



# Kawasaki Disease Shock Syndrome Versus Septic Shock: Early Differentiating Features Despite Overlapping Clinical Profiles

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**Objectives** To compare the clinical features and resuscitative measures of children with Kawasaki disease shock syndrome vs septic shock.

**Study design** In this retrospective case-control study, children with Kawasaki disease shock syndrome admitted to the intensive care unit from 2007 to 2017 were identified and compared with age-matched controls with septic shock. We studied 9 children with Kawasaki disease shock syndrome and 18 children with septic shock. Clinical characteristics were abstracted and between-group differences were compared.

**Results** Compared with septic shock controls, children with Kawasaki disease shock syndrome were less likely to have an underlying comorbid illness (1/9 [11%] vs 11/18 [61%];  $P = .02$ ) and were more likely to have at least 1 of the 5 classic diagnostic signs of Kawasaki disease at presentation (9/9 [100%] vs 0/18 [0%];  $P < .001$ ), a longer duration of illness before admission (9 days [IQR, 7-14 days] vs 3 days [IQR, 1-5 days];  $P = .004$ ), and a lower platelet count at presentation (140 [IQR 73, 167] vs 258 [IQR, 137-334];  $P = .02$ ). Among patients who underwent echocardiography, abnormalities such as ventricular dysfunction, valvulitis, and coronary artery dilation were more common in the Kawasaki disease shock syndrome cohort (5/9 [56%] vs 0/7 [0%];  $P = .03$ ). There were no differences in volume of fluid resuscitation, vasoactive-inotropic scores, duration of inotropic therapy, or biochemical markers of illness severity (other than platelet count) between the matched groups.

**Conclusions** A longer duration of illness before admission, lack of any significant underlying medical comorbidities, a lower platelet count, echocardiographic abnormalities, and the presence of classic diagnostic signs of Kawasaki disease at presentation may be useful early features to differentiate Kawasaki disease shock syndrome from septic shock. (*J Pediatr* 2021;231:162-7).

**K**awasaki disease is an acute systemic small-to-medium vessel vasculitis that occurs predominantly in infants and young children.<sup>1-4</sup> It is the leading cause of acquired heart disease in North American children, but timely treatment decreases the risk of coronary artery aneurysm formation to 2%-5%.<sup>5,6</sup> Approximately 6%-7% of patients with Kawasaki disease present with shock.<sup>7-9</sup> This newly recognized clinical entity was coined Kawasaki disease shock syndrome by Kanegaye et al in 2009.<sup>7</sup> Kawasaki disease shock syndrome is defined by a diagnosis of Kawasaki disease in patients with hypotension or shock who receive volume expansion, vasoactive infusions, or transfer to an intensive care setting.<sup>10</sup> Kawasaki disease shock syndrome is often initially misdiagnosed as sepsis or septic shock, resulting in therapeutic delays.<sup>8</sup>

The underlying pathophysiology of shock in these patients has not yet been elucidated, although cardiogenic, distributive, and mixed shock subtypes have been described.<sup>11,12</sup> Similar mechanisms may, therefore, underlie the pathophysiology of shock in both Kawasaki disease shock syndrome and septic shock, including the release of inflammatory cytokines decreasing peripheral vascular resistance and promoting capillary fragility and leakage, and inflammatory myocarditis causing myocardial dysfunction. Similar to children with septic shock, Kawasaki disease shock syndrome has been associated with multiple organ dysfunction syndrome.<sup>11,13</sup>

Kawasaki disease shock syndrome shares some clinical and pathophysiologic features with septic shock, but there have been no studies directly comparing the 2 entities. Septic shock is a life-threatening condition with circulatory and metabolic dysfunction caused by a dysregulated response to infection.<sup>14</sup> Our study objective was to compare clinical features, resuscitative measures, and hemodynamic response to treatment between children with Kawasaki disease shock syndrome and children with septic shock.

ICU	Intensive care unit
IVIg	Intravenous immunoglobulin
TSS	Toxic shock syndrome
VIS	Vasoactive-inotropic score

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The authors declare no conflicts of interest.

Portions of this study were presented at the 12th International Kawasaki Disease Symposium, June 12-15, 2018, Yokohama, Japan.

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<https://doi.org/10.1016/j.jpeds.2020.12.002>

## Methods

### Study Population

We performed a retrospective chart review of all patients less than 18 years of age admitted to the Hospital for Sick Children Intensive Care Unit (ICU) from January 1, 2007, to March 31, 2017, who met the criteria for Kawasaki disease shock syndrome as defined by the American Heart Association.<sup>10</sup> Children admitted to the ICU with an diagnostic code of septic shock using *International Classification of Disease-9/-10* terminology (depending on the year) and without preexisting cardiac disease were used as the control group. Our controls were first matched for age, and if there was more than 1 match then patients were matched by admission date (admission to hospital within the same calendar year). Two controls were chosen for each case.

### Study Analysis and Definitions

Clinical information was extracted from the medical record, including preceding comorbid disease, duration of illness before admission, duration of ICU stay and of hospital admission, and end-organ involvement. Coronary artery dilation was defined as a z-score of 2 or greater. Preceding comorbid diseases were determined to be significant after review by 2 physicians with full agreement. Results of echocardiograms during the acute phase of illness were documented.

The results of any laboratory tests obtained within 6 hours of ICU admission were collected; if more than 1 sample was taken, then the sample closest to the time of ICU admission was chosen with preference given to tests obtained before admission. Fluid resuscitation was defined as isotonic fluid boluses administered before and up to 1 hour after ICU admission. Inotropic therapy data were collected longitudinally through duration of ICU admission. A vasoactive-inotropic score (VIS) was calculated for each patient while on inotropic therapy to quantify hemodynamic support. The peak VIS during admission as well as the VIS at 6 hours and at 48 hours of ICU stay were documented. The VIS has been validated in pediatric sepsis as a surrogate outcome measure, with the VIS at 48 hours having the strongest correlation with important ICU outcomes.<sup>15</sup> The VIS is calculated by adding the dose of each inotrope or vasopressor, using doses in micrograms per kilogram per minute unless otherwise specified. The VIS is equal to: dopamine dose + dobutamine dose + 100 × epinephrine dose + 10 × milrinone dose + 100 × norepinephrine dose + 10 000 × vasopressin dose (U/kg/min).

Data are presented descriptively as median (IQR) for continuous data and as count (percentage) for categorical data. Between-group differences in clinical features and resuscitation measures were assessed using Wilcoxon rank-sum tests and Fisher exact tests as appropriate. A *P* value of less than .05 was considered statistically significant. This study was approved by the Hospital for Sick Children Institutional Review Board.

## Results

### Study Population

Between January 1, 2007, and March 31, 2017, 1024 children were admitted to our institution with acute Kawasaki disease. Of these, 9 children met the criteria for Kawasaki disease shock syndrome, all of whom were admitted to our institution's ICU. These cases were matched by age with 18 controls who were admitted with septic shock. The baseline demographics and clinical characteristics for the cohort, dichotomized by diagnosis, are displayed in **Table I**. Seven of 9 patients (78%) in the Kawasaki disease shock syndrome group and 9 of 18 patients (50%) in the septic shock group were female (*P* = .23). The median age at diagnosis was 6 years (IQR, 2-8 years) among the Kawasaki disease shock syndrome cohort and 6 years (IQR, 3-8 years) among the septic shock controls. The 2005 International Pediatric Sepsis Consensus Conference definition of septic shock was used to compare the cohorts.<sup>16</sup> Excluding the requirement for concern for infectious process in the patients with Kawasaki disease, 8 of 9 patients (89%) in the Kawasaki disease shock syndrome group and 15 of 18 controls (83%) with septic shock met the aforementioned definition (*P* > .99).

Children with Kawasaki disease shock syndrome were less likely than those with septic shock to have an underlying significant comorbid medical illness (1/9 [11%] vs 11/18 [61%]; *P* = .02). Among the Kawasaki disease shock syndrome cohort, 8 of 9 patients (89%) had no significant comorbid medical illness, and 1 (11%) had obstructive sleep apnea. Among the septic shock cohort, 7 of the 18 patients (39%) were previously healthy and 11 of the 18 (61%) had significant preceding comorbid diseases, including 3 patients with malignancy, 4 with genetic syndromes (all with severe neurologic sequelae), 2 with spastic cerebral palsy, 1 with juvenile idiopathic arthritis, and 1 with short bowel syndrome, severe gastrointestinal dysmotility, and a seizure disorder.

### Diagnostic Features and Management of Kawasaki Disease

All patients in the Kawasaki disease shock syndrome group had at least 1 of the 5 classic (or diagnostic) features of Kawasaki disease at presentation (**Table II**). Among the patients with Kawasaki disease shock syndrome, 2 of the 9 (22%) had 1

**Table I. Baseline demographics and clinical characteristics by diagnosis**

Clinical characteristics	Kawasaki disease shock syndrome	Septic shock	<i>P</i> value
No.	9 (33)	18 (67)	
Age at diagnosis (years)	6 (2-8)	6 (3-8)	.77
Sex (female)	7 (78)	9 (50)	.23
Significant comorbid disease	1 (11)	11 (61)	.02
Identified pathogen	3 (33)	12 (67)	.13
Echocardiographic abnormalities	5 (56)	0 (0)*	.03

Values are median (IQR) or number (%).

\*Only 7 patients underwent echocardiography.

**Table II. Presence of classic features of Kawasaki disease among patients with Kawasaki disease shock syndrome\***

Feature of Kawasaki disease	At presentation	Anytime during admission
Rash	7/9 (78)	7/9 (78)
Conjunctivitis	6/9 (67)	6/9 (67)
Mucous membrane changes	3/9 (33)	4/9 (44)
Cervical lymphadenopathy	1/9 (11)	2/9 (22)
Extremity changes	2/9 (22)	5/9 (56)

Values are number/total (%).

\*None of the patients with septic shock had any features of Kawasaki disease.

sign, 5 (56%) had 2 signs, 1 (11%) had 3 signs, and 1 (11%) had 4 signs at presentation. Only 3 of the 9 patients (33%) in the Kawasaki disease shock syndrome cohort met the criteria for complete Kawasaki disease. In comparison with the patients with Kawasaki disease shock syndrome, none of the patients in the septic shock cohort had any of the classic features of Kawasaki disease at presentation ( $P < .001$ ).

Six of the 9 patients (67%) with Kawasaki disease shock syndrome received intravenous immunoglobulin (IVIG) within 24 hours of hospital admission, and 3 of the 9 (33%) had a delay beyond 24 hours in IVIG administration (1 after 28 hours, 1 after 47 hours, and 1 did not receive IVIG because the diagnosis of Kawasaki disease was made after the patient was no longer febrile).

### Infectious Disease

An infectious pathogen was identified in 3 of 9 patients with Kawasaki disease shock syndrome (33%) vs 12 of 18 patients with septic shock (67%;  $P = .13$ ). Among the Kawasaki disease shock syndrome cohort, 8 of the 9 (89%) had septic shock and/or toxic shock syndrome (TSS) in their differential diagnosis and received empiric antibiotic coverage, 2 of the 9 (22%) had confirmed group A streptococcus bacteremia, and 1 (11%) had confirmed influenza A infection. Among the septic shock cohort, 6 of the 18 (33%) had culture-negative sepsis (3 of whom had positive viral swabs), 11 (61%) had confirmed bacterial infection (5/18 with both viral and bacterial sources identified and 6/18 with only bacterial sources identified), and 1 (6%) had a confirmed fungal infection.

### Cardiac Involvement

In the Kawasaki disease shock syndrome cohort, 5 of the 9 children (56%) had cardiac involvement. Two patients had impaired ventricular function (1 with qualitatively mildly reduced left ventricular systolic function and 1 with biventricular diastolic dysfunction consistent with constrictive physiology), and 1 patient had valvulitis (mild to moderate mitral regurgitation and moderate tricuspid regurgitation). Four of the 9 patients (44%) had coronary artery dilation at presentation; no patient had coronary artery aneurysms.

Among the septic shock controls, only 7 of the 18 patients (39%) had an echocardiogram performed during the acute phase of illness, and none demonstrated cardiac involvement.

Among patients who had an echocardiogram, cardiac involvement was more prevalent among the patients with Kawasaki disease shock syndrome than septic shock controls (5/9 [56%] vs 0/7 [0%];  $P = .03$ ).

### End-Organ Involvement

Among the Kawasaki disease shock syndrome cohort, 4 of the 9 patients (44%) received advanced respiratory support (noninvasive positive pressure ventilation in 1 and intubation in 3), 1 (11%) had a renal injury (acute kidney injury not requiring renal replacement therapy), and none had neurologic sequelae. Among the septic shock cohort, 12 of the 18 patients (67%) required respiratory support (noninvasive positive pressure ventilation in 4 and intubation in 8), and none had renal sequelae. Among those with no baseline neurologic comorbidity, 4 of the 7 patients (57%) had neurologic sequelae, which included seizures, parenchymal microabscesses with small bitemporal foci of acute ischemia, and hydrocephalus status postsurgical insertion of a drainage system in a patient with meningoencephalitis.

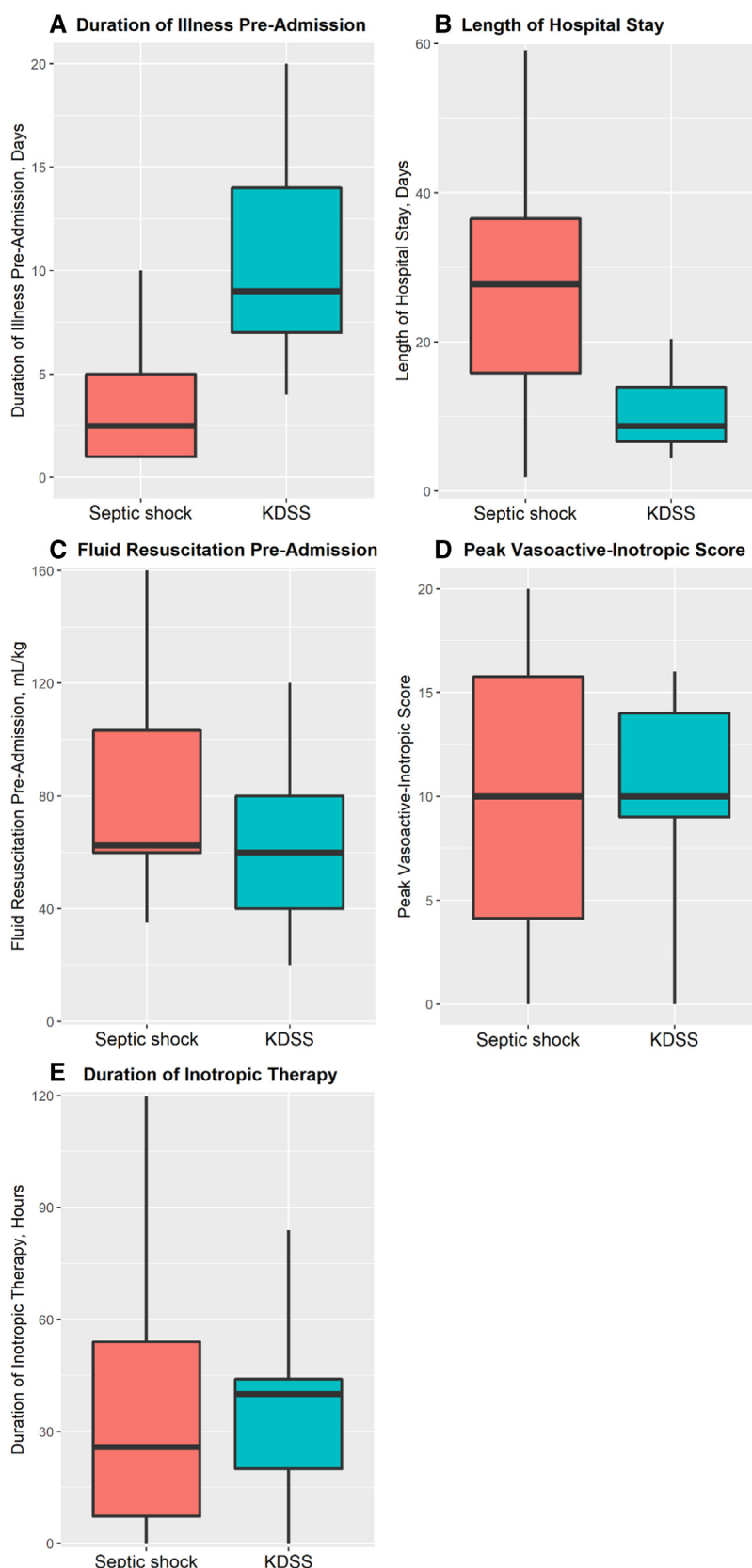
### Clinical Characteristics

An illness severity comparison was performed between the 2 cohorts, and the significant differences are presented in the **Figure**. Compared with septic shock controls, children in the Kawasaki disease shock syndrome cohort had a shorter duration of hospital stay (median, 9 days [IQR, 7-14 days] vs 28 days [IQR, 16-37 days];  $P < .001$ ) with no difference in length of ICU stay (median, 3 days [IQR, 2-5 days] vs 5 days [IQR, 2-9 days];  $P = .26$ ), which must be interpreted in light of the increased rate of comorbid illness among the septic shock controls. Children in the Kawasaki disease shock syndrome cohort had a longer duration of illness before admission than controls with septic shock (median, 9 days [IQR, 7-14 days] vs 3 days [IQR, 1-5 days];  $P = .004$ ). There was no significant difference in the peak VIS (median, 10 [IQR, 9-14] vs 10 [IQR, 4-16];  $P = .89$ ), in the VIS at 6 hours (median, 8 [IQR, 7.5-10] vs 8 [IQR, 0-10];  $P = .98$ ), in the VIS at 48 hours (median, 0 [IQR, 0-0] vs 0 [IQR, 0-4];  $P = .2$ ), or in the duration of inotropic therapy (median, 40 hours [IQR, 20-44 hours] vs median, 26 hours [IQR, 7-54 hours];  $P = .76$ ) between the 2 cohorts.

Biochemical markers at the time of ICU admission were compared (**Table III**). Patients with Kawasaki disease shock syndrome had a lower platelet count than patients with septic shock (median, 140 [IQR, 73-167] vs median, 258 [IQR, 137-334];  $P = .02$ ). There was otherwise no significant difference in the biochemical markers between the 2 cohorts, including lactate, hemoglobin, and inflammatory markers.

## Discussion

Kawasaki disease shock syndrome is often initially misdiagnosed as septic shock due to the high degree of clinical overlap between these 2 disease entities. Early and accurate differentiation between the 2 clinical entities is a conundrum



**Figure 5.** Illness severity comparison between patients with Kawasaki disease shock syndrome and septic shock. The box plots demonstrate minimum, 25th percentile, 50th percentile, 75th percentile, and maximum. Data are discussed as median (IQR). **A**, Children with Kawasaki disease shock syndrome had a longer duration of illness before admission than septic shock patients (median, 9 days [IQR, 7-14 days] vs median, 3 days [IQR, 1-5 days];  $P = .004$ ). **B**, Children with Kawasaki disease shock syndrome

**Table III. Biochemical markers of illness severity on admission, by diagnosis**

Biochemical marker	Kawasaki disease shock syndrome	No.	Septic shock	No.	P value
Alanine aminotransferase (U/L)	47 (44-49)	9	33 (26-49)	15	.05
C-reactive protein (mg/L)	164.2 (102.0-186.6)	8	101.2 (89.2-132.3)	8	.29
Erythrocyte sedimentation rate (mm/h)	53 (5-55)	3	28 (17-64)	3	.83
Hemoglobin (g/L)	101 (98-105)	9	115 (104-121)	17	.05
International normalized ratio	1.3 (1.3-1.3)	9	1.4 (1.0-1.6)	15	>.99
Lactate (mmol/L)	1.7 (1.3-2.5)	9	2.2 (1.9-2.8)	13	.13
Platelet count ( $\times 10^9/L$ )	140 (73-167)	9	258 (137-334)	17	.02
Partial thromboplastin time (seconds)	42 (35-44)	9	33 (30-45)	15	.27
White blood cell count ( $\times 10^9/L$ )	7.7 (5.3-11.4)	9	6.2 (3.3-14.0)	17	.73

Values are median (IQR) unless otherwise stated.

facing the clinician caring for a febrile child in shock, with important therapeutic and prognostic implications.<sup>8</sup> In this retrospective case-control study, we found that a longer duration of illness before admission, lack of significant underlying medical comorbidities, presence of at least 1 of the classic signs of Kawasaki disease at presentation, a lower platelet count, and echocardiographic abnormalities may be useful features to differentiate Kawasaki disease shock syndrome from septic shock at presentation. Children with Kawasaki disease shock syndrome and those with septic shock otherwise had many overlapping features in their illness profile; we identified no differences in the biochemical markers of illness severity on admission (other than platelet count), volume of fluid resuscitation, VIS, or duration of inotropic therapy between the 2 groups.

A delay in diagnosis is more common among children with Kawasaki disease shock syndrome than among children with hemodynamically normal Kawasaki disease, which in turn can lead to a delay in initiating Kawasaki disease-targeted therapy.<sup>8,17</sup> A delay in the administration of IVIG was noted in one-third of our Kawasaki disease shock syndrome cohort, including 1 patient who did not receive IVIG.

Cardiac involvement was seen in more than one-half of our Kawasaki disease shock syndrome cohort, including ventricular systolic and diastolic dysfunction and significant valvulitis. This finding is in keeping with findings in the literature. Kawasaki disease shock syndrome has been associated with atrioventricular valve regurgitation, and both systolic and diastolic myocardial dysfunction, with impairment of ventricular relaxation and compliance persisting beyond resolution of the clinical hemodynamic disturbance.<sup>7,18</sup> The prevalence of myocardial dysfunction in our Kawasaki disease shock syndrome cohort may have been underestimated, because echocardiograms were likely performed while patients were on inotropic therapy. Of note, there was no

evidence of cardiac involvement among the septic shock controls who had an echocardiogram performed during the acute phase of illness. Echocardiographic abnormalities were, therefore, considerably more common among patients with Kawasaki disease shock syndrome in our cohort and may be another discriminating factor between the 2 diseases.

An infectious pathogen was identified in twice as many patients with septic shock as with Kawasaki disease shock syndrome. This finding did not reach statistical significance, likely owing to the small sample size. Of note, one-third of patients in our Kawasaki disease shock syndrome cohort had an identified infectious pathogen. The exact etiology of Kawasaki disease remains elusive. Many proposed etiologies exist, including infectious diseases, and coincident infection has been identified in one-third of children with typical Kawasaki disease.<sup>19</sup> Both patients in our cohort with identified group A streptococcus bacteremia were managed for both Kawasaki disease shock syndrome and TSS; 1 had coronary artery dilation.

Although no studies have directly compared children with Kawasaki disease shock syndrome and septic shock, a 2015 study by Lin et al compared children with Kawasaki disease shock syndrome and TSS and found that children with Kawasaki disease shock syndrome had a significantly lower hemoglobin, higher platelet counts, and more echocardiographic abnormalities (such as valvulitis and coronary artery lesions) than children with TSS.<sup>20</sup> We did not find any differences in admission hemoglobin between children with Kawasaki disease shock syndrome and those with septic shock, although of interest our patients with Kawasaki disease shock syndrome had lower platelet counts at presentation than those with septic shock. Thrombocytopenia has been described in the acute phase of Kawasaki disease and has been associated with development of coronary artery aneurysms.<sup>21,22</sup> Patients with Kawasaki disease shock syndrome are more likely to have

had a shorter duration of hospital stay than patients with septic shock (median, 9 days [IQR, 7-14 days] vs median, 28 days [IQR, 16-37 days];  $P < .001$ ). **C**, There was no difference in median fluid resuscitation before ICU admission between patients with Kawasaki disease shock syndrome and patients with septic shock (median, 60 mL/kg [IQR, 40-80 mL/kg] vs median, 63 mL/kg [IQR, 60-103 mL/kg];  $P = .27$ ). **D**, There was no difference in peak VIS between patients with Kawasaki disease shock syndrome and patients with septic shock (median, 10 [IQR, 9-14] vs median, 10 [IQR, 4-16];  $P = .98$ ). **E**, There was no difference in duration of inotropic therapy between patients with Kawasaki disease shock syndrome and patients with septic shock (median, 40 hours [IQR, 20-44 hours] vs median, 26 hours [IQR, 7-54 hours];  $P = .76$ ). (Continues)

lower platelet counts than patients with hemodynamically stable Kawasaki disease.<sup>17</sup>

This study is limited by its small numbers and retrospective single-center design, with the occasional missing preadmission biochemical variable and fluid resuscitation, as well as practitioner-dependent differences in therapeutic management. Not all patients in the septic shock cohort had echocardiograms performed, which limited our assessment of the cardiac involvement in this patient group. Given our study design, it was not possible to determine whether differences in patient age may help to differentiate Kawasaki disease shock syndrome from septic shock. Finally, children with Kawasaki disease shock syndrome in our study cohort had fewer significant underlying medical comorbidities than patients with septic shock; although this finding is a potentially useful early differentiating feature, the remainder of the study findings must be interpreted in the light of the substantial burden of preexisting illness in the septic shock cohort.

A longer duration of illness before admission, lack of significant underlying medical comorbidities, presence of at least 1 of the classic signs of Kawasaki disease at presentation, lower platelet count, and cardiac involvement on echocardiography may be useful early features to differentiate Kawasaki disease shock syndrome from septic shock. ■

Submitted for publication May 6, 2020; last revision received Nov 13, 2020; accepted Dec 1, 2020.

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## Data Statement

Data sharing statement available at [www.jpeds.com](http://www.jpeds.com).

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