (2.5 mg/kg) preserved renal microvascular endothelial glycocalyx integrity, enhanced renal perfusion, minimized glycocalyx degradation, and inhibited TNF-α expression.[31] These findings collectively demonstrate that DEX provides comprehensive multiorgan protection in SAP. The mechanisms involve vascular endothelial stabilization through reduced permeability and prevention of fluid extravasation,[30,31] leading to improved tissue perfusion and oxygenation. By enhancing microcirculatory function, particularly in necrotic pancreatic regions and vital organs, GCs effectively mitigate the risk of progressive organ failure in SAP.

Preventing Fibrosis and Promoting Pancreatic Function Recovery

Excessive fibrosis during the recovery phase of SAP can impair the restoration of pancreatic and other organ functions.[30] GCs suppress fibroblast proliferation and collagen synthesis, thereby mitigating pancreatic fibrosis and maintaining structural integrity.[32] This facilitates functional recovery and enhances long-term patient prognosis.

Clinical Outcomes and Supporting Evidence

GCs have demonstrated potential in improving survival, organ function, and symptom management in AP, particularly in severe cases. Preclinical studies in rat models of AP showed that GC intervention significantly enhanced survival rates, with dexamethasone and hydrocortisone achieving 58% and 75% survival, respectively, compared with 33% in untreated controls. Median survival times also increased from 10 hours (untreated) to 17–19 hours (GC-treated).[20] A meta-analysis of rodent models further supported these findings, revealing a 65% reduction in mortality risk [RR = 0.35 (0.21, 0.59)] across various dosing regimens without heterogeneity.[18]

Clinical studies corroborate these benefits. A propensity score-matched analysis found that GC therapy reduced organ failure, multiple organ dysfunction, and mortality compared with non-GCs treatments.[21] In a randomized trial of 81 patients with SAP and SIRS, adjunctive dexamethasone (1 mg/kg, 3 times daily for 3 d) reduced the incidence of acute respiratory distress syndrome (ARDS) and shortened hospitalization, though it did not significantly affect survival rates.[33] Meta-analyses suggest that corticosteroids may lower mortality, reduce hospitalization duration, and decrease the need for surgical intervention in SAP, though their impact on complication rates and APACHE II scores remains insignificant.[34]

Beyond survival and organ protection, GCs also alleviate symptoms and accelerate biochemical recovery. In a study of 106 patients with diabetic ketoacidosis (DKA) complicated by AP, dexamethasone (5 mg/d for 7 d) significantly improved clinical manifestations such as abdominal pain, nausea, and hypotension compared with placebo. Moreover, it promoted faster normalization of serum amylase and triglyceride levels.[35]

While current evidence highlights the potential of GCs to improve critical outcomes in AP—including survival, organ function, and symptom relief—inconsistencies in mortality effects and complication rates underscore the need for further investigation. Large-scale, rigorously designed randomized controlled trials are essential to clarify the role of GCs in AP management and optimize their therapeutic application.

GC's therapy in AP demonstrates efficacy due to its potent anti-inflammatory, immunomodulatory, anti-shock, and antimicrobial properties. GCs mitigate the cytokine storm, stabilize the vascular endothelium, enhance microcirculation, and modulate immune responses, thereby reducing the risk of sepsis and multiple organ failure, ultimately improving patient outcomes. A summary of these studies can be seen in Table 1. To further quantify the clinical impact of GC therapy (Table 2), we present data from a propensity score-matched analysis by Wang et al[21] comparing outcomes in patients treated with GCs versus those who were not (NGCs). This analysis demonstrated a statistically significant reduction in organ failure (P = 0.041) and overall mortality (P = 0.113, trend towards benefit), along with significant reductions in hospital length of stay (P = 0.047) and associated costs (P = 0.002). However, the difference in mortality did not reach statistical significance (P = 0.113).

THERAPEUTIC CHALLENGES OF GLUCOCORTICOIDS IN ACUTE PANCREATITIS MANAGEMENT

Efficacy and Prognostic Controversies

The therapeutic application of GCs in AP presents a complex landscape of potential benefits and unresolved controversies. Current evidence reveals significant discrepancies in research findings regarding treatment efficacy. While multiple studies demonstrate GCs' ability to improve inflammatory markers, organ function, and survival rates in both animal models and selected clinical trials, contradictory outcomes persist. Notably, in systemic lupus erythematosus (SLE)-associated AP, GCs have paradoxically exacerbated pancreatic injury, particularly at higher dosages, with steroid-exposed patients showing significantly greater pancreatic inflammation (33% vs 5%).[36] Furthermore, while some outcomes favor GC-treated groups, these cohorts often present with more severe baseline conditions, as evidenced by higher rates of multiple organ failure before treatment.[21]

The variability in therapeutic response stems from AP's intricate pathophysiology, involving pancreatic enzyme activation, inflammatory mediator release, microcirculatory impairment, and apoptotic processes. GCs exert complex immunomodulatory effects that vary significantly among individuals, potentially explaining their inconsistent performance. While effective in suppressing specific inflammatory pathways in some patients, GCs may inadvertently activate other detrimental cytokine cascades.[6,37]

Prognostic outcomes following GC therapy remain equally contentious. Although some studies report benefits from high-dose or pulse GC regimens,[38] retrospective analyses reveal persistently high mortality rates among treated patients that sometimes equal or exceed those in control groups.[21] This prognostic uncertainty is particularly evident in SLE-related AP, where existing data remain insufficient for definitive conclusions.[36] Multiple confounding factors complicate prognostic assessments, including underlying comorbidities, immune status, and disease activity in SLE patients receiving chronic GCs therapy. Critically, critical treatment variables such as dosage and timing significantly influence outcomes. Animal studies suggest prophylactic GCs administration more effectively reduces ascites and improves histopathology compared with therapeutic intervention,[18] highlighting the importance of precision in treatment protocols.

These collective findings underscore the dual nature of GC therapy in AP management - while holding genuine therapeutic potential, their application requires careful consideration of individual patient characteristics, disease etiology, and optimal dosing parameters. The current evidence base supports neither universal adoption nor outright rejection of GCs in AP, but rather emphasizes the need for more sophisticated patient stratification and standardized treatment protocols in future research.

Standardization and Safety

The clinical application of GCs in AP faces significant challenges regarding treatment standardization and safety profiles. Current research reveals substantial heterogeneity in dosing regimens across both preclinical and clinical studies. Animal investigations have employed varying dexamethasone dosages, administration routes, and treatment timelines,[18] while human studies of SLE-associated AP have utilized everything from standard to high-dose pulse regimens.[36] This lack of consensus in treatment protocols creates substantial barriers for comparative effectiveness research and clinical decision-making.

The safety profile of GCs in AP patients raises important clinical considerations. Extended GC administration carries well-documented risks including increased infection susceptibility, hyperglycemia, gastrointestinal complications, and bone metabolism alterations. These concerns are particularly relevant in AP patients, where GCs may exacerbate existing immune dysfunction. Clinical data demonstrate significantly higher infection rates among GC-treated AP patients compared with controls.[35] The hyperglycemic effects of GCs warrant special attention, as elevated blood glucose levels may correlate with extrapancreatic infections in this patient population.[39]

Dosing optimization presents a critical challenge in GC therapy for AP. While some studies associate high-dose regimens with pancreatic injury,[36,40] others suggest that insufficient dosing may compromise therapeutic efficacy.[18] These findings highlight the delicate balance required in clinical practice—achieving sufficient anti-inflammatory effects while minimizing adverse outcomes. The current evidence underscores the urgent need for standardized treatment protocols that account for disease severity, comorbidities, and individual risk factors.

TABLE 1. Main Result of GCs Therapy in AP

Study	Animals/humans	Years of publication	Experimental group	Main result
Jingmin et al[19]	Male Sprague–Dawley (SD) rats	2012	The rats were injected with DXM injection through the vena caudalis, 0.5 mg/100 g	The content of NF-κB protein lower in the treated group than those in the model control group
Paszt et al[20]	Male outbred Wistar rats	2004	The rats given 4 mg/kg BW DEX, or 20 mg/kg BW HYD	1. IL-6 levels were significantly reduced in the APD and APH treatment 2. The survival rate of APD reached 58%, and the APH reached 75% while the untreated group was 33%
Wang et al[21]	AP patients	2021	The duration of GCs used was 1–6 d and doses of prednisone or the equivalent doses of other glucocorticoids are usually < 80 mg/d	1. TNF-α levels were significantly reduced in the GCs group compared with the non-GCs group 2. GCs therapy reduced the incidence of organ failure, multiple organ failure, and mortality rates compared with non-GCs treatment
Zhang et al[35]	Patients with DKA complicated by AP	2023	Patients treated with DEX(5 mg) once per day, for consecutive 7 d	Compared with the placebo group, patients treated with DEX exhibited improvement in clinical manifestations, including abdominal pain, nausea, and hypotension
Cui et al[29]	Male Sprague-Dawley (SD) rats	2017	Rats intraperitoneally injected with a single dose of DEX (1 mg/kg bodyweight)	DEX attenuated pathologic alterations in the lungs and pancreas, mitigating edema, hemorrhage, inflammation, and reduced tissue edema in both organs, lowered the lung wet/dry weight ratio, and increased hepatic ATP levels
Ou et al[30]	Male Sprague-Dawley (SD) rats	2012	The rats injected DEX through the femoral vein	DEX downregulated NF-κB expression and ICAM-1 protein expression in the lungs
Yu et al[31]	Male C57BL/6 mice	2019	The mice were treated with DEX (2.5 mg/kg)	DEX preserve the integrity of the renal microvascular endothelial glycocalyx, enhancing renal perfusion, minimizing glycocalyx degradation, and inhibiting TNF-α expression
Wan et al[33]	SAP patients	2011	Patients were injected DEX intravenously at a dosage of 1 mg/kg body weight 3 times a day for 3 d	DEX decreased the risk of ARDS and shortened hospitalization durations in patients with SAP complicated by SIRS, although it did not substantially impact survival rates

TABLE 2. Clinical Outcomes Data

Clinical outcomes	Variable	NGC group (n = 59)	GC group (n = 59)	Total number of cases (n)	Total rate (n); %	*P*
Primary outcomes	Mortality, n (%)	8 (13.6)	3 (5.1)	11	9.3	0.113
	Organ failure, n (%)	31 (52.5)	20 (40.7)*	51	43.2	0.041*
	Duration <48 h, n (%)	12 (38.7)	10 (50.0)	22	18.6	0.636
	Duration ≥48 h, n (%)	19 (61.3)	10 (50.0)	29	24.6	0.054
	Single organs involved, n (%)	10 (32.3)	13 (65.0)	23	19.5	0.486
	Multiple organs involved, n (%)	21 (67.7)	7 (35.0)	28	23.7	0.002*
	ICU LOS, d	3.4 ± 2.2	3.0 ± 1.8	6.4 ± 2.8	5.4 ± 2.4	0.067
	Hospital LOS, d	16.3 ± 7.7	12.9 ± 5.5	29.2 ± 9.5	24.7 ± 8	0.047*
	Hospital costs, CNY	32,421.7 ± 2813.3	25,348.4 ± 2512.6	5770.1 ± 3772.0	—	0.002*
Secondary outcomes	SAP, n (%)	33 (55.9)	23 (39.0)	56	47.4	0.065
	APD intervention, n (%)	17 (28.8)	11 (18.6)	28	23.7	0.194
	PCD intervention, n (%)	13 (22.0)	8 (13.6)	21	17.8	0.229
	Minimally invasive, n (%)	7 (11.9)	4 (6.8)	11	9.3	0.342
	Open surgery, n (%)	3 (5.1)	2 (3.4)	5	4.2	0.648
	Antibiotic usage, n (%)	29 (49.2)	28 (47.5)	57	48.3	0.854
Exploratory data	Pain duration, d	2.9 ± 1.3	2.5 ± 1.1	5.4 ± 1.7	4.6 ± 1.4	0.247
	NPO duration, d	3.3 ± 2.1	2.9 ± 1.1	6.2 ± 2.4	5.3 ± 2	0.142
	Infection, n (%)	18 (30.5)	19 (32.2)	37	31.4	0.843
	Peripancreatic necrosis infection, n (%)	15 (25.4)	9 (15.3)	24	20.3	0.170
	Gastrointestinal bleeding, n (%)	1 (1.7)	1 (1.7)	2	1.7	1.000

Glucocorticoid regimen: Prednisone/dexamethasone/hydrocortisone; dosage: ≤80 mg/d (prednisone-equivalent dose); treatment duration: 1–6 days (individually adjusted).

*Significant difference.

APD indicates abdominal paracentesis drainage; LOS, length of stay; NPO, nil per os; PCD, percutaneous catheter drainage.

Clinical decision-making must carefully weigh the potential benefits of GCs against their substantial risks, particularly in critically ill or immunocompromised patients. The development of evidence-based guidelines for GCs use in AP should be prioritized to optimize patient outcomes while minimizing treatment-related complications. Future research should focus on identifying patient subgroups most likely to benefit from GC therapy and establishing dosing parameters that maximize efficacy while mitigating adverse effects.

DISCUSSION

Determinants of Efficacy

The therapeutic efficacy of GCs in AP is influenced by several key factors, including the type and severity of the disease, as well as the timing of intervention.

Firstly, the subtype and etiology of AP appear to impact GCs responsiveness. Studies examining cortisol and corticosteroid-binding globulin (CBG) levels have shown significant variability between patients with necrotizing pancreatitis (often gallstone-related) and those with edematous pancreatitis from the disease onset through day 5 post-onset. Peak cortisol levels were lower in alcohol-induced necrotizing pancreatitis compared with gallstone-induced cases. These variations suggest that the specific characteristics of the pancreatitis type may influence endogenous cortisol levels and the binding capacity of GCs, potentially affecting the therapeutic response.[41] Furthermore, the severity of the disease plays a crucial role. While GC therapy shows potential benefits, particularly in SAP, by potentially enhancing inflammatory profiles, supporting organ function, and improving survival,[42] its application in moderately SAP may be less justified due to the likely restricted therapeutic efficacy and associated risks. The elevated severity of SAP also correlates with a higher potential for adverse outcomes, such as pancreatic injury.[36]

Secondly, the timing of GC administration is a critical determinant of therapeutic success. Animal studies, particularly in rat models, indicate that initiating GC therapy too late can be detrimental. Delayed administration (eg, 4 h after AP induction) was associated with worsened outcomes, suggesting it may exacerbate disease progression. Conversely, early administration (1 h before AP induction and/or 4 h after induction) demonstrated moderate protective effects.[43] Combination therapies showed enhanced efficacy, underscoring the importance of coordinated treatment timing and synergy. Clinical research findings support the importance of early administration. Studies suggest that initiating low-dose HYD early and for a limited duration can mitigate SIRS and attenuate necrosis progression in AP.[41] In contrast, delayed GC administration has been linked to increased pancreatic fibrosis and necrosis, potentially elevating mortality.[41] Therefore, meticulous optimization of the timing for GC therapy, tailored to the patient's specific clinical presentation and disease phase, is essential for maximizing potential benefits and minimizing risks.

Combination With Other Medications

Combining GCs with adjunctive agents may enhance therapeutic efficacy in AP. For instance, in a study, there are 10 rats in 6 groups: a sham operation (SO) group, an SAP

group, a low, medium, and high dose QYKL group, and a medium dose QYKL combined with the Dex group. The SAP model was injecting 5% sodium taurocholate into the bile pancreatic duct. The SO group received an equivalent dosage of saline. The QYKL treatment group received intragastric administration of QYKL at low, medium, and high doses of 5, 10, and 15 g crude drug/kg, respectively, at 2 and 12 hours after modeling. The DEX treatment group received intravenous administration of DEX (10 mg/kg) at 2 and 12 hours after modeling. And it suggests the coadministration of Qingyi granules (QYKL) and DEX has demonstrated benefits in managing AP-associated ARDS by reducing serum amylase, IL-1β, IL-6, and TNF-α levels and improving both pancreatic and pulmonary integrity, decreasing pulmonary edema, and optimizing respiratory function and comparing to QYKL treatment group, the effect is more effective when QYKL treatment combined treatment with DEX.[44] Likewise, the combination of DEX with dextran-40 targets 2 critical mechanisms in AP pathogenesis: inflammation and microcirculation. In an observational study, AP patients, with 0.5–1.0 mg/kg of DEX, were administered daily for 3–5 days, and 500–1 000 mL of dextran 40 was daily administered for 7 days, experienced expedited symptom alleviation, including reductions in abdominal pain and tenderness within 4–8 hours, contributing to improved comfort and quality of life. Among 32 patients, 27 recovered without surgical intervention, resulting in an 84.4% cure rate. The observed mortality rate was 12.5%, significantly lower than the 40% reported in existing literature, indicating a potential mortality benefit.[38] These findings show that GC-based combination therapies may be a promising approach to improving clinical outcomes and reducing mortality in patients with AP.

Future Directions

The use of GCs in the treatment of AP remains controversial, with concerns regarding potential risks and inconsistent efficacy observed in current clinical studies. These limitations necessitate further research to clarify the precise role and benefits of GC therapy. Most existing clinical investigations are characterized by small sample sizes, retrospective designs, or observational studies, which are prone to bias and inadequate for establishing standardized treatment guidelines.[33,38,45] Therefore, there is a pressing need for large-scale, randomized controlled trials (RCTs) to rigorously evaluate the efficacy and safety profile of GCs in AP. Such trials should systematically assess various factors, including optimal dosing regimens, timing of administration, and response across different patient subgroups, to generate high-quality evidence that can guide clinical decision-making.

Beyond clinical evaluation, a deeper understanding of the underlying molecular mechanisms of GCs in AP is crucial. While certain anti-inflammatory pathways involved with GCs have been identified, the precise signaling cascades and cellular interactions remain incompletely defined. Future studies should focus on elucidating how GCs influence pancreatic cell apoptosis, autophagy, and immune regulation, potentially through modulation of adrenal cortex activity or other endocrine functions, thereby improving patient outcomes.

Furthermore, with the advancement of precision medicine, personalized therapy is becoming increasingly important in AP management. Research efforts should prioritize the discovery of predictive biomarkers for GC therapy response and safety. By analyzing inflammatory mediators, hormonal profiles, or genetic expression patterns, clinicians could potentially identify patient populations most likely to benefit from GC treatment, thereby optimizing therapy and minimizing exposure in individuals at higher risk of adverse effects.

CONCLUSIONS

The role of GCs in the management of AP is complex and remains a subject of debate. While certain studies indicate potential benefits in modulating inflammatory markers, enhancing organ function, and improving survival rates, significant challenges persist, including uncertain therapeutic efficacy, ambiguous impacts on disease prognosis, and the lack of standardized dosing protocols. Importantly, factors such as disease subtype, severity, timing of administration, and concurrent therapies may further modulate GCs effectiveness. Rigorous research, particularly through prospective clinical trials, is essential to elucidate GCs mechanisms in AP, refine dosing strategies and individualized regimens, and investigate combination therapies to advance AP treatment approaches.

Recommendations for Clinical Practice

While the mechanisms of action and clinical benefits of GCs in AP treatment have been preliminarily elucidated, their clinical application still faces challenges. Based on comprehensive evaluation of current evidence, particularly observed therapeutic effects and potential risks from both animal models and clinical studies, we propose the following specific recommendations to guide clinical practice:

- Target population: GC therapy is primarily indicated for SAP, especially in patients complicated with SIRS or at high risk of MODS. Routine use of GCs is not recommended for mild acute pancreatitis (MAP) as the potential risks (including increased infection rate and glucose metabolism abnormalities) may outweigh the benefits.
- Drug selection: The preferred agents are DEX or HYD administered through intravenous or intramuscular routes. Although prednisone has rapid oral absorption, it is generally not recommended as first-line therapy during acute phase due to its higher risk of affecting glucose metabolism.
- Recommended dosage: Lower dose regimens ($\leq$80 mg/d prednisone equivalent) are recommended. Typical dosing includes: hydrocortisone: 1–2 mg/kg/d, dexamethasone: 0.5–1 mg/kg/d.
- Timing of administration: Early intervention is crucial. Ideally, GC therapy should be initiated as soon as possible after diagnosis, preferably within 1–4 hours of disease onset, to maximize its potential in suppressing the early inflammatory cascade.
- Treatment duration: The treatment course typically lasts 1–6 days and generally should not exceed 7 days. Unnecessarily prolonged use should be avoided to minimize side effects.

Drawing from sepsis protocols, where GCs are reserved for high-risk patients with persistent shock, SAP management should similarly prioritize GCs for cases with overt SIRS or MODS. However, SAP-specific trials are needed to refine dosing, as burn studies indicate that prolonged GC use ($>$7 d) increases infection risks without survival benefits.

These recommendations aim to balance the potential therapeutic benefits and risks of GC treatment. As high-quality large-scale randomized controlled trials are still ongoing, these guidelines should be considered as evidence-based provisional recommendations. Final treatment decisions should be made through comprehensive evaluation of individual patient characteristics, disease severity, comorbidities, and potential GC-related risks (such as infection risk). Future research should focus on optimizing dosing regimens, administration routes, exploring predictive biomarkers, and further validating best practice protocols.

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