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# A Four-Year-Old with History of Kawasaki Disease Presenting in Acute Shock

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Abstract

We present a case in which emergency medical services (EMS) intervened on a critically ill child with known giant coronary aneurysms as sequela to her severe complicated Kawasaki disease. This patient's severe shock ultimately ended in cardiac arrest and death. We discuss the keys to recognition, and critical importance to early intervention of pediatric shock in prehospital care. We also detail the cardiac ramifications of Kawasaki disease, steps for prompt identification of high risk complaints in these patients, and opportunities for treatment. **Key words:** pediatric cardiac arrest; pediatric chest pain; Kawasaki disease; coronary aneurysm; Juvenile Idiopathic Arthritis; chest pain

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## Case

This is a case of a four-year-old girl with Kawasaki disease (KD) who had been diagnosed with severe KD in Guam at the age of three and then transferred to Hawaii for treatment by a KD specialist who discovered her giant coronary artery aneurysms. Given a poor response to treatment and further complications with development of systemic onset Juvenile Idiopathic Arthritis, she was transferred to San Diego for care by the Kawasaki Disease Research Center and availability of pediatric rheumatology at the tertiary children's hospital (Table 1).

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The authors would like to thank the parents of the patient of this case report. Their offer to share their difficult experience, so that others may benefit, is sincerely appreciated.

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During her short time in San Diego, she had two hospital admissions. A month after arrival, she was admitted briefly to rule out a coronary artery thrombus. During this stay she had a cardiac Computed Tomography scan that demonstrated the severity of her giant coronary artery aneurysms (Figures 1 and 2). Four months later, the patient was readmitted to the hospital with lesions consistent with Coxsackie virus infection (hand-foot-mouth disease) and chest pain. The patient had an echocardiogram that showed her persistent and unchanged severe aneurysms of the left anterior descending, right coronary, and circumflex arteries without stenosis or thrombosis and with ejection fraction 60%, normal in pediatrics is $\geq$ 55% and a normal ECG as read by the pediatric cardiologists. She was discharged home in stable condition after restarting methotrexate and folate for her juvenile idiopathic arthritis in addition to continuing her warfarin, atorvastatin and aspirin for her cardiac disease, canakinumab (for JIA), and naproxen as needed for joint pain.

Two weeks later, the patient began having waxing and waning substernal chest pain and epigastric discomfort with increasing fatigue. The parents attributed the discomfort to the re-initiation of methotrexate. On the second day of chest pain, the patient had mild shortness of breath, worsening fatigue and one episode of non-bloody, non-bilious vomiting. In the early hours of the morning, her father was awakened by the patient making an abnormal sound and found her in bed, gritting her teeth and cyanotic with extensor posturing in her upper extremities. 911 was promptly called.

A first responding advanced life support (ALS) unit was dispatched lights-and-sirens for altered level of consciousness. The patient had decreased responsiveness and increased work of breathing, not significantly improved by 15 liters non-rebreather mask (NRB). Intravenous access was attempted by ground ambulance responders but unsuccessful, and ALS monitoring was initiated. Given the distance to the nearest pediatric specialty center and the acuity of the patient, a critical care medevac helicopter was dispatched for transport.

On arrival of the helicopter, the transporting providers, two specialty trained critical care nurses, found an altered, pale, cyanotic child, with increased work of breathing and epigastric pain. Their initial assessment revealed a clammy patient with delayed

TABLE 1. Timeline of Patient Location

| |
|---|
| 2012 |
| Birth |
| 2015, Guam |
| Diagnosis of KD and Juvenile Idiopathic Arthritis (JIA) |
| 2015, Hawaii |
| Care transferred to Hawaii for KD Specialist |
| January 2016, San Diego |
| Family relocated to Southern California for KD And JIA Management |
| July 1, 2016, San Diego, Rady Children's Hospital |
| Patient admitted and discharged for Coxsackie infection and multisystem complaints |
| July 17, 2016, San Diego, Rady Children's Hospital |
| Patient presents with respiratory distress, and progresses to cardiac arrest and death |

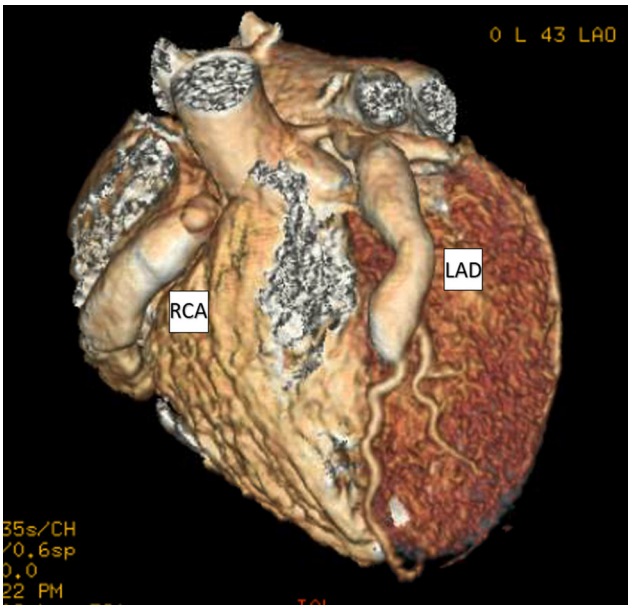


FIGURE 1. Patient's coronary computed tomography (CT) angiogram showing giant coronary artery aneurysms of both the left and right coronary arteries. (RCA: right coronary artery; LAD: left anterior descending)

capillary refill, GCS 14, who was complaining of epigastric and lower sternal pain. Initial vital signs were blood pressure 168/123; heart rate 72; respiratory rate 28; 96% pulse oximetry on high flow non-rebreather; 33.8 °C skin temperature.

The family told the flight crew the patient had altered level of consciousness with difficulty breathing and had two days of chest pain and several episodes of vomiting. The prehospital providers obtained the following medical history: KD with coronary artery aneurysms and juvenile rheumatoid arthritis. The

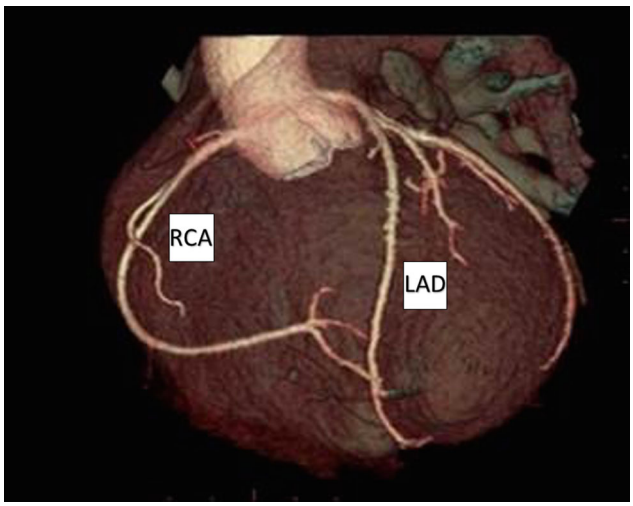


FIGURE 2. Comparison computed tomography (CT) angiogram of a pediatric heart without aneurysms. (RCA: right coronary artery; LAD: left anterior descending)

prehospital crew, both ground and air, did not know what medications the patient was taking.

The flight crew made contact with the base hospital to inform them that they were headed to the children's hospital with a four-year-old female with altered mental status and a Glasgow Coma Scale (GCS) of 14. The base hospital notified the children's hospital emergency staff (1).

[1]In San Diego, a base hospital system is utilized to communicate incoming patient information and provide online medical direction. Base hospitals have mobile intensive care unit nurses (MICNs) who coordinate ambulance transport locations, manage prehospital protocol variances, and can consult with and bring a physician to the radio for direct medical oversight. The satellite hospitals, which include the only children's hospital in the region, are notified of advance life support level transports via the base hospitals and do not have direct communication with the transporting agency.

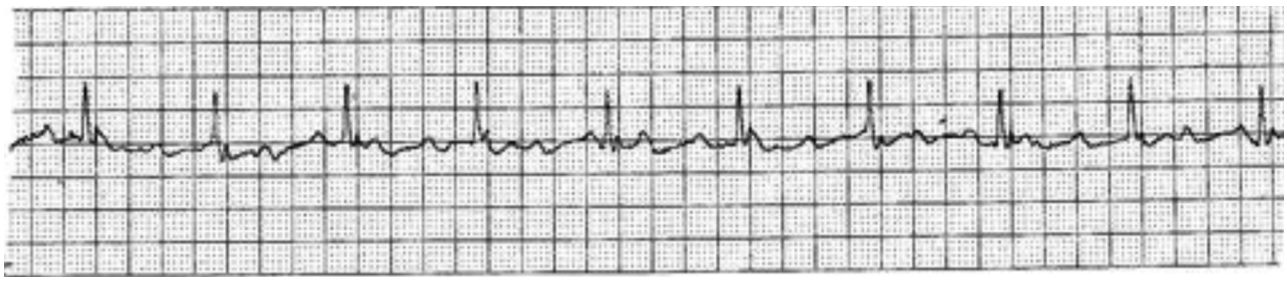

Figure 3. Prehospital helicopter transport rhythm strip.

En route, an ECG was obtained which showed 3rd degree heart block with a ventricular rate of 70 (Figure 3). Peripheral intravenous (IV) attempts were not successful. Intraosseous (IO) access was considered, but the providers held off given proximity to the children's hospital. The patient became anxious and restless, and increasingly tachypneic with central cyanosis despite 15 liters oxygen and a pulse oximetry reading of 96%. The patient's blood pressure dropped 20 minutes after initial assessment to 78/36 with a heart rate of 63. End-tidal capnography was not obtained.

The patient was brought directly to the resuscitation bay where she was immediately attended by two pediatric emergency medicine physicians. Given the cardiac history, the pediatric intensivist and pediatric cardiac intensivists were also called to bedside. Patient was pale and dusky despite the blow by oxygen on arrival. She was moved to the ED gurney and noted to have a low heart rate of 63 with periods of apnea. Pupils were unresponsive, and the patient did not respond to painful stimuli. Bag-valve-mask (BVM) ventilation was initiated. Patient had one episode of coffee-ground emesis. Within several minutes, the patient's heart rate dropped to the 50 s and chest compressions were initiated.

The patient received high quality chest compressions with minimal interruptions and had end tidal CO2 (ETCO2) readings greater than 15 mmHg during compressions with good chest rise with BVM. Unfortunately, the patient progressed from bradycardia, to pulseless electrical activity, to asystole within two minutes of CPR initiation. No shockable rhythm was appreciated. Vascular access was difficult throughout resuscitation with bilateral tibial and distal femoral IOs infiltrating, and a humeral IO successfully placed followed by a femoral central line. During the resuscitation the patient was intubated and received a total of six timed epinephrine doses followed by an epinephrine drip of 1-2 mcg/kg/min, a 20 ml/kg bolus of saline, two doses of sodium bicarbonate, and two doses of calcium. The patient received a total of 35 minutes of CPR without return of spontaneous circulation. Her family and social worker remained at the bedside for the resuscitation, and the KD team arrived to the bedside after the arrest. Both intensivists were present for the resuscitation and a discussion of ECMO (extracorporeal membrane oxygenation) cannulation took place but it was determined that the patient was not a viable candidate. Ultimately, revival attempts were unsuccessful. Myocarditis secondary to hand-foot-mouth-disease, coronary thrombus, or intracranial hemorrhage were the leading differentials considered by the physicians who cared for the patient in the Emergency Department.

Cardiac findings on autopsy revealed diffuse patchy, pale areas of scar tissue in the interventricular septum, with associated severe ischemic changes of cardiomyocytes. Pericarditis and myocarditis were not appreciated on exam. Additionally, the patient had luminal obliteration of her coronary aneurysms ($2.0 \times 0.8$ cm in her left anterior descending and $2.5 \times 1.0$ cm in her right coronary artery) with organized thrombi. However, there was no evidence of an acute infarct. The pathologist deemed the likely cause of death to be an arrhythmia leading to cardiac arrest.

## Discussion

There are many lessons to learn from this patient's tragic case. This case highlights pediatric shock as well as the cardiac ramifications of KD.

This patient had a classic presentation of pediatric shock (Table 2). Shock is a clinical state in which delivery of oxygen and metabolic substrates is insufficient to meet the body's need. Early recognition is critical and the diagnosis is often missed in children. However, early intervention and management of shock leads to significant improvement in outcomes. Clinically, there are three stages to pediatric shock (1,2). The first stage is: *compensated shock*. During this first stage, the pediatric patients' compensatory vasoconstriction is so profound that the systolic blood pressure is maintained in a normal range despite

TABLE 2. Stages and Treatment of Pediatric Shock (2,21).

| | **Compensated Shock** | Uncompensated Shock | Irreversible Shock |
|---|---|---|---|
| **Symptoms** | Blood Pressure **Maintained**<br><br>Symptoms:<br>Lethargy/Agitation<br>Tachycardia<br>Tachypnea<br>Oliguria<br>Gastrointestinal Distress<br>Cool Skin<br>Delayed Capillary Refill<br>Weak Pulses | Compensated Shock Symptoms<br>AND<br>Hypotension* | Irreversible Organ Injury<br><br>Especially to the:<br>Heart<br>Brain<br>Kidneys<br><br>Symptoms:<br>Bradycardia<br>Hypoxemia<br>Death |
| **Treatment** | Initial Shock Treatment:<br>1. Assessment and Intervention on Airway, Oxygenation or Ventilation Issues<br>2. Vascular Access (IV/IO) per PALS Guidelines<br>3. Fluid Resuscitation 20 mL/kg Isotonic Saline or Colloid Boluses q5min Up to 60 mL/kg (Complete as tolerated. Defer or begin with smaller boluses if known or suspected cardiogenic shock.)<br>4. Determine and Treat Primary Source of Shock:<br>a. Ex: Sepsis, Anaphylaxis, Myocarditis, Hemorrhage, Adrenal Insufficiency<br>5. Close Monitoring of Pulse Oximetry, ECG, Blood Pressure, Urine Output, and Mental Status<br><br>If Shock is Resistant to Above Interventions (Fluid-Resistant Shock):<br><br>1. Begin Inotrope Peripherally While Establishing Central IV Access (Transition inotrope to central line as soon as possible.)<br>2. Dopamine is preferred agent in pediatrics. Consider epinephrine as first line if known/suspected anaphylaxis.<br>3. Establish Central IV Access<br>4. If Persistent Hypotension, Add a Second Agent<br>5. Cold Shock (Ex: Neurologic Shock): Consider Epinephrine<br>6. Warm Shock (Ex: Distributive Shock in Sepsis): Consider Norepinephrine<br>7. If at Risk for Adrenal Insufficiency: instead of, Consider Stress-Dose Steroids<br>8. If Persistent Shock: Consider Extracorporeal Membrane Oxygenation (ECMO)<br><br>Therapeutic Endpoints to Monitor:<br>1. Heartrate Adjusted for Age:<br>2. Infants: 90–160 bpm<br>3. Young Children: 70–150 bpm<br>4. Capillary Refill Less Than 2 Seconds<br>5. Strong Pulses Without Central or Peripheral Differential<br>6. Warm Extremities<br>7. Blood Pressure Adjusted for Age:<br>8. Infants: 55 mmHg MAP<br>9. Older Children: 65 mmHg MAP | | |

*Hypotension Parameters (Systolic BP, mmHg): Term Neonate: < 60 Infants: < 70 Children: 1-10 years < 70 + (Age in years x 2) Children: > 10 years < 90.

significant circulatory compromise. This is the critical stage to recognize and intervene. Clinically, the patient will have signs of peripheral vasoconstriction (cool skin, delayed capillary refill, weak pulses, lethargy or agitation) despite a normal blood pressure. Additionally, evidence of decreased organ perfusion are present to varying degrees throughout the body, including altered mental status, tachycardia or tachypnea, oligouria, and gastrointestinal distress. To avoid further deterioration, it is optimal to intervene at this stage, before hypotension occurs (1–3). Without intervention, the patient will go into the second stage, *uncompensated shock*, characterized by hypotension. This is an ominous finding and can quickly proceed to the third stage of shock: *irreversible shock*. At the third stage, there has been irreversible organ injury, especially of the vital organs (heart, brain, and kidneys) and intervention at this stage is unsuccessful and death will occur despite therapeutic intervention (2). Hypotension in the pediatric

Table 3. Diagnostic Criteria for Complete Kawasaki Disease (7).

| **Diagnostic Criteria for Kawasaki Disease** | |
|---|---|
| Requires $\geq$ 5 days of fever $\geq$ 100.4 With 4 of 5 criteria needed for complete KD: (Consider the memory aid of "CRASH") | |
| **C** | **C**onjunctivitis: limbic sparing, bilateral bulbar injection, without exudate |
| **R** | **R**ash: maculopapular, diffuse erythroderma, or erythema multiforme-like |
| **A** | **A**denopathy $\geq$1.5 cm in diameter, cervical, often unilateral |
| **S** | **S**trawberry tongue, cracking of lips and/or erythema of oral and pharyngeal mucosa |
| **H** | **H**and or feet swelling, redness, edema, and/or periungual desquamation in subacute phase |
| Patients without the clinical features of complete KD are often evaluated for incomplete KD | |
| Incomplete KD includes children with fever for $\geq$ 5 days and 2 to 3 of the clinical criteria | |
| OR | |
| Infants with fever $\geq$ 7 days without other explanation | |
| If CRP $\geq$ 3.0 mg/dL and/or ESR $\geq$ 40 mm/hr | |
| AND | |
| The patient has 3 or more laboratory findings: | |
| 1. Anemia for age | |
| 2. Platelets $\geq$ 450,000 after day 7 of fever | |
| 3. Albumin $\leq$ 3.0 g/dL | |
| 4. Elevated ALT level | |
| 5. WBC $\geq$ 15,000/mm$^3$ | |
| 6. Urine $\geq$ 10 WBC/hpf | |
| OR | |
| A positive echocardiogram | |
| If the CRP is $<$ 3.0 mg/dL and ESR $<$ 40 mm/hr, serial clinical and lab evaluations occur for persistent fevers, and an echocardiogram is recommended if peeling occurs | |
| If coronary artery abnormalities are identified with the suspicion of incomplete KD, the diagnosis of KD is confirmed | |

population leads quickly to bradycardia, hypoxemia and death. Early recognition and management of shock is critical to saving lives.

Initial resuscitation of shock is directed toward maintaining oxygenation, ventilation, and perfusion (Table 2) (1–3). Vascular access is a critical step in shock management. If intravenous access is not successful, early intervention using intraosseous access is advised. Pediatric advanced life support (PALS) and advanced trauma life support (ATLS) recommend IO attempt if access is unsuccessful with three IV attempts or an IV takes $>$ 90 seconds. Notably, in our patient, there was success with a humeral IO, after failure of tibial and femoral IOs. The proximal tibia, distal tibia, proximal humerus, and the distal femur are the main IO sites for pediatric patients. While no large studies evaluating flow rates in pediatrics have been published at this time, proximal tibia and proximal humerus have shown high flow rates in adults, which is significantly improved with the use of pressure bags to increase infusion rates (12).

KD was first described in Japan in 1967 and is the most frequently diagnosed acquired heart disease of children in the developed world (4,5). It is a medium vessel vasculitis that occurs in children where 85% of cases occur in patients less than five years of age. It can occur in any ethnic or racial group, however the highest incidence rate is among patients of Asian descent (4,5). This is a syndrome with an unknown etiology that leads to a vasculitis. The classic diagnosis is clinical. If a patient has $\geq$ 5 days of fever, and 4 of 5 clinical findings (**C**onjunctivitis that is limbic sparing, bilateral and without exudate, **R**ash [maculopapular, diffuse erythroderma, or erythema multiforme-like], **A**denopathy [$\geq$1.5 cm in diameter, often unilateral], **S**trawberry tongue, cracking of lips and/or erythema of oral and pharyngeal mucosa, and **H**and swelling/redness/desquamation), they meet criteria for KD (Table 3) (7). Initial treatment is with aspirin and IV immunoglobulin (4,5). In recent years, previous treatment with high dose aspirin has been studied in greater depth, and dosing has been decreased from previous regiments, to continue to provide antiplatelet therapy, while also lessening side effects (Table 4) (13,14,19,20). Untreated KD leads to the development of coronary artery aneurysms in 25% of cases, which may progress to arterial stenosis in 20%, myocardial infarction in 7.5% and death in 3% (6). With proper recognition and treatment, the rate of coronary artery aneurysms decreases to 2-3% of patients (8).

While the acute phase of KD can be self-limiting and the diagnosis missed, it may also be associated with significant cardiac damage including giant coronary aneurysms ($\geq$8 mm) that may have sluggish blood flow, increasing the risk of thrombosis, coronary artery stenosis, or even end-stage cardiac failure leading to transplant (5,6). The acute inflammatory process can lead to scarring with increased risk for severe ventricular arrhythmias, sudden death, end

TABLE 4. Treatment of Kawasaki Disease (7).

| Treatment of Kawasaki Disease |
|---|
| **Initial Treatment:** |
| 1. Intravenous Immunoglobulin (IVIG) 2 g/kg infusion over 10-12 hours |
| 2. IVIG is most successful at decreasing coronary artery abnormalities if given within 10 days of illness onset |
| 3. IVIG can be started > 10 days after illness onset if they have evidence of ongoing systemic inflammation with elevated ESR or CRP, with persistent fever without other explanation, and no coronary artery aneurysm |
| 4. Aspirin (high-dose) every six hours for 14 days, or 72 hours after last fever while hospitalized |
| 5. Aspirin dosing and end time varies by institution: 30-50 mg/kg/d (many institutions in the US, Japan and Europe) or 80-100 mg/kg/d (divided every 6 hours) |
| 6. Low-dose (3-5 mg/kg/d) aspirin can be started following completion of the high-dose regimen |
| 7. Low-dose aspirin continues for 2-6 weeks until confirmation of no coronary artery abnormalities and inflammation has subsided, or indefinitely if coronary artery changes are found |
| ***If the patient has Kawasaki Disease Shock Syndrome (KDSS), Or is at high risk for nonresponding to IVIG (IVIG resistance), Or is determined to be at increased risk of coronary artery aneurysms, Adjuvant therapy can be considered.*** |
| **Adjuvant Treatment:** |
| 1. Corticosteroids |
| 2. Dosing and type of steroid vary |
| 3. Studies have shown decreased coronary artery aneurysm rates in high-risk patients in Japan |
| 4. Administration of a 2-3 week taper may be considered for high-risk patients with KD |
| 5. Single-dose methylprednisolone should not be administered with IVIG as primary therapy for KD |
| 6. Pulsed high-dose steroids are not recommended |
| 7. Infliximab (10 mg/kg/day) |
| 8. A second IVIG infusion |
| Other treatments that have been used include: Anakinra, cyclosporine, cyclophosphamide, etanercept, plasma exchange and ECMO (Extracorporeal Membrane Oxygenation) |

stage cardiomyopathy, inoperable stenotic coronary artery disease, valvular incompetence, and myocardial infarctions (5,9).

Kawasaki Disease Shock Syndrome (KDSS) is a rare presentation of KD, that is differentiated by hypotension (> 20% decrease from baseline or systolic hypotension per age), intensive care unit (ICU) care requirements, or clinical signs of inadequate perfusion in patients with KD. It is most common in males, patients with resistance to intravenous immunoglobulin (IVIG) treatment, cardiac failure, abdominal pain, neurological symptoms and inotrope treatment. KDSS is associated with atypical presentation and multiorgan system injury. The mortality was found to be 6.8% with one study. In addition to the standard KD treatment of IVIG, pulse steroids, plasmapheresis, and immune modulators like infliximab, anakinra, cyclosporine can be used (15). KDSS patients are noted to more commonly have lower platelet counts, and hold a greater risk of consumptive coagulopathies than hemodynamically normal KD. Aspirin dosing and use vary in KDSS, potentially due to platelet function and clotting abnormalities, and further studies will require evaluation of the best practices (15,17–19). ECMO may also be used for cardiac dysfunction secondary to KD (Table 4) (16). Based on this patient's low blood pressure, initial complaint of abdominal and chest pain, and multisystem involvement, her disease process likely progressed to KDSS. Key to survival of KDSS is early recognition.

To date, reports of prehospital complications due to KD are not in the EMS literature, in spite of myocardial infarcts and dysrhythmias being a high risk in these patients. Based on the pathologist's autopsy, this patient is suspected to have died from an arrhythmia. KD patients have increased occurrences of ventricular arrhythmia, especially torsades de pointes, ventricular fibrillation and AV heart block. These occurred more frequently in patients with coronary artery lesions, reduced left ventricular function, and large coronary aneursyms (11). This patient had several of these risk factors. In writing this report, we hope to increase recognition of the potential in these young patients for cardiac-related morbidity and mortality. Specifically, we hope to increase vigilance for those involved in EMS.

While well-established clinical decision-making rules exist for risk-stratifying adults with chest pain, these are not used regularly with children. The authors suggest that children complaining of chest pain should be screened for any history of KD, and

more specifically for a history of coronary artery aneurysms from KD. The Denver Metropolitan Prehospital Protocols (as of 2018) include the following wording on their causes of pediatric chest pain side note on the 3060 chest pain protocol "ischemia is rare but can be seen with a history of KD with coronary aneurysms" (10). If a history of KD is confirmed or suspected in a patient with chest pain, the prehospital provider should ensure adequate oxygenation, ventilation, and perfusion. Additionally, EMS can monitor for arrhythmias, ensure a twelve-lead is performed, and if a ST elevation myocardial infarction is present, begin a prehospital cardiac catheterization lab alert. A myocardial infarction is an unusual problem in pediatrics, and screening for KD history can speed the diagnosis of this dangerous complication.

With pre-arrival forewarning by EMS to the ED, preparations for these sick children can make the difference between life and death. Knowing their potential to have coronary artery associated pathology, physicians can ready the department for the ill child and have the necessary specialists primed to assist and potentially intervene. While our case was not a candidate for ECMO the discussion did take place and this technology is being increasingly used. In fact, extracorporeal cardiopulmonary resuscitation has been suggested by 2015 PALS to be considered for pediatric patients with cardiac diagnoses who have in hospital cardiac arrests in settings with existing ECMO protocols, expertise and equipment (3). Prehospital warning about these patients and the acuity of their condition, if in shock, can help prepare for the necessary personnel and equipment upon patient arrival.

KD, both in the acute and chronic phases, can be associated with major adverse cardiovascular events that require prehospital recognition and early warning to the receiving facility. While we were unable to resuscitate this patient, we hope this report will both highlight the importance of shock recognition as well as provide EMS agencies and physicians with the knowledge to more effectively identify and treat cardiac events in high risk individuals with KD.

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