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Kidney injury in hand, foot, and mouth disease; focus on immune and metabolic dysregulation

Hojjat Eghbali Jelodar[1], Baharak Maddahi[2], Faezeh Nesaei[3], Mohammad Pourmahmoudian[4], Elham Kebriyaei[5], Shirin Taraz Jamshidi[6], Ahmad Shajari[7], Arsalan Afzal Toosi[8], Ali Emadzadeh[9*]

[1]Department of Surgery and Orthopedic, School of Medicine, Ardabil University of Medical Sciences, Ardabil, Iran
[2]Pediatric Health Research Center, Tabriz University of Medical Sciences, Tabriz, Iran
[3]Department of Nursing, Imam Hossein Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[4]Department of Orthopedic Surgery, Shohada-e Tajrish Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[5]Clinical Research Development Unit, Valiasr Hospital, Fasa University of Medical Sciences, Fasa, Iran
[6]Department of Pathology, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran
[7]Department of Medicine, YMS.C., Islamic Azad University, Yazd, Iran
[8]Department of Orthopedic and Trauma Surgery, Imam Hossein Hospital, School of Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[9]Department of Internal Medicine, MMS.C., Islamic Azad University, Mashhad, Iran

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ABSTRACT

Hand, foot, and mouth disease (HFMD), primarily caused by enteroviruses, notably EV-A71 is typically a self-limiting childhood illness. However, severe cases, often linked to EV-A71, can manifest systemic complications, including acute kidney injury (AKI), which significantly increases morbidity and mortality. The neurological and cardiopulmonary involvement are well-recognized; however, renal impairment is increasingly documented but mechanistically underexplored. Several studies showed that AKI in severe HFMD is not merely a consequence of hypovolemia or shock but involves significant immune and metabolic dysregulation. A dysregulated host immune response, characterized by a cytokine storm, drives systemic inflammation and endothelial damage, potentially leading to acute tubular necrosis and glomerular dysfunction. Viral persistence or molecular mimicry may further exacerbate renal inflammation. Concurrently, metabolic disturbances are serious, like severe systemic inflammation induces insulin resistance, catabolism, and mitochondrial dysfunction in renal tubules. Electrolyte imbalances, lactic acidosis from tissue hypoperfusion or direct viral effects, and potential rhabdomyolysis-associated myoglobinuria contribute to renal stress and injury. The interaction of hyperinflammation and metabolic chaos disrupts renal hemodynamics, cellular energy production, and repair mechanisms. Therefore, recognizing the dual pathway in this disease is crucial, as it shifts management beyond fluid resuscitation towards targeted immunomodulation and meticulous metabolic support.

Implication for health policy/practice/research/medical education:
The hand, foot, and mouth disease (HFMD) is typically self-limiting disease. In severe cases, which is often linked to enterovirus A71, can trigger acute kidney injury (AKI), contributing to poor outcomes. Emerging evidence implicates profound immune and metabolic dysregulation as central mechanisms beyond direct viral cytopathy. A dysregulated host immune response, characterized by excessive pro-inflammatory cytokine release, drives systemic inflammation and endothelial damage, potentially leading to renal hypoperfusion, microthrombosis, and direct tubular injury. Concurrently, metabolic disturbances, including severe lactic acidosis and electrolyte imbalances from systemic stress and neurogenic pulmonary edema, further impair renal perfusion and function. This immune-metabolic axis creates a vicious cycle, exacerbating AKI. Identification of the intertwined pathways is crucial for identifying at-risk patients and developing targeted interventions beyond supportive care to mitigate renal complications in severe HFMD.

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***Corresponding author**: Ali Emadzadeh, Email: ali_emadzadeh@iau.ac.ir

Review

Introduction

Hand, foot, and mouth disease (HFMD), is a mild and self-limiting childhood illness caused by enteroviruses, most notably coxsackievirus A16 and enterovirus 71 (EV-A71) is typically characterized by fever, oral enanthem, and a vesicular rash on the hands, feet, and occasionally buttocks (1). While the vast majority of cases resolve uneventfully within 7-10 days, a small but significant subset, particularly those infected with EV-A71, can progress to severe neurological complications such as aseptic meningitis, brainstem encephalitis, acute flaccid paralysis, and neurogenic pulmonary edema (2). However, an under-recognized and potentially devastating complication lurking within this clinical spectrum is acute kidney injury (AKI) (3). Though neurological manifestations dominate the discourse on severe HFMD, renal involvement, often intertwined with profound immune and metabolic dysregulation, represents a critical determinant of morbidity and mortality, especially in critically ill children (4). This overview sought to study kidney injury in HFMD, through a focus on immune and metabolic dysregulation.

Method of the search

To identify relevant literature for this narrative review, we queried multiple databases including PubMed, Scopus, Embase, Web of Science, EBSCO, DOAJ, and Google Scholar, using keywords such as 'acute kidney injury', 'cytokine storm', 'chronic kidney disease', 'acute tubular necrosis', 'endothelial damage', 'kidney injury', 'rhabdomyolysis', 'reactive oxygen species', 'inflammation' and 'Hand, foot, and mouth disease'.

The pathogenesis of renal involvement in HFMD

The pathogenesis of kidney injury in HFMD is extending far beyond simple dehydration as a common initial assumption (3). In infections, AKI often arises from dual mechanisms of prerenal azotemia driven by dehydration due to reduced oral intake, vomiting, and fever-induced insensible losses, and intrinsic renal damage. While direct viral cytopathic effects may contribute, dysregulation of the host immune response, manifesting as cytokine release, microthrombosis, and inflammatory injury, which is the predominant driver of intrinsic AKI in critical illness (5). Enteroviruses, particularly EV-A71, exhibit a surprising tropism for renal tissue (3). The virus gains entry through specific cellular receptors, notably scavenger receptor class B member 2 and P-selectin glycoprotein ligand-1, which are expressed on various renal cell types (6). Previous studies detected that scavenger receptor class B member 2 which is crucial for EV-A71 uncoating and infection, represented on proximal tubular cells. Direct viral cytopathic effects can disrupt tubular integrity, impair reabsorptive functions, and trigger local inflammatory cascades (7). However, the magnitude of renal damage observed in severe HFMD often exceeds what can be explained by direct viral infection alone, directing towards the host immune response as the primary driver of significant kidney injury (3). Notably, immune dysregulation is the cornerstone of severe HFMD pathogenesis, and its impact on the kidneys is profound and complex (8). Accordingly, EV-A71 infection in young children with immature immune systems, can trigger an overwhelming and maladaptive systemic inflammatory response, often described as a cytokine storm (9). This condition is characterized by a massive, uncontrolled release of pro-inflammatory cytokines and chemokines (10). Key players include interleukin-6 (IL-6), interleukin-1 beta (IL-1β), tumor necrosis factor-alpha (TNF-α), interferon-gamma (IFN-γ), and high-mobility group box 1 (HMGB1) (10). Levels of these mediators are significantly elevated in the serum and cerebrospinal fluid of children with severe HFMD compared to mild cases, and their concentrations often correlate with disease severity and poor outcomes, including multi-organ failure involving the kidneys (11). The renal consequences of this cytokine storm are different. Pro-inflammatory cytokines like TNF-α and IL-1β directly damage glomerular endothelial cells and podocytes, increasing vascular permeability and disrupting the crucial glomerular filtration barrier (12). This state manifests clinically as proteinuria, sometimes in the nephrotic range, and hematuria (13). Meanwhile, TNF-α can induce apoptosis in podocytes and tubular cells; since, IL-6, beyond its pro-inflammatory role, promotes mesangial cell proliferation and can contribute to glomerular hypercellularity (12). The surge in cytokines also activates the complement system, another arm of innate immunity. Excessive complement activation, particularly by the alternative and lectin pathways, generates potent anaphylatoxins (C3a, C5a) and the membrane attack complex (C5b-9) (14). Then, C5b-9 deposition on glomerular and tubular cells causes direct lysis and sublytic activation, leading to further inflammation, oxidative stress, and tissue injury (15). Furthermore, the cytokine milieu profoundly alters renal hemodynamics. In this regard, TNF-α and IL-1β induce systemic vasodilation and myocardial depression, contributing to hypotension and reduced renal perfusion pressure (16). Simultaneously, within the kidney itself, these cytokines promote intense intrarenal vasoconstriction. They upregulate endothelin-1 and down-regulate nitric oxide production by endothelial cells (17). This dual hit of reduced systemic perfusion and intrarenal vasoconstriction drastically diminishes renal blood flow and glomerular filtration rate, precipitating or exacerbating AKI (18). This hemodynamic component is often superimposed on direct cellular injury. The dysregulation extends to the adaptive immune system (19); since, EV-A71 infection can trigger aberrant T-cell activation. There is evidence of a skewed T-helper (Th)

response, with a predominance of pro-inflammatory Th1 and Th17 subsets over regulatory T cells (Tregs) in severe cases (20). In the next step, Th17 cells produce IL-17, which further amplifies neutrophil recruitment and activation within renal tissue, contributing to tubulointerstitial inflammation and damage (21). At this condition, the impaired Treg function fails to adequately suppress this excessive inflammation (22). On the other hand, B-cell activation and autoantibody production might also play a role in some cases of persistent renal dysfunction (23). In total, this immune-mediated assault on the kidneys is inextricably linked to profound metabolic derangements that both drive and are exacerbated by AKI (24). In parallel, the systemic inflammatory response syndrome triggered by the cytokine storm induces a hypermetabolic state. Fever, tachycardia, and increased work of breathing significantly elevate basal metabolic rate and oxygen consumption. This hypercatabolism rapidly depletes energy stores, particularly glycogen and protein reserves (25). Then, skeletal muscle breakdown releases amino acids, but the stressed body struggles to utilize them efficiently for repair. Concurrently, insulin resistance develops due to the antagonistic effects of cytokines like TNF-α and IL-6 on insulin signaling pathways. This condition impairs glucose uptake by peripheral tissues, leading to hyperglycemia despite increased energy demands (26). Hyperglycemia itself can be nephrotoxic, promoting oxidative stress and inflammation within the renal microvasculature and tubules (27). Another feature of this disease is electrolyte imbalances, which are rampant and critically impact renal function (28). Profuse sweating from high fever, reduced oral intake due to painful oral ulcers, and sometimes vomiting lead to significant sodium and water loss, causing hypovolemia and prerenal AKI (29). Meanwhile, syndrome of inappropriate antidiuretic hormone secretion (SIADH) causes water retention and hyponatremia, diluting the extracellular fluid (30). The resultant hyponatremia can be profound and is associated with worse neurological outcomes, across with complication in fluid management (31). Importantly, aggressive fluid resuscitation to correct prerenal AKI in the setting of SIADH risks worsening hyponatremia and cerebral edema (32). Hypokalemia is another common and dangerous electrolyte disturbance. It arises from gastrointestinal losses, renal losses due to secondary hyperaldosteronism from hypovolemia, and intracellular shifts driven by catecholamine surges and alkalosis. Hypokalemia directly impairs renal tubular function, reducing the kidney's ability to concentrate urine and exacerbating AKI (33). It also predisposes to cardiac arrhythmias, further compromising hemodynamics and renal perfusion. Likewise, acid-base homeostasis is severely disrupted (34). Lactic acidosis frequently develops due to multiple factors, like tissue hypoperfusion from shock, increased anaerobic metabolism in the hypermetabolic state, and potentially direct viral or cytokine-mediated inhibition of mitochondrial function in tissues including the kidneys (35). The kidneys are central to acid-base regulation, primarily through ammoniagenesis in the proximal tubule and hydrogen ion excretion in the distal tubule (36). At this state, AKI especially acute tubular necrosis, severely impairs these compensatory mechanisms (37). The resulting metabolic acidosis further depresses myocardial contractility, worsens vasoplegia, and can directly inhibit renal tubular cell function, creating a vicious cycle (38). Hypoalbuminemia, common in severe illness due to capillary leak, reduced synthesis, and losses (including renal if proteinuria is significant), contributes to oncotic pressure reduction, exacerbating edema and potentially impairing renal perfusion. It also reduces the binding capacity for toxins and drugs, altering their pharmacokinetics (39). The metabolic demands placed on the kidneys themselves during this crisis are huge. Renal tubular cells, particularly the proximal tubule, are highly energy-dependent, requiring substantial ATP for active transport processes like sodium reabsorption (40). The combination of hypoperfusion, direct viral or cytokine-induced mitochondrial dysfunction within tubular cells, and systemic acidosis creates a state of energy crisis in the nephron (41). This ATP depletion directly impairs tubular reabsorptive capacity, contributing to electrolyte wasting and reducing the kidney's ability to maintain homeostasis (41). Furthermore, the inflammatory milieu generates high levels of reactive oxygen species within renal tissue. Depletion of endogenous antioxidants like glutathione, coupled with reduced blood flow limiting oxygen delivery paradoxically needed for some antioxidant enzymes, leads to oxidative stress (42). Reactive oxygen species damage cellular lipids, proteins, and DNA, triggering apoptosis and necrosis in tubular and glomerular cells, propagating the injury initiated by the immune response (43). Besides, rhabdomyolysis-associated myoglobinuria contributes to kidney damage.

Clinically presentations of renal injury in HFMD

Clinically, kidney injury in severe HFMD often presents insidiously or is masked by more dramatic neurological symptoms (3). Initial signs may be subtle like reduced urine output despite adequate fluid administration, unexplained tachycardia or tachypnea, or worsening lethargy (3). Laboratory findings are crucial for diagnosis. Elevated serum creatinine and blood urea nitrogen are the hallmarks of AKI, but their rise may lag behind actual injury (44). More sensitive early markers gaining traction include neutrophil gelatinase-associated lipocalin, kidney injury molecule-1, and liver-type fatty acid-binding protein, which are released by damaged tubular cells (45). Urinalysis often reveals proteinuria, hematuria, and granular casts or renal tubular epithelial cells (46).

Significant electrolyte abnormalities consisting of hyponatremia, hypokalemia, or hyperkalemia in advanced AKI, and metabolic acidosis are harmful signs (47). The presence of severe proteinuria, especially if persistent, may indicate a predominant glomerular pathology like acute glomerulonephritis, potentially immune-complex mediated (48).

Management modalities

Differentiating the primary drivers of AKI in a critically ill HFMD patient is challenging but essential for management (3). Prerenal AKI due to hypovolemia requires careful fluid resuscitation (49). Intrinsic AKI due to acute tubular necrosis or glomerulonephritis demands different strategies, focusing on mitigating ongoing injury and supporting renal function (50). The profound immune and metabolic dysregulation underlying intrinsic injury necessitates a multifaceted approach beyond simple fluid management (50). Therapeutic strategies should address the core pathophysiological triad, comprising viral replication, immune hyperactivation, and metabolic instability. Given that no specific antiviral therapy is universally approved for HFMD, pleconaril as a capsid inhibitor has shown some efficacy in severe enteroviral infections and may be considered in life-threatening cases with renal involvement, though access is limited (51). Intravenous immunoglobulin (IVIG) is frequently used in severe HFMD, primarily for its immunomodulatory effects (52). Remarkably, IVIG can neutralize circulating cytokines, inhibit complement activation, block Fc receptors on macrophages to reduce phagocytosis and cytokine release, and potentially provide neutralizing antibodies against the virus (53). Its efficacy specifically for preventing or treating HFMD-associated AKI is not definitively proven in large trials (54, 55), but clinical experience suggests benefit in modulating the overall cytokine storm that drives multi-organ injury, including renal (56). Corticosteroids are another immunomodulatory option, particularly in cases with strong evidence of hyper-inflammation, detected by very high cytokine levels and rapidly progressive organ failure. They suppress broad inflammatory pathways but carry significant risks of immunosuppression and hyperglycemia, requiring careful patient selection and monitoring (57). It should remember that aggressive metabolic support is non-negotiable. Meticulous fluid management is utmost. Isotonic crystalloids are preferred for initial resuscitation to restore intravascular volume and renal perfusion, but volumes must be titrated carefully using dynamic parameters like stroke volume variation if available, clinical assessment of perfusion, serial lactate levels, rather than fixed formulas, to avoid overload (58). Electrolyte disturbances require vigilant monitoring and correction: hypertonic saline for severe symptomatic hyponatremia, guided by sodium levels and neurological status, cautious potassium replacement for hypokalemia, and management of hyperkalemia if AKI progresses (59). Bicarbonate therapy for severe metabolic acidosis may be necessary to support cardiac function, though it does not address the underlying cause (60). Nutritional support with adequate calories and protein, while respecting fluid restrictions if needed, is crucial to counteract catabolism and support tissue repair, including renal tubular regeneration (61). Glycemic control with insulin infusion may be required to manage stress-induced hyperglycemia and its detrimental effects (62). Moreover, renal replacement therapy, such as continuous renal replacement therapy, becomes necessary in severe AKI with life-threatening complications: refractory hyperkalemia, severe metabolic acidosis unresponsive to medical therapy, fluid overload causing pulmonary edema or compromising hemodynamics, or uremic symptoms (63). Recent studies found that renal replacement therapy is often preferred over intermittent hemodialysis in critically ill children with hemodynamic instability, as it provides slower, more continuous fluid and solute removal, minimizing hemodynamic fluctuations (64). It also has an immunomodulatory effect by removing inflammatory cytokines, although the clinical significance of this cytokine clearance in HFMD-associated AKI remains debated (65). The decision to initiate renal replacement therapy should not be delayed in the presence of severe, uncorrectable metabolic derangements threatening survival (66).

Prognosis of HFMD-associated AKI

The prognosis for kidney injury in severe HFMD is variable (3). Most children with mild AKI related to dehydration or transient hemodynamic changes recover fully with supportive care. However, AKI resulting from significant immune-mediated intrinsic damage or prolonged severe hypoperfusion carries a worse prognosis (67). Persistent proteinuria or reduced GFR beyond the acute phase may indicate incomplete recovery or the development of chronic kidney disease, although long-term data is limited (68). Mortality is significantly higher in children who develop severe AKI requiring RRT compared to those without renal involvement (69). Factors associated with poor renal outcomes include the need for mechanical ventilation, indicating severe neurological or pulmonary involvement, shock requiring vasoactive support, extremely high initial serum creatinine or urea levels, oliguria/anuria unresponsive to initial fluid resuscitation, and the presence of multi-organ dysfunction syndrome (70). Hence, early identification of patients exhibiting systemic hyperinflammation, hemodynamic instability, metabolic dysregulation, and biomarkers of severe inflammation is critical (71). Then, prompt, targeted intervention to modulate immune activation and correct metabolic derangements can prevent progression to

multi-organ dysfunction, significantly improving survival and preserving long-term organ function (72).

Conclusion

In summary, kidney injury in HFMD, particularly severe cases driven by EV-A71, is not merely a consequence of dehydration but a complex manifestation of profound systemic immune and metabolic dysregulation. The cytokine storm initiated by viral infection unleashes a cascade of events: direct and immune-mediated cellular damage to glomeruli and tubules, severe intrarenal vasoconstriction, complement activation, and a hypermetabolic state inducing catabolism, insulin resistance, and electrolyte disturbance. These processes synergistically impair renal perfusion, disrupt filtration and reabsorption, and deplete cellular energy reserves, culminating in AKI. Recognizing the signs of evolving renal dysfunction amidst the more obvious neurological symptoms of severe HFMD is critical. Management necessitates combats against viral replication, modulates the runaway immune response, and aggressively corrects life-threatening metabolic derangements, fluid status, electrolytes, acid-base balance, and nutrition, while being prepared to initiate renal replacement therapy when necessary.

Authors' contribution

Conceptualization: Hojjat Eghbali Jelodar and Ali Emadzadeh.
Data curation: Hojjat Eghbali Jelodar and Faezeh Nesaei.
Investigation: Ali Emadzadeh, Arsalan Afzal Toosi, and Shirin Taraz Jamshidi.
Supervision: All authors.
Validation: Baharak Maddahi and Ahmad Shajari.
Visualization: Mohammad Pourmahmoudian and Elham Kebriyaei.
Writing–original draft: All authors.
Writing–review and editing: All authors.

Conflicts of interest

The authors declare that they have no competing interests.

Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this work, the authors utilized Perplexity to refine grammar points and language style in writing. Subsequently, the authors thoroughly reviewed and edited the content as necessary, assuming full responsibility for the publication's content.

Ethical issues

Ethical issues (including plagiarism, data fabrication, and double publication) have been completely observed by the authors.

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