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ТЕРАПИЯ ГЕМОРРАГИЧЕСКОЙ ЛИХОРАДКИ С ПОЧЕЧНЫМ СИНДРОМОМ: ПАТОФИЗИОЛОГИЧЕСКОЕ ОБОСНОВАНИЕ И ПРАКТИЧЕСКОЕ ПРИМЕНЕНИЕ

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Treatment of Hemorrhagic Fever with Renal Syndrome: Pathophysiologic Rationale and Practical Application

Резюме

Современная терапия геморрагической лихорадки с почечным синдромом (ГЛПС) преимущественно основывается на мнении экспертов и данных небольших обсервационных исследований, результаты которых не всегда воспроизводятся в клинической практике. В связи с отсутствием эффективных противовирусных средств лечения ГЛПС продолжается поиск оптимальной патогенетической терапии. Клиническое течение ГЛПС характеризуется последовательным развитием периодов лихорадки, гипотензии, олигурии, полиурии и реконвалесценции. Для каждого из периодов свойственны определенные патофизиологические механизмы, знание которых необходимо для правильной организации лечения больных ГЛПС. В данной работе рассмотрены патогенетическое обоснование и опыт практического применения используемых при ГЛПС методов лечения, таких как противовоспалительная терапия, коррекция водно-электролитных, гемодинамических и гемокоагуляционных нарушений, экстракорпоральная детоксикация и симптоматическая терапия.

Ключевые слова: *геморрагическая лихорадка с почечным синдромом, хантавирусы, патогенез, терапия*

Конфликт интересов

Авторы заявляют, что данная работа, её тема, предмет и содержание не затрагивают конкурирующих интересов

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Abstract

Current treatment of hemorrhagic fever with renal syndrome (HFRS) is primarily based on expert opinion and data from small observational studies, the results of which are not always confirmed in clinical practice. Due to the lack of effective antiviral agents for the treatment of HFRS, the search for optimal supportive therapy continues. The clinical course of HFRS is characterized by the sequential development of phases of fever, hypotension, oliguria, polyuria and convalescence; each of these phases is characterized by certain pathophysiological mechanisms, knowledge of which is necessary for the correct management of patients with HFRS. This narrative review provides the pathophysilogic rationale and practical experience of using treatment methods for HFRS, such as anti-inflammatory therapy, correction of fluid, electrolyte, hemodynamic and hemocoagulation disorders, as well as, renal replacement therapy and symptomatic therapy.

Key words: *hemorrhagic fever with renal syndrome, hantavirus, pathogenesis, treatment*

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Abbreviations: AKI — acute kidney injury, ARDS — acute respiratory distress syndrome, CVP — central venous pressure, DIC — disseminated intravascular coagulation, ECMO — extracorporeal membrane oxygenation, HFRS — hemorragic fever with renal syndrome, HPS — hantavirus cardiopulmonary syndrome, MAP — mean arterial pressure, RCT — randomised clinical trial, RRT — renal replacement therapy, SBP — systolic blood pressure

Introduction

Hemorrhagic fever with renal syndrome (HFRS), widespread in Eurasia, along with hantavirus pulmonary syndrome (HPS), endemic to North and South America, is a clinical manifestation of human hantavirus infections and is characterized by severe progression with frequent life-threatening complications.

Annually, an average of approximately 23,500 cases of HFRS are reported, with one-third occurring in the Russian Federation. The case fatality rate, which varies depending on the pathogen strain, endemic region, and detection rate of mild disease forms, ranges from 0.1% in Puumala-virus infections in Northwestern Europe to 14% in Dobrava/Belgrade-virus infections in Southwestern Russia [1, 2].

HFRS is an acute, self-limiting viral disease that typically resolves with complete recovery in mild cases without therapeutic intervention. However, in severe disease progression — observed in 20-25% of hospitalized patients — lack of treatment, delayed initiation, inadequate therapy, or overtreatment may result in adverse clinical outcomes.

The potential for specific prophylaxis of HFRS caused by hantaviruses circulating in Russia remains limited. Culture-derived inactivated bivalent and polyvalent HFRS vaccines, developed by researchers at the M.P.Chumakov Federal Scientific Center for Research and Development of Immunobiological Preparations under the direction of E.A.Tkachenko, have successfully completed preclinical studies and are currently in preparation for clinical trials [3].

Current management of HFRS is based on expert opinion and data from small observational studies, the results of which are not always reproducible in clinical practice. To date, only four randomized clinical trials have been published: two evaluating ribavirin for HFRS [4,5], one assessing ribavirin for HPS [6], and one investigating glucocorticoids for HPS [7]. Treatment often employs syndromic management approaches developed for bacterial sepsis that fail to account for HFRS-specific pathogenesis. Some pharmacologic agents traditionally used in HFRS, such as nonsteroidal anti-inflammatory drugs, may pose safety concerns [8]. Given these limitations, a critical review of therapeutic approaches to HFRS is warranted, incorporating emerging pathophysiological insights and available clinical observations.

Pathophysiological rationale for the treatment of HFRS

HFRS has been divided into six stages (incubation, febrile, hypotensive, oliguric, diuretic, and convalescent). Each stage exhibiting distinct pathophysiological mechanisms and corresponding therapeutic opportunities. This periodicity is most pronounced in severe cases, though during the acute phase, key clinical and pathogenetic features of HFRS stages may overlap (Figure 1).

Incubation period. Following exposure to a sufficient infectious dose of viral particles that enter through the respiratory and/or digestive tract mucosa, hantaviruses first interact with antigen-presenting cells before contacting microvascular endothelial cells whose surface receptors serve as viral targets [9,10]. Viral entry into endothelial cells and subsequent replication with release of new virions occurs without significant cytopathic effects [9,10]. While hantaviruses may be detected within or on other cell types (dendritic cells, macrophages, epithelial cells, etc.), this likely reflects their phagocytic and adhesive functions rather than active viral replication. The prevailing hypothesis suggests preferential infection of venous microvascular endothelium — renal in HFRS and pulmonary in HPS.

The incubation period typically lasts 1-2 weeks. Reported extensions to 6 weeks may represent post-exposure infections from contaminated fomites after leaving endemic areas. Both the number of infected endothelial cells and viremia levels likely peak at the end of the incubation period, declining with the onset of neutralizing antibody production and subsequent inflammatory responses [9,10].

The ability to diagnose HFRS during the incubation period by detecting viremia in individuals at risk of infection has provided the rationale for exploring post-exposure passive immunization and antiviral chemoprophylaxis [11, 12]. However, the likelihood of implementing these therapeutic approaches in clinical practice appears remote.

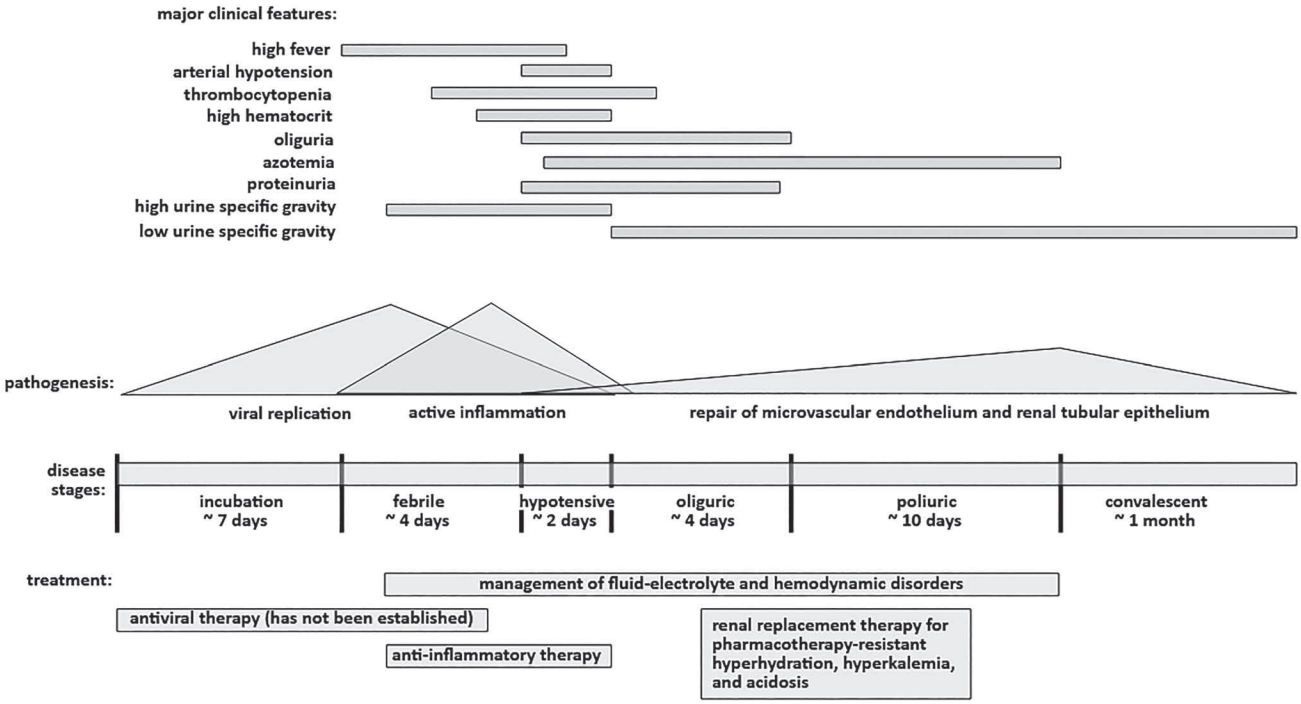

Figure 1. *Proposed framework for clinical timeline, pathogenesis and management of HFRS*

Febrile stage. The acute onset of high fever marks the initiation of an inflammatory response aimed at suppressing viral replication. Antibody binding to viral particles on the surface of infected endothelium serves as a signal for the activation of cytotoxic immune effector cells (polymorphonuclear leukocytes, monocytes/macrophages, and cytotoxic T-lymphocytes) [13, 14]. By attacking infected endothelial cells, these effector cells generate proinflammatory cytokines and cytotoxic mediators (including phagocyte-derived hydrolases and atomic oxygen) [15, 16]. Inflammatory activity peaks at the end of the febrile period and remains elevated during the next hypotensive stage [17].

Endothelial damage in the microcirculatory vessels, corresponding to the degree of inflammatory activity, manifests as increased vascular permeability with plasma extravasation and interstitial edema (so-called "capillary leak"), along with vasodilation and thrombus formation predominantly observed in the venous segment of the microvasculature [18, 19].

Clinical manifestations of inflammatory microcirculatory disturbances may become apparent during the latter half of the febrile period, presenting as: erythema and puffy edema of the facial, cervical, and shoulder skin regions, conjunctival edema and injection, decreased visual acuity (resulting from edema of ocular structures), nausea, vomiting, and diarrhea (secondary to gastrointestinal microcirculatory dysfunction), lumbar and abdominal pain (due to renal edema), headache (indicating developing cerebral edema), non-productive cough (suggesting incipient pulmonary interstitial edema).

The main therapeutic approaches during the febrile period should include antiviral and anti-inflammatory medications, along with maintenance of normal fluid balance.

Hypotensive stage. The hypotensive phase, a hallmark of severe HFRS, represents the most critical stage of the disease. This phase is driven by generalized endothelial dysfunction secondary to a hyperergic inflammatory response, which precipitates hypovolemia (due to plasma extravasation from increased vascular permeability and dehydration caused by persistent high-grade fever) and venodilation with subsequent blood pooling in the venous compartment. These pathophysiological changes may culminate in shock. Notably, in a subset of HFRS patients with predominant pulmonary capillary and venular endothelial involvement, shock may be preceded by acute respiratory distress syndrome (ARDS). Both shock and ARDS constitute the most severe, life-threatening complications of HFRS and serve as the primary contributors to disease-related mortality [18].

Extensive damage to the microvascular endothelial lining, accompanied by concurrent thrombosis and fibrinolysis, can lead to disseminated intravascular coagulation (DIC) when the balance between these processes is disrupted. DIC may manifest with either thrombotic or hemorrhagic complications. In the most severe cases of HFRS, thrombotic-hemorrhagic pituitary involvement may occur. In less severe disease, microcirculatory disturbances during the hypotensive phase are predominantly localized to the kidneys, initially presenting as

prerenal (ischemic) acute kidney injury (AKI). However, prolonged renal ischemia rapidly progresses to intrinsic renal AKI due to acute tubular necrosis.

The intense inflammatory response mediates viral clearance, as evidenced by multiple studies demonstrating rapid reduction in viral load coinciding with the hypotensive phase [5,20-22]. This decline in antigenic load is subsequently followed by marked attenuation of inflammatory activity. By the onset of the oliguric phase, this is clinically manifested by resolution of high-grade fever and disappearance of microvascular inflammatory signs.

Pathophysiologically-guided management during the hypotensive phase should include: continued anti-inflammatory and antiviral therapy, maintenance of normovolemia, vasopressor support when indicated, and respiratory support as clinically warranted.

The precarious balance between concurrent thrombosis and fibrinolysis [19,23] renders the following interventions particularly hazardous: anticoagulants, anti-platelet agents, fibrinolytic inhibitors, blood products and coagulation factors. For the same reason, extracorporeal detoxification methods should be avoided during active inflammation, as they may precipitate decompensation of existing DIC [24,25]. The toxemia in HFRS is mediated by short-lived inflammatory mediators (cytokines) and ischemic byproducts (lactate). Consequently, effective detoxification can be achieved through anti-inflammatory therapy and restoration of tissue perfusion.

Oliguric stage. The oliguric phase of HFRS represents the clinical manifestation of acute tubular necrosis, which develops secondary to renal hypoperfusion during the febrile and hypotensive phases due to inflammatory microcirculatory disturbances. Renal ischemia leading to tubular epithelial necrosis results from both systemic hypovolemia (due to capillary leak syndrome and dehydration) and renal-specific microcirculatory dysfunction (characterized by venular thrombosis, increased vascular permeability, and interstitial edema that collectively impair hemodynamics and urinary flow).

While some studies have characterized HFRS-associated renal pathology as interstitial or tubulointerstitial nephritis based on biopsy findings from convalescent patients [26,27], we contend this classification may not fully capture the disease's pathophysiological complexity. During the oliguric phase of HFRS, renal histopathology does not meet diagnostic criteria for interstitial/tubulointerstitial nephritis. Rather, the findings are consistent with acute tubular necrosis secondary to inflammatory microcirculatory disturbances [18,28].

During the oliguric phase, following resolution of active inflammation, vascular endothelial repair commences. The disease transitions to the polyuric phase as vascular permeability normalizes and microthrombosis ceases within the renal microvasculature. The oliguric phase in HFRS is typically short-lived. However, prolonged oliguria may occur in patients who experienced sustained shock during the acute phase. Prolongation of the oliguric phase may also result from either renal microvascular re-thrombosis (triggered by extracorporeal therapies or transfusion of coagulation factors/platelets), or fluid imbalance, particularly iatrogenic hyperhydration that impairs resolution of renal interstitial edema.

Volume overload represents a critical iatrogenic complication during the oliguric phase, potentially leading to hydrostatic pulmonary edema, cerebral edema and spontaneous renal rupture as a result of severe renal parenchymal edema. These life-threatening complications arise from combined effects of increased intravascular hydrostatic pressure and compromised tissue integrity due to inflammatory-mediated vascular leakage.

Optimal fluid management constitutes the cornerstone of oliguric phase treatment and is typically sufficient when properly implemented. This requires strict monitoring of intake/output balances and precise volume titration to maintain euvolemia. With meticulous management, most patients (including those with anuria) avoid renal replacement therapy (RRT) which remains high-risk until endothelial integrity is restored and hemostatic stability is achieved.

Poliuric stage. The polyuric phase of HFRS reflects gradual recovery of glomerular filtration alongside slower restoration of tubular reabsorptive capacity [26, 27]. At the onset of the polyuric phase, the glomerular filtration rate may be as low as a few milliliters per minute, with excreted urine essentially representing plasma ultrafiltrate that has bypassed tubular reabsorption. Consequently, this phase can be marked by progressive azotemia, hyperkalemia, and acidosis. In rare cases of HFRS, uremic encephalopathy or pericarditis may develop. A hallmark feature of this stage is arterial hypertension (potentially escalating to hypertensive crisis with encephalopathy and seizure syndrome), resulting from prior renal ischemia and persistent endothelial dysfunction. Additionally, due to preceding microcirculatory disturbances in the gastrointestinal system, patients frequently exhibit gastric and intestinal paresis.

Management during the polyuric phase should focus on maintaining fluid and electrolyte balance. When pharmacological management fails to correct hyperhydration, hyperkalemia, or acidosis, RRT may be required. In HFRS patients, azotemia — even with serum creatinine levels elevated 10-fold or higher — typically resolves without uremic toxicity or long-term sequelae.

Convalescent stage. The convalescent stage, commencing with the resolution of polyuria, typically lasts one to several months, during which nearly all HFRS patients achieve complete recovery. The asthenia and laboratory evidence of renal dysfunction observed during convalescence generally require no pharmacological intervention.

Patient Management

A presumptive diagnosis of HFRS should be considered in patients presenting with otherwise unexplained high-grade fever and a history of exposure to endemic areas during the incubation period. The clinical diagnosis is established based on recognition of the characteristic disease course with pathognomonic symptoms appearing in each disease phase. Definitive diagnosis requires serological confirmation through detection of anti-hantavirus IgM antibodies and demonstration of rising anti-hantavirus IgG titers during the course of illness. The diagnostic workup for HFRS must include exclusion of clinically similar conditions requiring specific diagnostic evaluation and treatment, such as systemic bacterial infections, tropical malaria and systemic vasculitides.

Patients with HFRS typically require hospitalization between days 3-4 of illness. Admission to a facility equipped with RRT capabilities is strongly recommended. In severe cases, appropriate stabilization measures must be implemented prior to transfer to prevent clinical deterioration during transportation. Given the risk of rapid clinical deterioration (including shock, ARDS, overt DIC, and AKI with pulmonary or cerebral edema), patients with severe HFRS require intensive care unit admission under the supervision of clinicians experienced in managing this disease [29].

Patients may be discharged for outpatient follow-up during the polyuric phase when the following conditions are met: subjective well-being is satisfactory, and there is a consistent trend toward normalization of renal function parameters.

Antiviral therapy

No targeted antiviral therapy for hantavirus infections has been established to date [1]. The clinical utility of ribavirin, proposed nearly 40 years ago for HFRS treatment based on in vitro activity, remains uncertain. While one randomized controlled trial (RCT) demonstrated therapeutic benefit [4], subsequent RCT failed to replicate these findings [5]. Moreover, a separate RCT conducted in HPS showed no clinical effect [6]. In current HFRS treatment guidelines, ribavirin — when considered at all — is categorized as an optional rather than essential therapeutic agent [30].

Preclinical studies utilizing cell cultures and animal models have identified several compounds capable of inhibiting hantavirus replication [31, 32]. However, none of these agents have progressed to clinical application for human treatment.

The potential utility of antiviral therapy in HFRS is constrained by the brief window of active viral replication. Viral loads typically declines following symptom onset, and by the time of hospitalization, viral replication may have already been terminated by the adaptive immune response.

The hyperergic immune response characteristic of HFRS raises significant concerns regarding the potential efficacy of passive immunization strategies — whether through donor immunoglobulins or antiviral monoclonal antibodies. Low antibody titers observed in patients during early disease stages likely reflect active immunoglobulin binding to virion surfaces rather than impaired antibody production.

The therapeutic use of interferons or interferon inducers in HFRS may pose significant safety risks due to their potential to exacerbate inflammatory responses.

Anti-inflammatory therapy

Glucocorticoids currently represent the treatment of choice for HFRS-associated inflammation [30]. The primary therapeutic effect of these agents involves suppression of polymorphonuclear leukocyte and monocyte/macrophage activity. This results in decreased synthesis and secretion of inflammatory mediators responsible for increased vascular permeability ("capillary leak"), pathological vasodilation, endothelial structural integrity disruption, and microcirculatory thrombosis secondary to endothelial damage.

Glucocorticoid therapy in HFRS was first proposed seventy years ago [33], yet specific indications, optimal dosing regimens, and treatment duration remain poorly defined to date.

According to the Chinese Medical Association's consensus guidelines [30] — which reflect the most extensive clinical experience with HFRS management — glucocorticoids are recommended for febrile-phase patients with marked exudative manifestations (facial/conjunctival hyperemia/edema, serous cavity effusions, hemoconcentration, proteinuria, etc.), and hypotensive-phase patients developing shock. Chinese clinical guidelines recommend short-course intravenous glucocorticoid therapy (typically 3-5 days, not exceeding 7 days) using one of the following protocols: hydrocortisone (100 mg once or twice daily), or dexamethasone (5-10 mg once or twice daily), or methylprednisolone (20-40 mg once or twice daily).

In our clinical view, indications for glucocorticoid therapy in HFRS align with those for intravenous fluid resuscitation during both febrile and hypotensive phases. Critically, the initial glucocorticoid dose should be administered prior to fluid infusion to mitigate vascular permeability. Glucocorticoid dosing and administration frequency should be individualized, guided by anti-inflammatory response criteria including resolution of high-grade fever and prevention of febrile recurrence. Notably, anti-inflammatory therapy becomes unnecessary upon transition to the oliguric phase, necessitating immediate glucocorticoid withdrawal.

The lack of mortality benefit with glucocorticoid therapy, demonstrated in an RCT of 60 HPS patients

(30 treated with methylprednisolone versus 30 receiving placebo) [7], has often been interpreted as conclusive evidence against their efficacy in hantavirus infections. This analysis importantly overlooks that the investigated methylprednisolone pulse therapy (16 mg/kg/day for 3 days) was initiated during the cardiopulmonary phase of HPS — that is, after establishment of the hyperergic inflammatory response. Furthermore, the study authors themselves note the insufficient statistical power of this RCT to adequately assess between-group mortality differences (8 fatalities in the methylprednisolone group versus 12 in the placebo group).

Other therapeutic options for anti-inflammatory management in HFRS remain constrained. Notably, administration of non-steroidal anti-inflammatory drugs — which impair compensatory mechanisms maintaining renal blood flow — results in exacerbated renal injury in HFRS patients [8,30]. Several studies have investigated targeted modulation of specific inflammatory mediators in HFRS management. Initial case reports described successful use of icatibant (a selective bradykinin B2 receptor antagonist) in two patients with severe HFRS [34,35]. However, subsequent observations failed to confirm consistent therapeutic efficacy of this high-cost agent. Further clinical trials are required to establish evidence-based recommendations for its incorporation into routine practice [36]. The use of long-acting anti-inflammatory medications (e.g., anti-cytokine monoclonal antibodies) or agents with delayed onset of action (e.g., JAK inhibitors, aminoquinoline derivatives) appears clinically unwarranted in HFRS given the transient nature of inflammatory activation in this condition.

Management of Fluid-Electrolyte, Hemodynamic, and Hemostatic Disorders

Maintaining normal fluid balance is an essential component of HFRS therapy. Measures to normalize fluid status should be implemented in two stages: replenishing the water deficit within the first 3–6 hours of therapy initiation, followed by maintaining the equilibrium of fluid intake and excretion [30].

Hospitalization of HFRS patients is typically preceded by 2–4 days of high fever, with daily fluid loss amounting to approximately 1% of the patient's body weight. Oral fluid rehydration is often impeded by the lack of pronounced thirst (due to the iso- or hypotonic dehydration typical in early-stage HFRS) and frequent concomitant nausea and vomiting. Compounding this, dehydration coincides with hypovolemia resulting from capillary leak syndrome and vasodilation. Notably, the external signs of these processes (e.g., facial edema and flushing) may mask the underlying fluid deficit, creating a false impression of euvolemia.

Intravenous fluid therapy should be initiated with isotonic polyionic crystalloids or 0.9% sodium chloride. The initial infusion volume and rate must be tailored to the estimated fluid deficit and adjusted according to hemodynamic status. Close clinical monitoring is essential during the initial resuscitation phase.

In patients without arterial hypotension, the initial infusion rate during the first 1-2 hours of therapy should be approximately 500 mL/hour (or ~8 mL/kg/hour), followed by isotonic crystalloid administration at 250 mL/hour for the subsequent 2-4 hours. A total initial fluid volume of 1500-2000 mL is typically sufficient, provided there is marked clinical improvement in the patient's condition and the ability to resume oral intake.

In patients with systolic blood pressure (SBP) below 90 mm Hg or mean arterial pressure (MAP) below 65 mm Hg, intravenous fluid therapy should be initiated in the prehospital setting (concurrently with glucocorticoid administration). During the first hour of treatment, a minimum of 1000 mL (approximately 15 mL/kg) should be infused. If target hemodynamic parameters are achieved (SBP >90 mm Hg and MAP >65 mm Hg), the infusion rate should be reduced to 500 mL/hour for the next 2 hours, followed by 250 mL/hour for 4 hours, and may be discontinued after 6 hours of sustained blood pressure stabilization. The total initial fluid volume typically amounts to approximately 3 liters.

For persistent hypotension during the first hour of therapy, the infusion rate should be increased. If no clinical improvement is observed after administration of approximately 30 mL/kg of isotonic crystalloids, vasopressors and albumin solution should be initiated. Notably, in HFRS patients, dehydration rarely exceeds 5% of total body weight. Fluid replacement should therefore not exceed 50 mL/kg, after which ongoing fluid therapy must be strictly matched to measured fluid losses.

A frequent management error in HFRS is the continued administration of large-volume fluids to correct central venous pressure (CVP). Importantly, the observed CVP reduction results primarily from inflammatory vasodilation in the venous microcirculation rather than significant hypovolemia.

The infusion rate should be reduced upon clinical signs of incipient inflammatory pulmonary edema (unproductive cough, dyspnea). If ARDS develops, standard management (including lung-protective ventilation and dexamethasone) should be initiated while continuing slow fluid replacement over 12-18 hours to address the estimated minimal fluid deficit.

In cases of progressive ARDS with refractory hypoxemia, venoarterial extracorporeal membrane oxygenation (ECMO) should be considered [1]. While venovenous ECMO is the recommended modality for sepsis-associated ARDS [37], this approach may be contraindicated in HFRS-related ARDS due to the disease-specific propensity for pulmonary microvascular thrombosis.

In HFRS patients with ARDS who receive inappropriate fluid therapy (excessive volume and/or rate), continuous RRT may be required to eliminate fluid overload [38,39]. When considering RRT during the hypotensive phase of HFRS — particularly in the context of persistent inflammatory activity and unstable hemostasis — a careful risk-benefit assessment is essential.

Current HFRS treatment guidelines recommend vasopressor therapy only when fluid resuscitation fails (defined as persistent hypotension in adults after infusion of 3000 mL over 2-3 hours) or if hypotension recurs after initially successful fluid administration [30].

The dose of vasopressors — preferably norepinephrine — should target a MAP of 65-75 mm Hg. Higher doses may exacerbate microcirculatory dysfunction. In HFRS, assessing vasopressor efficacy based on urine output restoration is misguided, as oliguria is only partially attributable to hypotension. Similarly, initiating vasopressors concurrently with fluid resuscitation — a strategy sometimes advocated in bacterial sepsis [37] — is inappropriate in HFRS. Sepsis-induced hypotension (typically observed in surgical or nosocomial infections) is primarily distributive in nature and, unlike in HFRS, frequently occurs in patients without significant hypovolemia.

If vasopressor therapy proves ineffective, clinicians should assess for potential pituitary hemorrhage with acute adrenal insufficiency (requiring hydrocortisone replacement) [40] and consider venoarterial ECMO for hemodynamic support [1].

After initial volume status correction, the majority of patients require only sustained anti-inflammatory treatment and careful fluid balance management. Failure to maintain proper fluid balance (with daily fluid intake exceeding losses by >750 mL) is particularly hazardous during the oliguric phase, potentially precipitating hydrostatic pulmonary and/or cerebral edema. Fluid overload results in dilutional hyponatremia, which may prompt inappropriate sodium-containing fluid administration, thereby exacerbating iatrogenic volume overload.

In HFRS patients with clinical signs of volume overload during the oliguric phase, loop diuretics may be considered. According to guidelines from the Chinese Medical Association, furosemide is the diuretic of choice, initiated at 20-40 mg IV, with dose escalation (if no response occurs within 2-4 hours) to 100-200 mg administered 2-4 times daily, up to a maximum daily dose of 800 mg [30]. For refractory cases with pulmonary or cerebral edema, RRT should be initiated. Importantly, oligo(an)uria without hypervolemia should not be considered an indication for diuretic therapy.

After volume overload, hyperkalemia unresponsive to medical management represents the second most frequent indication for RRT in HFRS, with onset typically occurring during the polyuric stage. Pharmacological intervention for "asymptomatic" hyperkalemia is warranted when serum potassium levels exceed 6.5 mmol/L, whereas neuromuscular or electrocardiographic manifestations necessitate treatment at levels above 5.5 mmol/L. Management of hyperkalemia in HFRS patients typically involves infusion of an insulin-glucose solution. In cases with ECG abnormalities, intravenous calcium chloride or gluconate administration is additionally required. For refractory cases, adjunctive therapies may include furosemide, potassium-binding cation-exchange resins (e.g., Kalimate), or beta-2 adrenergic agonists (e.g., salbutamol). In hyperkalemia complicated by metabolic acidosis, intravenous sodium bicarbonate (50-100 mmol as a 4% solution, 50-100 mL infusion) should be administered.

In patients with HFRS, metabolic acidosis primarily develops due to lactate accumulation resulting from inflammatory microcirculatory disturbances. Acidosis correction is typically achieved through tissue perfusion restoration with anti-inflammatory and infusion therapy. Attempts to correct lactic acidosis through RRT during active inflammation (febrile phase, hypotensive phase, or early oliguric stage) may lead to further microcirculatory thrombosis and prove both ineffective and potentially hazardous. In rare cases of HFRS with prolonged oliguria, acidosis may progress due to impaired renal excretory function. When pharmacological management fails, this may necessitate RRT.

Uremic intoxication requiring RRT is an exceptionally rare manifestation of AKI in HFRS. Typically, diagnoses of uremic encephalopathy and/or pericarditis in HFRS patients are misattributed to either hypervolemia-related complications (cerebral edema, serous cavity transudation) or hypertensive encephalopathy.

In HFRS patients, anuria and azotemia are typically reversible. In the absence of progressive hypervolemia, hyperkalemia, or acidosis, these findings alone should not be considered absolute indications for RRT.

Arterial hypertension (with potential progression to hypertensive encephalopathy and seizure activity) is a hallmark feature of the polyuric phase in HFRS. In most cases, a short-term course of combination therapy with an angiotensin-converting enzyme inhibitor and calcium channel blocker proves sufficiently effective. Hypertensive crisis requires emergent vasodilator therapy (sodium nitroprusside or nitroglycerin) or alpha-adrenergic blockade (urapidil), with mandatory continuous medical supervision during administration.

Sinus bradycardia, which may occur during any phase of HFRS, typically follows a benign course. However, cardiac monitoring is essential, with preparedness to administer atropine or initiate temporary pacing in cases of hemodynamic instability [41].

Correction of hemostatic abnormalities in HFRS is indicated only in cases of active bleeding. Over 97% of HFRS cases in Russia are caused by Puumala virus infection [42], which typically presents without overt

clinical signs of hemorrhagic syndrome. In Puumala virus infections, overt DIC manifestations (thrombotic or hemorrhagic events) typically occur following interventions that disrupt the thrombo-fibrinolytic balance, such as platelet/plasma transfusions (for laboratory parameter correction), antifibrinolytic administration, or RRT [18].

Notably, thrombocytopenia in HFRS (often considered an indication for platelet transfusion) likely reflects not a true platelet deficiency, but rather reversible aggregation and sequestration in the microvasculature. This is supported by the rapid, substantial platelet count increase during the oliguric phase: following resolution of active inflammation, levels typically rise from 20-40×10^3/μL to 200-400×10^3/μL or higher within 2-3 days.

In our view, prophylactic anticoagulation in HFRS should also be considered potentially harmful. The characteristic microvascular thrombotic activation in this disease reflects inflammatory mechanisms (so-called 'immunothrombosis') [19]. We posit that appropriately administered glucocorticoid therapy — targeting the underlying inflammation — should suffice for thromboprophylaxis in HFRS.

Adjunctive Symptomatic Management

For pain management — typically resulting from combined inflammatory and hydrostatic renal edema — opioid analgesics may be warranted in select cases after excluding emergent conditions (renal rupture, renal vessel thrombosis, urinary obstruction, mesenteric thrombosis, pancreatitis, or acute coronary syndrome).

Gastrointestinal dysfunction in HFRS, resulting from inflammatory microcirculatory disturbances, may cause elevated intra-abdominal pressure. This can exacerbate renal impairment and compromise respiratory function. In severe cases, nasogastric/intestinal decompression is required, while milder presentations may be managed with cleansing enemas.

Vasopressor therapy may exacerbate gastrointestinal hypoperfusion, potentially leading to erosive-hemorrhagic mucosal injury [43, 44]. Therefore, when vasopressors are required in HFRS patients, concomitant acid-suppressive therapy (e.g., proton pump inhibitors) should be initiated.

Nausea, vomiting, and hiccups — frequent and distressing symptoms in HFRS — may arise from either gastropathy or metabolic disturbances. For persistent cases, central dopamine and serotonin receptor antagonists (e.g., metoclopramide, domperidone, ondansetron) can be employed as antiemetic therapy.

Other pharmacologic agents frequently recommended in HFRS management include vitamins, angio- and cardiocytoprotective drugs, and antiplatelet agents, though their clinical utility remains unestablished.

Conclusion

The infectious and pathological processes in HFRS are self-limiting, and well-structured supportive care is generally sufficient to ensure patient recovery. The distinct pathophysiological features of HFRS that differentiate it from bacterial sepsis must be considered when managing syndrome-based complications such as shock, ARDS, DIC, and AKI. The lack of consensus in HFRS management guidelines reflects both limited high-quality evidence and inconsistent research methodologies in existing studies. Multicenter clinical trials could help establish optimal therapeutic approaches for this disease.

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