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Research Progress on Step-Wise Therapy of Urosepsis

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Abstract

Urosepsis is a life-threatening condition: organ dysfunction arises when the host response to a urinary-tract infection becomes dysregulated. It still causes substantial illness and death worldwide, particularly in older patients and those with multiple comorbidities. Conventional empirical antibiotics and supportive care run into clear practical limits in complicated cases and as antimicrobial resistance rises. Step-wise therapy has gradually become the main management approach for urosepsis. It brings together anti-infective treatment, comprehensive organ support and timely surgical source control, and adjusts intervention intensity dynamically according to disease severity, physiological status and real-time clinical response. This review covers the etiology, immunopathogenesis, current diagnostic criteria and risk stratification of urosepsis. It then discusses, component by component, therapeutic indications, practical efficacy metrics and targeted complication-prevention strategies under step-wise management. The aim is to consolidate existing clinical evidence, give front-line urologists and intensive-care clinicians a standardized decision-making reference, and ultimately improve long-term survival and quality of life for affected patients.

Keywords

Urosepsis, Step-Wise Therapy, Antimicrobial Therapy, Supportive Care, Surgical Source Control, Risk Stratification

1. Introduction

Urosepsis starts from an ascending or obstructive urinary tract infection and can deteriorate with alarming speed. Its progression is shaped jointly by bacterial virulence, anatomical urinary abnormalities, host comorbidities and the magnitude

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of endogenous immune activation [1]. The clinical spectrum is wide: some patients have uncomplicated urinary infection without organ dysfunction, while others develop refractory septic shock with multiple-organ dysfunction. Early recognition and appropriate early intervention remain the cornerstones for reducing preventable deaths [2].

Over the past decade, minimally invasive endourological procedures have become widespread, and they have introduced new clinical challenges. Percutaneous nephrolithotomy, flexible ureteroscopy and ureteroscopic lithotripsy are routinely used for urinary stone disease. Yet preoperative asymptomatic bacteriuria, elevated pelvic pressure during operation, prolonged operative time and oversized access tracts are well-documented independent risk factors for postoperative urosepsis [3]. Severe infectious complications cannot be completely eliminated even with modern perioperative antibiotic prophylaxis [4].

Source control combined with prompt antimicrobial initiation is the fundamental therapeutic principle for urosepsis [5]. In this context, multiple circulating biomarkers have been investigated to support early warning and prognostic judgment. Procalcitonin (PCT), C-reactive protein (CRP), neutrophil-to-lymphocyte ratio (NLR) and some derived composite ratios show complementary diagnostic value. They help clinicians distinguish simple urinary infection from evolving sepsis and monitor treatment response [6] [7]. Clinical trajectories vary highly between individual patients, so rigid one-size-fits-all protocols are discouraged; individualized step-wise management has gained increasing consensus. This review focuses on the practical framework, latest advances and existing challenges of step-wise therapy for urosepsis.

2. Main Text

2.1. Etiology and Pathogenesis

2.1.1. Pathogens and Routes of Infection

Gram-negative enteric organisms dominate the pathogen spectrum of urosepsis. *Escherichia coli* remains the most frequently isolated pathogen, followed by *Klebsiella pneumoniae* and *Proteus mirabilis* [8]. Gram-positive isolates such as enterococci and fungal pathogens, primarily Candida albicans, are encountered more often in immunocompromised populations: patients receiving long-term immunosuppressive agents, transplant recipients, and those with repeated prior antibiotic exposure. Fungal infection accounts for approximately 5% - 6% of total urosepsis episodes [9].

Most infectious episodes stem from ascending upper-urinary-tract infection or obstructive pyelonephritis. Urinary tract obstruction induced by nephrolithiasis, urothelial malignancy or urethral stricture produces urinary stasis and provides a favorable microenvironment for bacterial replication [2]. Invasive urological interventions, including ureteral stent placement and intracorporeal lithotripsy, disrupt natural urinary mucosal defense barriers and substantially elevate the risk of bacterial translocation into the bloodstream [4]. Systemic comorbidities such as

poorly controlled diabetes mellitus and chronic kidney disease impair local and systemic immune defense; they serve as independent clinical risk factors for urosepsis [10] [11].

2.1.2. Immune Imbalance and Systemic Inflammatory Injury

Bacterial components, especially lipopolysaccharide endotoxin, activate pattern-recognition receptors on innate immune cells. This drives robust release of pro-inflammatory mediators including TNF-*a*, IL-1 and IL-6, which further propagate a dysregulated systemic inflammatory response [12]. Moderate inflammatory activation is a necessary host defense against invading pathogens. Exaggerated and uncontrolled inflammatory cascades, however, inflict endothelial injury, microcirculatory disturbance and impaired tissue oxygen delivery, eventually progressing to multiple-organ dysfunction syndrome (MODS) [1]. Advanced age, uncontrolled diabetes or inherent immune deficiency are associated with significantly higher MODS incidence and mortality [10]. Persistent unresolved urinary obstruction keeps amplifying inflammatory signals and accelerates irreversible damage to target organs. In the late stage of sepsis, immune paralysis may occur, making patients more susceptible to secondary opportunistic infection [5].

2.1.3. High-Risk Factors

Well-established risk factors for urosepsis include mechanical urinary obstruction, diabetes mellitus, iatrogenic immunosuppression and chronic kidney disease [11]. Complex staghorn calculi and common endourological manipulations are major triggers for nosocomial or post-procedural urosepsis [13]. Previous clinical studies report that the overall incidence of urosepsis following ureteroscopic lithotripsy reaches approximately 5.0%; preoperative positive urine culture and a history of recurrent urinary tract infection are strong predictive markers [4]. For high-risk subgroups, enhanced pre-procedural risk screening, optimized perioperative antimicrobial prophylaxis and close postoperative physiological monitoring are required. These measures allow early prediction and timely intervention before deterioration into full-blown sepsis [3].

2.2. Diagnosis and Disease Stratification

2.2.1. Clinical Manifestations and Laboratory Indicators

Clinical presentations combine local urinary irritative symptoms with systemic manifestations of organ dysfunction. Patients commonly present with fever, chills, dysuria, urinary frequency and urgency. As the disease aggravates, tachycardia, hypotension, confusion and disturbed consciousness may emerge, indicating progression toward septic shock [14]. Blood and urine cultures are the gold standard for definitive etiological diagnosis. Ideally, specimens should be collected before antimicrobial administration to maximize pathogen-isolation yield [8].

Circulating biomarkers including PCT, CRP, total white blood cell count and NLR provide important auxiliary diagnostic information [6]. Serum PCT concentration correlates reasonably well with infectious severity and supports risk strat-

ification and serial assessment of therapeutic response [15] [16]. Radiological imaging such as computed tomography or ultrasound can identify hydronephrosis, renal parenchymal inflammatory changes, urinary calculi and abscess formation, facilitating localization of obstructive infectious sources [2]. One caveat deserves emphasis: elderly or immunocompromised patients might present atypically without prominent fever, which increases the possibility of diagnostic delay [17].

2.2.2. Diagnostic Criteria and Staging

Following the Sepsis-3 international consensus, sepsis is defined as suspected or confirmed infection accompanied by an acute increase in the Sequential Organ Failure Assessment (SOFA) score of at least 2 points. The baseline SOFA score is assumed to be zero in patients without known pre-existing organ dysfunction. SIRS criteria are not required for the diagnosis of sepsis, and uncomplicated urinary tract infection, characterized by local symptoms without organ dysfunction, is not classified as a sepsis grade. Septic shock is a subset of sepsis identified by vasopressor dependence to maintain a mean arterial pressure of at least 65 mmHg together with a serum lactate concentration above 2 mmol/l despite adequate fluid resuscitation.

For urosepsis, the diagnostic construct therefore requires two elements: 1) a confirmed or suspected urinary source of infection; and 2) an acute SOFA increase of ≥2 points attributable to that infection. The following categories should be distinguished rather than presented as graded sepsis stages: uncomplicated urinary infection (no organ dysfunction); sepsis (infection plus acute SOFA increase ≥ 2); and septic shock (vasopressor-dependent hypotension plus lactate > 2 mmol/l despite adequate fluids). Risk stratification according to these categories determines monitoring intensity, antimicrobial route and the urgency of source-control evaluation. Uncomplicated urinary infection may be managed with oral antimicrobial agents; sepsis and septic shock mandate intravenous antimicrobial therapy, organ-support measures and immediate evaluation for urinary obstruction requiring decompression [18].

2.3. Concept and General Framework of Step-Wise Therapy

Step-wise therapy means dynamically adjusting therapeutic intensity according to real-time disease evolution. Interventions are de-escalated upon clinical improvement, while therapeutic intensity is escalated when clinical deterioration occurs [5]. Importantly, antimicrobial treatment, resuscitation and indicated source control are not sequential phases to be completed one after another; they are concurrent priorities from the moment urosepsis is recognized.

The 2021 Surviving Sepsis Campaign recommends that antimicrobials be administered immediately, ideally within 1 hour of recognition, and that any required source-control intervention be implemented as soon as medically and logistically practicable. The EAU urological infection guidelines state that infected urinary obstruction requires urgent decompression; antibiotics alone cannot sterilize an obstructed collecting system. Accordingly, the practical framework should be pre-

sented as three concurrent workstreams rather than as a staged surgical "phase":

Antimicrobial workstream: prompt initiation of appropriate empiric agents, with cultures obtained before the first dose whenever feasible, followed by pathogen-guided optimization and de-escalation.

Resuscitation and organ-support workstream: goal-directed fluid resuscitation, hemodynamic stabilization and multi-organ protection, initiated in parallel with antimicrobials.

Source-control workstream: urgent decompression of an infected obstructed urinary tract and drainage of infected collections. This is not conditional on the failure of pharmacological or supportive treatment; it is an initial-recognition priority whenever obstruction is present or suspected.

Once clinical remission is achieved, broad-spectrum antimicrobial coverage should be appropriately de-escalated, aiming to shorten hospital stay and reduce the selective pressure driving antimicrobial resistance [8]. Definitive stone-removal surgery, by contrast, is appropriately deferred until systemic inflammation has stabilized. This distinction between urgent decompression and deferred definitive lithotripsy is essential to avoid conflating source control with elective stone clearance.

2.4. Step-Wise Implementation of Anti-Infective Therapy

2.4.1. Initial Empiric Antimicrobial Therapy

Prompt administration of empiric antibiotics is essential for urosepsis. Empiric regimen selection should be guided by illness severity, individual risk factors for multidrug-resistant organisms, local institutional susceptibility data and baseline renal function [8]. Third- or fourth-generation cephalosporins, piperacillin-tazobactam or carbapenems are reasonable broad-spectrum options depending on the resistance context. Carbapenems should not be applied as a blanket default for all severe urosepsis; they are best reserved for patients with risk factors for extended-spectrum β-lactamase-producing or carbapenem-resistant organisms, or when local resistance prevalence precludes narrower β-lactams. Aminoglycosides may be added as adjunctive initial coverage in selected severe cases. Their use should be individualized according to renal function, concurrent nephrotoxic exposures and the likelihood of gram-negative resistance; they are not universally indicated. Retrospective evidence indicates that delayed administration of an appropriate empiric regimen is associated with increased mortality, supporting early presumptive treatment while definitive susceptibility data are pending [17]. Blood and urine culture samples should be collected before the first antimicrobial dose whenever feasible [2].

2.4.2. Pathogen-Guided Optimization, De-Escalation, and Efficacy Monitoring

Once culture and susceptibility results are available, clinicians should narrow the antimicrobial spectrum when the isolated pathogen is susceptible to a narrower agent. De-escalation reduces unnecessary broad-spectrum exposure, drug toxicity

and the selection pressure favoring opportunistic superinfection [19]. A distinction must be drawn between correction of initially inadequate empiric therapy—escalation because the initial regimen lacked activity against the causative organism, and de-escalation after adequate broad coverage has been confirmed. The former reflects a need to broaden therapy; the latter reflects planned spectrum reduction.

The frequently cited finding that approximately 46% of patients required antimicrobial-regimen adjustment by day 3 derives from a post-hoc analysis of kidney transplant recipients with urosepsis, not from a general urosepsis population. In that cohort, escalation of initially inadequate empiric therapy was observationally associated with higher mortality, need for acute renal replacement therapy and non-recovery from acute kidney injury. These are associations within a specifically immunosuppressed transplant population and should not be generalized as causal estimates or as de-escalation failure rates in all urosepsis patients.

Serial monitoring of body temperature, PCT, CRP and peripheral leukocyte counts supports objective judgment of therapeutic efficacy [6]. Sustained fever or persistently elevated inflammatory biomarkers should prompt evaluation for unrelieved urinary obstruction or undrained infected collections rather than reflexively broadening antimicrobial coverage alone [18].

2.4.3. Adjuvant and Emerging Strategies

The global threat of antimicrobial resistance warrants investigation of alternative and adjunctive approaches [8]. Claims for combined multi-antibiotic regimens and antibiotic-cycling strategies must nevertheless be qualified. Current evidence does not support a general assertion that combination therapy or cycling improves outcomes or reduces resistance across unselected urosepsis populations. These strategies should be regarded as context-dependent and not yet established as routine practice. When combination therapy is used empirically for suspected multidrug-resistant gram-negative infection, it should be followed by timely de-escalation once susceptibility results permit.

Mechanistic studies, including work on TR4-GSDMD signaling in experimental urosepsis, provide insight into inflammatory amplification pathways. They do not, however, constitute evidence of clinical treatment benefit from immunomodulation in patients. Targeted immunomodulators and anti-inflammatory adjuvants remain investigational in urosepsis. The Surviving Sepsis Campaign continues to recommend against routine use of immunoglobulins in adult sepsis or septic shock, and immunomodulatory strategies outside selected corticosteroid indications are not first-line interventions. Administration timing, dosage and safety require validation in adequately powered prospective trials before routine adoption [5].

2.5. Supportive Treatment and Complication Management

2.5.1. Hemodynamic Support

Early goal-directed fluid resuscitation with crystalloid solution, roughly 30 mL/kg,

is recommended to restore effective tissue perfusion. Clinicians must stay alert to volume-overload complications such as pulmonary edema. Dynamic hemodynamic indicators, including stroke volume variation (SVV) and pulse-pressure variation (PPV), predict fluid responsiveness better than static parameters such as central venous pressure [20]. When hypotension persists after adequate fluid supplementation, norepinephrine is the preferred vasopressor. Its purpose is to maintain mean arterial pressure and preserve end-organ perfusion.

2.5.2. Respiratory and Organ Protection

Patients complicated by acute respiratory distress syndrome (ARDS) and respiratory failure should receive lung-protective mechanical ventilation with a low tidal volume strategy. This approach improves oxygenation and minimizes ventilator-induced lung injury [20]. Urosepsis frequently precipitates acute kidney injury (AKI), driven jointly by bacterial toxins, inflammatory mediators and renal hypoperfusion [11]. Close surveillance of serum creatinine, hourly urine output and serum electrolytes is therefore mandatory [11]. Severe refractory AKI requires timely initiation of renal-replacement therapy [20]. Active correction of electrolyte imbalances helps avert secondary cardiac arrhythmia and neurological dysfunction [1].

2.5.3. Nutrition and Metabolic Management

Individualized nutritional support is an indispensable component of comprehensive care [21]. Adequate calorie and protein supplementation should be implemented in the early disease phase, and immunonutrients may be supplemented selectively to rebuild host immune competence [21]. Septic patients commonly suffer stress-induced hyperglycemia and metabolic acidosis [21]. Glycemic control and timely correction of acid-base disturbance alleviate inflammation amplification and immune suppression driven by metabolic derangement, thereby reducing overall complication rates and mortality risk [21].

2.6. Timing of Surgical Intervention and Minimally-Invasive Advances

2.6.1. Urinary Obstruction Relief Is an Initial Priority for Infection Control

Antimicrobial agents alone rarely achieve satisfactory curative efficacy if mechanical urinary obstruction remains unresolved. Unrelieved obstruction has been verified as an independent predictor of 30-day mortality among urosepsis patients [17]. Urgent decompression of an infected obstructed urinary tract is therefore a source-control priority at initial recognition. It is not a rescue measure reserved for failure of pharmacological and supportive treatment.

Two primary emergency urinary-drainage modalities are percutaneous nephrostomy (PCN) and retrograde ureteral stenting [18]. The choice between them should be determined by clinical stability, anatomical considerations (stone location, degree and level of obstruction, presence of pyonephrosis, feasibility of retrograde access) and procedural feasibility. A 2024 systematic review and meta-

analysis found no significant difference between PCN and retrograde ureteral stenting in time to temperature normalization [22]. Accordingly, the evidence does not support a general superiority of PCN over stenting for this outcome. Either approach is acceptable when it can be performed expeditiously by an experienced operator. Stenting carries less procedural trauma and may be preferred when retrograde access is feasible and the patient is unfit for percutaneous access. PCN may be preferred when retrograde access is not feasible, when the collecting system is markedly dilated, or when percutaneous drainage of a large collection is also required. Potential complications of stenting include stent migration, encrustation and stent-associated infection, requiring post-intervention surveillance [22].

2.6.2. Application of Minimally-Invasive Endourological Techniques

Mini-percutaneous nephrolithotomy (mini-PCNL) and retrograde intrarenal surgery (RIRS) represent mainstream minimally-invasive surgical modalities for urinary-stone disorders [23]. Mini-PCNL delivers favorable stone-free rates and is applicable for relatively large and complex renal calculi [3]. RIRS exploits natural urinary luminal passages with minimal soft-tissue trauma and is preferred for small-to-moderate-size renal or ureteral stones [23]. Even with minimally-invasive approaches, postoperative urosepsis may still occur in cases of pre-existing uncontrolled infection or excessively prolonged operative duration [13] [23]. Consequently, pre-operative infectious-status screening, intraoperative intrarenal-pressure restriction and rigorous post-operative monitoring are essential safety precautions [3].

2.6.3. Deferred Definitive Surgery and Multidisciplinary Evaluation

During the acute phase of urosepsis, clinical priorities are concurrent antimicrobial therapy, resuscitation and urgent decompression of any obstructed collecting system. Definitive stone-removal surgery should be deferred until systemic inflammation has stabilized. Comprehensive assessment incorporating inflammatory biomarkers, organ-function status and baseline comorbidities is required. Multidisciplinary collaboration between urology and intensive-care teams is recommended by urological infection guidelines when urosepsis is suspected, specifically to optimize intervention timing and reduce procedural-related infectious risks. Individualized risk-benefit evaluation prevents premature definitive stone surgery in highly unstable patients, which may trigger secondary exacerbation of sepsis [24]. One clarification is worth adding: reference [25] addresses artificial-intelligence-based infection-risk assessment in urolithiasis and does not provide direct evidence for multidisciplinary surgical timing. The recommendation for multidisciplinary timing is grounded in urological guideline consensus rather than in that AI scoping review.

3. Conclusions

Step-wise therapy provides a practical stratified management framework for

urosepsis. It integrates rational antimicrobial strategies, concurrent resuscitation and multi-organ supportive care, and timely surgical source-control measures [5]. The core management principles are: early appropriate empiric antimicrobial treatment followed by pathway-directed optimization and de-escalation; concurrent hemodynamic stabilization, organ-function protection and metabolic-nutritional optimization; and urgent decompression of any infected obstructed urinary tract at initial recognition, with definitive stone surgery deferred until stabilization.

Future research directions include developing high-performance risk-prediction models combining clinical parameters and circulating biomarkers to facilitate precision individualized therapy [24]. Multi-center large-sample prospective clinical trials are urgently needed to further refine step-wise therapeutic algorithms [5]. Additionally, mechanistically informed adjunctive strategies, including immunomodulatory agents, require adequately powered clinical trials to establish safety and efficacy before they can be incorporated into standard urosepsis management [12].

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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