**Name of Journal:** *World Journal of Clinical Pediatrics*

**Manuscript NO: 40374**

**Manuscript Type:** MINIREVIEWS

**Clinical features of acute kidney injury in patients with Kawasaki disease**

Watanabe T. AKI in Kawasaki disease

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**Author contributions:** Watanabe T solely contributed to this paper.

**Conflict-of-interest statement:** None.

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**Manuscript source:** Invited manuscript

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**Received:** June 19, 2018

**Peer-review started:** June 20, 2018

**First decision:** July 19, 2018

**Revised:** August 1, 2018

**Accepted:** August 6, 2018

**Article in press:**

**Published online:**

**Abstract**

Although acute kidney injury (AKI) is a common complication in hospitalized children, AKI has rarely been reported in patients with Kawasaki disease (KD). Herein, we review the clinical trajectories of AKI in patients with KD. A total of 39 patients with KD who developed AKI have been reported in 28 publications as case reports. The causes of AKI include prerenal AKI associated with acute heart failure (AHF), intrinsic AKI caused by tubulointerstitial nephritis (TIN), acute nephritic syndrome (ANS), hemolytic uremic syndrome (HUS), immune complex-mediated nephropathy, rhabdomyolysis, and KD shock syndrome (KDSS). Six of the 39 patients (15.4%) underwent renal replacement therapy. While AHF and multiple organ dysfunction syndrome developed in 41% and 68% of KD patients with AKI, respectively, all patients recovered without any renal sequelae. Although the precise pathogenic mechanism underlying the development of AKI in patients with KD is unknown, several possible mechanisms have been proposed, including T-cell-mediated immunologic abnormalities for TIN, renal and glomerular endothelial injury resulting from vasculitis for HUS, immune complex-mediated kidney injury for immune complex-mediated nephropathy and ASN, and capillary leak and an increased release of cytokines with myocardial dysfunction for KDSS.

**Key words:** Kawasaki disease; Kidney involvement; Multiple organ dysfunction syndrome; Acute kidney injury

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**Core tip:** Acute kidney injury (AKI) has rarely been reported in patients with Kawasaki disease (KD). We review the clinical characteristics of AKI in patients with KD and show that AKI is caused by a number of pathologic changes induced by KD. Patients with KD and AKI had good outcomes, despite the developed of multiple organ dysfunction syndrome. The possible mechanisms underlying the development of AKI in KD include T-cell-mediated immunologic abnormalities, renal and glomerular endothelial injury resulted from vasculitis, immune complex-mediated kidney injury, and capillary leak and the increased release of cytokines with myocardial dysfunction.

Watanabe T. Clinical features of acute kidney injury in patients with Kawasaki disease. *World J Clin Pediatr* 2018; In press

**INTRODUCTION**

Kawasaki disease (KD) is a systemic vasculitis that occurs mainly in infants and children[1]. Although clinical and epidemiologic studies suggest an infectious etiology, the causative agent has yet to be determined[2]. Recent studies have suggested that an immunologic reaction is induced in genetically-susceptible hosts upon exposure to the KD trigger[2]. Because KD is a systemic vasculitis, KD can involve multiple organs and tissues, including the kidneys[3].

Kidney complications in KD include pyuria, trace proteinuria, prerenal acute kidney injury (AKI), intrinsic AKI resulted from tubulointerstitial nephritis (TIN), hemolytic uremic syndrome (HUS), immune complex-mediated nephropathy, intrinsic AKI associated with KD shock syndrome (KDSS), acute nephritic syndrome (ANS), nephrotic syndrome (NS), and renal tubular abnormalities[4]. Although patients with KD often present with sterile pyuria and trace proteinuria, other kidney complications in KD are uncommon[4]; however, several laboratory and imaging studies have shown that a number of patients with KD develop subclinical kidney injury[5,6].

AKI is a common complication in hospitalized children[7]. Recent studies have shown that AKI developed in 26.9% of children and young adults admitted to the intensive care unit (ICU)[8], and in at least 5% of non-critically ill hospitalized children and young adults[9]. Because AKI is associated with poor outcomes, including a high mortality rate and long-term morbidity[7,10], it is important to establish the causes and clinical features of hospitalized children with AKI, as well as patients with KD. The clinical trajectories of AKI in patients with KD are the subject of this mini-review.

We conducted a computerized search of the English, French, and Spanish literature using the PubMed database with a search engine and the Japanese literature using the Japan Medical Abstract Society database with a search engine from January 1967 through April 2018. The search used a combination of the following terms: “Kawasaki disease” with “acute kidney injury” or with “acute renal failure”. Also, a direct search of cited references was conducted. The clinical criteria in the 2004 American Heart Association/American Academy of Pediatrics guidelines were used to diagnose KD[11]. AKI is usually defined as serum creatinine level elevation ≥ 1.5 times the baseline level, according to Kidney Disease: Improving Global Outcomes Clinical Practice Guideline for Acute Kidney Injury[12]. Because the baseline level of serum creatinine was not documented in most of the patients searched in this study, AKI was defined as a serum creatinine level ≥ 1.5 times the upper limit of the normal age-specific serum creatinine reference level[13,14]. Studies which had insufficient clinical information for each patient were excluded from detailed analysis of the clinical manifestations of KD patients with AKI.

**PREVALENCE OF AKI IN PATIENTS WITH KD**

Chuang *et al*[13] studied the clinical characteristics and laboratory data of 336 Taiwanese patients with KD, including serum creatinine levels, and reported that 28% of the patients with KD developed AKI. Moreover, young age and elevated alanine transaminase level were reported to be the main factors associated with AKI. Based on our review of the clinical and laboratory data of 249 Japanese children with KD, however, no patients developed AKI[15]. Although it is not clear why the two reports yielded a different prevalence for AKI in patients with KD, it is possible that differences in disease severity influenced the results[15].

**EPIDEMIOLOGY**

Thirty-nine patients with KD who developed AKI have been reported in 28 publications as case reports[16-43]. The median age was 4.8 years (range, 3 mo-to-45 years). Twenty-seven patients were male (male-to-female ratio, 2.07:1). Thirty-two patients developed complete KD, while 7 patients had incomplete KD.

**CAUSES OF AKI**

The causes of AKI are usually divided into the following three pathophysiologic categories: prerenal AKI, which is characterized by effective hypoperfusion of the kidneys and a lack of parenchymal damage to the kidney; intrinsic AKI, which involves renal parenchymal damage; and postrenal AKI, which is associated with acute obstruction of the urinary tract[44]. In patients with KD, prerenal AKI associated with acute heart failure (AHF)[16,17] and intrinsic AKI have been reported. The causes of intrinsic AKI in KD include TIN[18-21], ANS[22-24], HUS[25-27], immune complex-mediated nephropathy[28], rhabdomyolysis[29], and KDSS[30-34] (Table 1); however, because only 8 of the reported KD patients with AKI underwent renal biopsies, the etiology of AKI was unknown in 25% of the patients[35-43].

**CLINICAL MANIFESTATIONS**

Oliguria, edema, hypotension, and hypertension occurred in 62% (18/29), 31% (2/29), 41% (16/39) and 15.4% (6/39) of the KD patients, respectively, and AHF developed in 41% (16/39) of the KD patients. Based on the Goldstein diagnostic criteria, 68.4% of patients had multiple organ dysfunction syndrome (MODS)[45], and the median number of affected organs was 2 (range, 1-5). The dysfunctional systems included the cardiovascular system in 41% (16/39) of the patients, the respiratory system in 10.2% (4/39), the nervous system in 25.6% (10/39), the hematologic system in 5.1% (2/39), and the hepatobiliary system in 33.3% (13/39).

The median blood urea nitrogen level was 58 mg/dL (range, 8-194 mg/dL), and the median serum creatinine level was 2.2 mg/dL (range, 0.5-7.43 mg/dL). Sixteen of 20 patients (80%) had hyponatremia (serum sodium < 135 mEq/L), 82.1% had proteinuria, 46.4% (13/28) had hematuria, and 73.9% (17/23) had pyuria. Three patients with KDSS developed NS, and 3 patients with ANS had macroscopic hematuria.

Only 8 patients underwent renal biopsies, which revealed TIN in 4 patients, ATN in 2, immune complex-mediated nephropathy in 1, and minor abnormalities in 1. Thirty of the 39 patients (76.9%) underwent intravenous immunoglobulin (IVIG) therapy. IVIG therapy was effective in 73.3% (22/30) of the patients, while 26.7% (8/30) were IVIG-resistant. Six of the 39 patients (15.4%) had renal replacement therapy, which included hemodialysis in 4 patients, continuous hemodialysis in 1, and peritoneal dialysis in 1.

All patients recovered from AKI without any renal sequelae. Although transient coronary artery dilatation occurred in 28.2% (11/39) of the patients, coronary artery aneurysms (CAAs) developed in 5.1% (2/39).

***Prerenal AKI***

Two patients with KD who developed prerenal AKI have been reported. Senzaki *et al*[16] reported an 8-year-old boy with KD who developed AHF and AKI. The results of the fractional excretion of sodium (0.04%), the renal failure index (0.02), the urine-to-plasma creatinine ratio (54), and the urine-to-plasma osmolality ratio (1.7) were consistent with prerenal AKI. Adachi described a 2-year-old girl with KD who developed prerenal AKI caused by hypovolemia due to gastrointestinal losses and AHF[17]. An intravenous fluid infusion and IVIG therapy resolved AKI following improvement of AHF in both patients, probably due to correction of hypovolemia and myocardial dysfunction, respectively.

AHF causes renal hypoperfusion due to decreased cardiac output[44]. In addition, KD is associated with hypovolemia due to decreased oral intake, gastrointestinal losses, or third spacing resulting from increased vascular permeability[16]. Therefore, both hypovolemia and AHF may have central roles in the development of prerenal AKI in patients with KD.

***Intrinsic AKI***

**TIN:** AKI due to TIN has been reported in 5 patients with KD. None of the patients had a *Yersinia pseudotuberculosis* infection[46]. Veiga *et al*[18] reported a 2-year-old boy with KD who developed AKI based on a renal biopsy, which showed diffuse interstitial infiltration of mononuclear and polymorphonuclear leukocytes. The patient was treated with IVIG, oral aspirin, fluid restriction, and furosemide, and recovered without any untoward sequelae. Kawamura[19] reported a 9-year-old girl with KD who developed AKI based on a renal biopsy, which showed mild interstitial mononuclear cell infiltration. The patient underwent hemodialysis and recovered without any renal sequelae. Ashida *et al*[20] reported a 5-year-old boy with KD who developed AKI based on a renal biopsy, which revealed interstitial infiltration of mononuclear cells. After fluid restriction and IVIG therapy, the boy recovered without sequelae. Bonany *et al*[21] reported an 8-year-old boy with KD who developed AKI and NS based on a renal biopsy, which showed TIN and acute tubular necrosis; the patient recovered with supportive care alone.

TIN is an immune-mediated cause of AKI that is characterized by the presence of an inflammatory cell infiltrate in the interstitium of the kidney[47]. Although acute TIN is largely due to medications, autoimmune diseases are associated with acute TIN, including anti-tubular basement membrane disease, TIN with uveitis, and KD[48]. Although the pathogenesis underlying TIN has not been completely described, T cell activation and the resultant cytokine and protease activity may play central roles in TIN. Because T cell activation and extensive cytokine release also occur in KD[1,2], these immunologic abnormalities may cause acute TIN in some patients with KD.

**ANS:** AKI due to ANS has been reported in 3 patients with KD. Suzue *et al*[22] reported a 5-mo-old boy with KD who developed AKI due to ANS 2 wk after IVIG therapy with a transient decrease in serum C3 and C4 levels. The patient recovered with supportive care alone. Yoshida *et al*[23] reported a 3-mo-old girl with KD who developed AHF and AKI due to ANS 6 d after IVIG therapy with a transient decrease in serum C3 and C4 levels. While the pathogenesis underlying the development of ANS in these patients with KD was not established, an immune complex-mediated mechanism was suspected because both patients had transient hypocomplementemia following IVIG therapy.

In contrast, Motoyama *et al*[24] reported a 6-year-old boy with ANS and AKI who subsequently developed KD. The patient was administered intravenous corticosteroids and oral aspirin and recovered without any sequelae.

**HUS:** AKI due to HUS has been reported in 3 patients with KD. Ferriero and Wolfsdorf[25] reported a 2-year-old girl with KD who developed AKI and metabolic encephalopathy due to HUS. She recovered with supportive care alone[25]. Heldrich *et al*[26] reported a 3-year-old girl with KD who developed AKI due to HUS and Henoch-Schönlein purpura, which required adjustment to therapy. Saviour *et al*[27] reported a 2-year-old boy with KD who developed AKI due to HUS. The patient underwent IVIG therapy and supportive management of fluids and electrolytes. She recovered without any sequelae.

Without renal biopsy findings, the pathogenesis of HUS in patients with KD cannot to be ascertained; however, it is possible that vasculitis-associated KD may involve the kidney causing injury to the renal and glomerular endothelium, thus leading to HUS[25].

**Immune complex-mediated nephropathy:** Nagamatsu *et al*[28] reported a 3-year-old boy with KD who developed AKI. The patient was treated with IVIG, dopamine, and furosemide. Electron microscopy of a renal biopsy specimen showed electron-dense deposits in the subepithelial spaces and podocytes, which suggested the possibility of glomerular derangement by immune complexes.

**Rhabdomyolysis:** Sevin *et al*[29] reported a 10-year-old girl with KD who developed AKI due to rhabdomyolysis that was possibly caused by hyperthermia. A renal biopsy showed renal tubular necrosis without glomerular or vascular changes[29]. The patient recovered from AKI with IVIG and supportive care alone.

**KDSS:** KDSS is a condition characterized by systolic hypotension or clinical signs of poor perfusion in patients with KD[49,50]. Although the pathogenesis underlying KDSS is unknown, intensive vasculitis with capillary leak and hypercytokinemia with myocardial dysfunction may cause KDSS[49-51].

Mac Ardle *et al*[30] reported a 2-year-old boy with KDSS who developed encephalopathy, respiratory failure and AKI. A renal biopsy showed normal glomeruli and a patchy immune-type infiltrate consisting of plasma cells and eosinophils, with evidence of recovering acute tubular necrosis. The patient received an intravenous fluid infusion, underwent peritoneal dialysis, and was mechanically ventilated. The boy recovered with mild neurologic sequelae. Nakanishi *et al*[31] reported a 12-year-old boy with KDSS who developed AHF, a coagulopathy, and AKI. A renal biopsy showed no glomerular or tubular abnormalities. The patient recovered with IVIG, hemodialysis, and the intravenous administration of catecholamines. An 11-year-old girl with KDSS who developed AKI and AHF due to myocarditis was reported[32]. The patient was mechanically ventilated, and received a diuretic intravenously, and IVIG therapy. She recovered but had CAAs. Umei *et al*[33] reported a 12-year-old boy with KDSS who developed AHF, hepatic dysfunction, a coagulopathy, and AKI. The patient was treated with IVIG, plasma exchange, continuous hemodialysis, and the intravenous administration of catecholamines. He recovered without any sequelae. Gatterre *et al*[34] studied 11 patients with KDSS and reported that 10 developed AKI. Nine of the patients had proteinuria, 3 of whom exhibited NS. All of the patients underwent IVIG therapy and recovered without sequelae.

**Undetermined etiologies:** Eleven patients with AKI of unknown etiologies have been reported. Yamawaki *et al*[35] reported a 5-year-old boy with KD who developed oliguric AKI. The patient underwent hemodialysis and recovered without any sequelae. Nardi *et al*[36] reported a 6-year-old girl with KD who developed oliguric AKI and hepatic dysfunction. The patient recovered with supportive care alone. Lande *et al*[37] reported a 3-year-old girl with KD who developed oliguric AKI. The patient received IVIG and underwent hemodialysis. She recovered without any sequelae. Ashida *et al*[20] reported a 3-year-old boy with KD who developed AKI. He was treated with IVIG and recovered without any sequelae. El Karoui *et al*[38] reported a 45-year-old man with adult-onset KD who developed AKI. He was treated with IVIG, which resulted in rapid improvement and recovery of normal renal function. Nandi and Mondal[39] reported a 4-year-old boy with KD who developed oliguric AKI. The patient recovered with supportive care alone. Keeswijk and Walle[40,41] reported a 2-year-old boy with KD who developed oliguric AKI. The patient recovered completely with IVIG therapy, fluid restriction, and a diuretic. Tiewsoh *et al*[42] reported 3 boys with incomplete KD who developed AKI. All of the patients were treated with IVIG and recovered without any sequelae. Martínez Vázquez *et al*[43] reported a 9-year-old girl with KD who developed oliguric AKI and cholestasis. The patient was treated with IVIG and intravenous pulses of methylprednisolone, which led to an improvement in the AKI and clinical features of KD, but she had CAAs.

**THERAPEUTIC STRATEGIES TO KD PATIENTS WITH AKI**

Treatment of KD patients with prerenal AKI and AHF consists of appropriate restoration of the normal circulating blood volume, heart function support[44], and specific therapy for KD[44]. Among KD patients with intrinsic AKI, renal damage results from vasculitis of the renal arteries, or T cell- or B cell-mediated immuno-regulatory abnormalities caused by KD. Therefore, treatments adapted to the severity of KD can improve AKI in addition to supportive therapies to ameliorate derangements of fluid and electrolyte homeostasis, which include fluid restriction, diuretic usage and renal replacement therapy[10,44].

**CONCLUSION**

AKI in patients with KD is uncommon and includes the following conditions: prerenal AKI; intrinsic AKI caused by TIN; ANS; HUS; immune complex-mediated nephropathy; rhabdomyolysis; KDSS; and undetermined etiologies.

Although the pathogenic mechanism underlying renal involvement in patients with KD who develop AKI is unknown, several possible mechanisms have been proposed, which include T-cell-mediated immunologic abnormalities for TIN, muscle injury caused by hyperthermia for rhabdomyolysis, renal and glomerular endothelial injury resulting from vasculitis for HUS, immune complex-mediated kidney injury for immune-complex mediated nephropathy and ANS, and capillary leak and hypercytokinemia with myocardial dysfunction induced by intensive vasculitis for KDSS.

**REFERENCES**

1 **Newburger JW**, Takahashi M, Burns JC. Kawasaki Disease. *J Am Coll Cardiol* 2016; **67**: 1738-1749 [PMID: 27056781 DOI: 10.1016/j.jacc.2015.12.073]

2 **Shulman ST**, Rowley AH. Kawasaki disease: insights into pathogenesis and approaches to treatment. *Nat Rev Rheumatol* 2015; **11**: 475-482 [PMID: 25907703 DOI: 10.1038/nrrheum.2015.54]

3 **Watanabe T**, Abe Y, Sato S, Uehara Y, Ikeno K, Abe T. Sterile pyuria in patients with Kawasaki disease originates from both the urethra and the kidney. *Pediatr Nephrol* 2007; **22**: 987-991 [PMID: 17323086 DOI: 10.1007/s00467-007-0449-7]

4 **Watanabe T**. Kidney and urinary tract involvement in kawasaki disease. *Int J Pediatr* 2013; **2013**: 831834 [PMID: 24288547 DOI: 10.1155/2013/831834]

5 **Wang JN**, Chiou YY, Chiu NT, Chen MJ, Lee BF, Wu JM. Renal scarring sequelae in childhood Kawasaki disease. *Pediatr Nephrol* 2007; **22**: 684-689 [PMID: 17151872 DOI: 10.1007/s00467-006-0385-y]

6 **Wu JM**, Chiou YY, Hung WP, Chiu NT, Chen MJ, Wang JN. Urinary cytokines and renal Doppler study in Kawasaki disease. *J Pediatr* 2010; **156**: 792-797 [PMID: 20171655 DOI: 10.1016/j.jpeds.2009.11.046]

7 **Sutherland SM**, Kwiatkowski DM. Acute Kidney Injury in Children. *Adv Chronic Kidney Dis* 2017; **24**: 380-387 [PMID: 29229169 DOI: 10.1053/j.ackd.2017.09.007]

8 **Kaddourah A**, Basu RK, Bagshaw SM, Goldstein SL; AWARE Investigators. Epidemiology of Acute Kidney Injury in Critically Ill Children and Young Adults. *N Engl J Med* 2017; **376**: 11-20 [PMID: 27959707 DOI: 10.1056/NEJMoa1611391]

9 **McGregor TL**, Jones DP, Wang L, Danciu I, Bridges BC, Fleming GM, Shirey-Rice J, Chen L, Byrne DW, Van Driest SL. Acute Kidney Injury Incidence in Noncritically Ill Hospitalized Children, Adolescents, and Young Adults: A Retrospective Observational Study. *Am J Kidney Dis* 2016; **67**: 384-390 [PMID: 26319754 DOI: 10.1053/j.ajkd.2015.07.019]

10 **Bellomo R**, Kellum JA, Ronco C. Acute kidney injury. *Lancet* 2012; **380**: 756-766 [PMID: 22617274 DOI: 10.1016/S0140-6736(11)61454-2]

11 **Newburger JW**, Takahashi M, Gerber MA, Gewitz MH, Tani LY, Burns JC, Shulman ST, Bolger AF, Ferrieri P, Baltimore RS, Wilson WR, Baddour LM, Levison ME, Pallasch TJ, Falace DA, Taubert KA; Committee on Rheumatic Fever, Endocarditis and Kawasaki Disease; Council on Cardiovascular Disease in the Young; American Heart Association; American Academy of Pediatrics. Diagnosis, treatment, and long-term management of Kawasaki disease: a statement for health professionals from the Committee on Rheumatic Fever, Endocarditis and Kawasaki Disease, Council on Cardiovascular Disease in the Young, American Heart Association. *Circulation* 2004; **110**: 2747-2771 [PMID: 15505111 DOI: 10.1161/01.CIR.0000145143.19711.78]

12 **Kellum J**, Lameire N, Aspelin P, Barsoum R, Burdmann E, Goldstein S, Herzog C, Joannidis M, Kribben A, Levey A, MacLeod A, Mehta R, Murray P, Naicker S, Opal S, Schaefer F, Schetz M, Uchino S. Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group: KDIGO clinical practice guideline for acute kidney injury. *Kidney Int Suppl* 2012; **2**: 1-138

13 **Chuang GT**, Tsai IJ, Lin MT, Chang LY. Acute kidney injury in patients with Kawasaki disease. *Pediatr Res* 2016; **80**: 224-227 [PMID: 27064240 DOI: 10.1038/pr.2016.81]

14 **Søeby K**, Jensen PB, Werge T, Sørensen S. Mining of hospital laboratory information systems: a model study defining age- and gender-specific reference intervals and trajectories for plasma creatinine in a pediatric population. *Clin Chem Lab Med* 2015; **53**: 1621-1630 [PMID: 25719320 DOI: 10.1515/cclm-2014-0949]

15 **Watanabe T**, Abe T, Tsukano S. Acute kidney injury occurs only rarely in patients with Kawasaki disease. *Pediatr Res* 2017; **82**: 890-891 [PMID: 28817559 DOI: 10.1038/pr.2017.191]

16 **Senzaki H**, Suda M, Noma S, Kawaguchi H, Sakakihara Y, Hishi T. Acute heart failure and acute renal failure in Kawasaki disease. *Acta Paediatr Jpn* 1994; **36**: 443-447 [PMID: 7942014 DOI: 10.1111/j.1442-200X.1994.tb03220.x]

17 **Adachi K**. A two-year-old girl with Kawasaki disease who developed acute renal failure (in Japanese). *Prog Med* 1998; **18**: 394-395

18 **Veiga PA**, Pieroni D, Baier W, Feld LG. Association of Kawasaki disease and interstitial nephritis. *Pediatr Nephrol* 1992; **6**: 421-423 [PMID: 1457322 DOI: 10.1007/BF00873999]

19 **Kawamura I**. A case of acute renal failure, anemia and thrombophlebitis in a patient with Kawasaki disease (in Japanese). *Shoni Zinfuzen Kenkyukai Shi* 1993; **13**: 158-160

20 **Ashida A**, Katayama H, Nakamura H, Tamai K, Yoshikawa K, Takahashi T. Acute renal failure in patients with Kawasaki disease (in Japanese). *Shoni Zinfuzen Kenkyukai Shi* 2000; **20**: 169-172

21 **Bonany PJ**, Bilkis MD, Gallo G, Lago N, Dennehy MV, Sosa del Valle JM, Vallejo G, Cánepa C. Acute renal failure in typical Kawasaki disease. *Pediatr Nephrol* 2002; **17**: 329-331 [PMID: 12042888 DOI: 10.1007/s00467-002-0844-z]

22 **Suzue T**, Ohuchi T, Ichioka T, Tamura Y, Tsuno K. An infant with Kawasaki disease associated with nephritis (in Japanese). *Shonika Rinsho* 1989; **42**: 2196-2200

23 **Yoshida S**, Ai Y, Imai K, Mimasu S. A case of Kawasaki disease complicated by acute glomerulonephritis (in Japanese). *Progress in Medicine* 2002; **22**: 1598-1593

24 **Motoyama O**, Tarui H, Ishihara C, Komatsu H, Matsuyama G, Sawada K, Tateno A, Iitaka K. Kawasaki disease presenting with macroscopic hematuria. *Pediatr Int* 2008; **50**: 260-261 [PMID: 18353075 DOI: 10.1111/j.1442-200X.2008.02566.x]

25 **Ferriero DM**, Wolfsdorf JI. Hemolytic uremic syndrome associated with Kawasaki disease. *Pediatrics* 1981; **68**: 405-406 [PMID: 7279468]

26 **Heldrich FJ**, Jodorkovsky RA, Lake AM, Parnes CA. Kawasaki syndrome: HUS and HSP complicating its course and management. *Md Med J* 1987; **36**: 764-766 [PMID: 3683104]

27 **Saviour MJ**, Hassan S. Kawasaki Disease Presenting with Bloody Diarrhea and Acute Renal Failure: First Case. *Pediatr Rep* 2017; **9**: 7163 [PMID: 28706619 DOI: 10.4081/pr.2017.7163]

28 **Nagamatsu K**, Ikuta K, Aoki S, Sakata K, Onouchi Z. An acute renal disease which developed in 3-year-old boy during Kawasaki disease. *J Clin Electron Microscopy* 1990; **23**: 5-6

29 **Sevin C**, Heidet L, Gagnadoux MF, Chéron G, Niaudet P. [Acute renal insufficiency in Kawasaki disease]. *Arch Fr Pediatr* 1993; **50**: 505-507 [PMID: 8135613]

30 **Mac Ardle BM**, Chambers TL, Weller SD, Tribe CR. Acute renal failure in Kawasaki disease. *J R Soc Med* 1983; **76**: 615-616 [PMID: 6876053 DOI: 10.1177/014107688307600718]

31 **Nakanishi S**, Iwasaki T, Koga Y, Kamishiro M, Yamagishi M. A case of acute renal failure probably due to Kawasaki disease (in Japanese). *Shoni Zinfuzen Kenkyukai Shi* 1994; **14**: 53-56

32 Case records of the Massachusetts General Hospital. Weekly clinicopathological exercises. Case 36-1998. An 11-year-old girl with fever, hypotension, and azotemia. *N Engl J Med* 1998; **339**: 1619-1626 [PMID: 9867524 DOI: 10.1056/NEJM199811263392208]

33 **Umei N**, Atagi K, Shimaoka H, Kinishi Y, Suga T, Otsuka Y, Uziro A. A case of Kawasaki disease initially diagnosed as septic shock (in Japanese). *J Jpn Soc Intensive Care Med* 2012; **19**: 405-408 [DOI: 10.3918/jsicm.19.405]

34 **Gatterre P**, Oualha M, Dupic L, Iserin F, Bodemer C, Lesage F, Hubert P. Kawasaki disease: an unexpected etiology of shock and multiple organ dysfunction syndrome. *Intensive Care Med* 2012; **38**: 872-878 [PMID: 22273753 DOI: 10.1007/s00134-012-2473-8]

35 **Yamawaki Y**, Hattori M, Nishikawa R, Chishiro H, Fujizaki Y. A case of MCLS with acute renal failure (in Japanese). *Shonika Shinryo* 1984; **47**: 350-353

36 **Nardi PM**, Haller JO, Friedman AP, Slovis TL, Schaffer RM. Renal manifestations of Kawasaki's disease. *Pediatr Radiol* 1985; **15**: 116-118 [PMID: 3883299 DOI: 10.1007/BF02388716]

37 **Lande MB**, Gleeson JG, Sundel RP. Kawasaki disease and acute renal failure. *Pediatr Nephrol* 1993; **7**: 593 [PMID: 8251330 DOI: 10.1007/BF00852560]

38 **El Karoui K**, Servais A, Fadel F, Jablonski M, Fakhouri F, Lesavre P, Hummel A. Acute renal failure and febrile rash--infectious or not? Adult Kawasaki disease (KD). *Nephrol Dial Transplant* 2007; **22**: 949-951 [PMID: 17210597 DOI: 10.1093/ndt/gfl792]

39 **Nandi M**, Mondal R. Acute renal failure in a child with Kawasaki disease. *East J Med* 2010; **15**: 122-124

40 **Keenswijk W**, Walle JV. An atypical case of a 2-year-old boy with acute kidney injury: a race against time. Questions. *Pediatr Nephrol* 2017; **32**: 1175-1176 [PMID: 27704254 DOI: 10.1007/s00467-016-3497-z]

41 **Keenswijk W**, Walle JV. An atypical case of a 2-year-old boy with acute kidney injury: a race against time. Answers. *Pediatr Nephrol* 2017; **32**: 1177-1179 [PMID: 27704255 DOI: 10.1007/s00467-016-3516-0]

42 **Tiewsoh K**, Sharma D, Jindal AK, Bhisikar S, Suri D, Singh S. Acute Kidney Injury in Kawasaki Disease: Report of 3 Cases From North India and a Brief Review of Literature. *J Clin Rheumatol* 2018; **24**: 231-234 [PMID: 29293117 DOI: 10.1097/RHU.0000000000000687]

43 **Martínez Vázquez JA**, Sánchez García C, Rodríguez Muñoz L, Martínez Ramírez RO. Acute kidney injury and cholestasis associated with Kawasaki disease in a 9-year-old: Case report. *Reumatol Clin* 2017; **pii**: S1699-258X(17)30282-6 [PMID: 29254742 DOI: 10.1016/j.reuma.2017.11.008]

44 **Sharfuddin AA**, Weisbord SD, Palevsky PM, Molitoris BA. Acute kidney injury. In: Skorecki K, Chertow GM, Marsden PA, Taal MW, Yu ASL. Brenner and Rector's the kidney. 2nd ed. Philadelphia: Elsevier, 2016: 958-1011

45 **Goldstein B**, Giroir B, Randolph A; International Consensus Conference on Pediatric Sepsis. International pediatric sepsis consensus conference: definitions for sepsis and organ dysfunction in pediatrics. *Pediatr Crit Care Med* 2005; **6**: 2-8 [PMID: 15636651 DOI: 10.1097/01.PCC.0000149131.72248.E6]

46 **Watanabe T**. Acute renal failure in Kawasaki disease. *Pediatr Nephrol* 2003; **18**: 200; author reply 201 [PMID: 12579412 DOI: 10.1007/s00467-002-1027-7]

47 **Ulinski T**, Sellier-Leclerc AL, Tudorache E, Bensman A, Aoun B. Acute tubulointerstitial nephritis. *Pediatr Nephrol* 2012; **27**: 1051-1057 [PMID: 21638156 DOI: 10.1007/s00467-011-1915-9]

48 **Neilson EG**. Tubulointerstitial nephritis. In: Goldman L, Schafer AI. Goldman's Cecil medicine. 25th ed. Philadelphia: Elsevier, 2016: 793-799

49 **Kanegaye JT**, Wilder MS, Molkara D, Frazer JR, Pancheri J, Tremoulet AH, Watson VE, Best BM, Burns JC. Recognition of a Kawasaki disease shock syndrome. *Pediatrics* 2009; **123**: e783-e789 [PMID: 19403470 DOI: 10.1542/peds.2008-1871]

50 **Taddio A**, Rossi ED, Monasta L, Pastore S, Tommasini A, Lepore L, Bronzetti G, Marrani E, Mottolese BD, Simonini G, Cimaz R, Ventura A. Describing Kawasaki shock syndrome: results from a retrospective study and literature review. *Clin Rheumatol* 2017; **36**: 223-228 [PMID: 27230223 DOI: 10.1007/s10067-016-3316-8]

51 **Natterer J**, Perez MH, Di Bernardo S. Capillary leak leading to shock in Kawasaki disease without myocardial dysfunction. *Cardiol Young* 2012; **22**: 349-352 [PMID: 21933461 DOI: 10.1017/S1047951111001314]

**P-Reviewer:** Agrawal A, Das RR, Teng RJ, Tommasini A, Uwaezuoke SN **S-Editor:** Ji FF **L-Editor: E-Editor:**

**Specialty type:** Pediatrics

**Country of origin:** Japan

**Peer-review report classification**

Grade A (Excellent): A

Grade B (Very good): B

Grade C (Good): C, C

Grade D (Fair): 0

Grade E (Poor): E

**Table 1 Causes of acute kidney injury in patients with Kawasaki disease**

|  |  |
| --- | --- |
| Cause  | *N* |
| 1 Prerenal AKI associated with acute heart failure  | 2 |
| 2 Intrinsic AKI  |  |
| Tubulointerstitial nephritis  | 4 |
|  Acute nephritic syndrome  | *3* |
|  Hemolytic uremic syndrome  | *3* |
|  Immune complex-mediated nephritis  | *1* |
|  Rhabdomyolysis  | *1* |
|  Kawasaki disease shock syndrome  | *14* |
|  Undetermined etiology  | *11* |

AKI: Acute kidney injury.