Management of Myocardial Infarction in Children with Giant Coronary Artery Aneurysms after Kawasaki Disease

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Acute myocardial infarction (AMI) is one of the most important causes of morbidity and mortality in Kawasaki disease, and patients with large or giant coronary aneurysms (z-score of ≥10 or absolute lumen diameter of ≥8 mm) are at greatest risk.[1] For this reason, systemic anticoagulation together with antiplatelet therapy is recommended for all patients with Kawasaki disease with large/giant aneurysms.[1] Even in the presence of therapeutic levels of anticoagulant medications and antiplatelet therapy, thrombosis in giant aneurysms can occur owing to unfavorable flow mechanics and decreased wall sheer stress in the aneurysm.[2,3] Although coronary artery bypass grafting can benefit selected patients with giant coronary artery aneurysms and demonstrated stenosis, surgery does not play a role in the setting of AMI.[4] In a Japanese survey of patients with Kawasaki disease, the risk of myocardial infarction (MI) was highest in the first 2 years after disease onset.[5] Despite lower risk after this time, MIs can present several decades later.[6-8] Tsuda et al demonstrated that ≥1 MI occurred in 57 of 245 patients (23%) with giant aneurysms by 20 years after the onset of Kawasaki disease.[5] Fewer data are available in the US population. In a series of 500 children with coronary aneurysms evaluated at 2 US centers, major adverse cardiac events occurred only among those with large or giant coronary aneurysms. Overall, 24 of 92 of the children (26%) with Z scores of ≥10.0 experienced major adverse cardiac events.[9] Consistent with the life-long risk of thrombosis, coronary aneurysms secondary to Kawasaki disease accounted for 5% of new-onset acute coronary syndromes in patients <40 years of age in San Diego County.[10]

For the purposes of this discussion, AMI is defined by the a rise or fall of cardiac troponin levels with ≥1 value >99th percentile upper reference limit in conjunction with ≥1 of the following: (a) symptoms of ischemia, (b) changes in the electrocardiogram (ECG) including new or presumed new significant ST-segment–T wave changes, new left bundle branch block, or the development of pathological Q waves, (c) imaging evidence of new loss of viable myocardium or new regional wall motion abnormality, or (d) identification of an intracoronary thrombus by angiography.[11] AMI is divided into infarction with or without ST-elevation. An ST segment-elevation MI (STEMI) occurs when there is sudden, complete occlusion of a coronary artery segment with resulting transmural ischemia associated with myocardial injury or necrosis (**Figure**). In contrast, a non-STEMI occurs when there is a mismatch between myocardial oxygen demand and blood flow resulting in myocardial injury with elevated troponin, but without the extensive myocardial necrosis associated with STEMI that leads to ST-segment elevation.[12]

The management of MI in children with Kawasaki disease and giant coronary artery aneurysms is a special challenge for pediatric cardiologists and emergency medicine physicians who are less familiar than their adult counterparts with the acute management of MI. The treatment of STEMI is a true medical emergency that requires rapid restoration of antegrade flow through the occluded coronary artery. Although guidelines for adult STEMI have been issued by the American College of Cardiology and the American Heart Association,[13] guidance for the pediatric population is limited, and pediatric STEMI intervention with thrombolysis and mechanical restoration of flow are recommended for the first time in the recently released 2017 American Heart Association Kawasaki disease guidelines.[1] In recognition of the urgent and coordinated response required to manage pediatric patients with Kawasaki disease presenting with new onset ischemia, we here propose a STEMI management protocol in these children.

For any patient presenting with a STEMI, timely restoration of coronary blood flow is critical to preserve myocardial function.[13] The most effective intervention in adults involves cardiac catheterization techniques for revascularization, that is, percutaneous coronary intervention (PCI). A standard procedure in adults, PCI in children may be limited by available technical expertise, patient size, and the availability of appropriately sized guide catheters. Thus, the ultimate decision about whether a child is a candidate for PCI must be made by the interventional cardiologist while considering both patient and medical factors. With the advent of smaller catheters and guides, patients with coronary artery internal dimensions of ≥1.5 mm are suitable candidates for PCI in

AMI	Acute myocardial infarction
ECG	Electrocardiogram
PCI	Percutaneous coronary intervention
STEMI	ST segment-elevation MI
tPA	Tissue plasminogen activator

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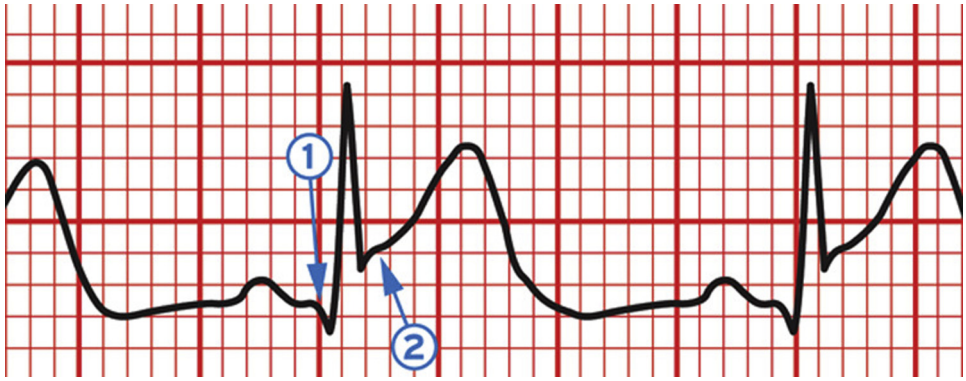

Figure. Example of ST segment elevation on an ECG. Arrow 1 shows the initial onset of the Q wave and arrow 2 shows the J-point or onset of the ST-segment. The difference between these 2 points identifies the magnitude of the displacement. Adapted from Thygesen et al.[26]

the setting of STEMI.[14,15] Given the unique nature of giant aneurysm patients who likely have a large thrombus burden, use of fibrinolytic therapy in conjunction with PCI may be considered.[16] This strategy has only been reported in adult patients. The tradeoffs of bleeding vs coronary occlusion must be weighed in the choice of approach. Whereas all patients with Kawasaki disease with giant aneurysms should already be on both systemic anticoagulants and antiplatelet agents as part of their standard outpatient management, in the event of thrombosis, the addition of thrombolytic agents and more potent antiplatelet agents is justified in an attempt to save cardiac muscle at risk. The significant risk of bleeding must be accepted and managed as appropriate.

Although there is no evidence base to guide therapeutic decisions in children with coronary aneurysms and evolving STEMI, a carefully conceived plan, adapted for local context and in place before the emergency situation occurs, is important in ensuring a timely and smoothly orchestrated response to a STEMI event. Our proposed protocol addresses the need for first medical encounter to device time to be <90 minutes, a time modeled after adult protocols. Similarly, we have adapted adult protocols for thrombolysis for the pediatric population in whom transfer to a STEMI center will be delayed >30 minutes. We recommend, above all, that pediatric centers involved in the medical management of patients with giant aneurysms as a complication of Kawasaki disease should establish relationships with adult interventional cardiologists who will be available and willing to help in the event of a pediatric STEMI.

Recognizing that published data do not define best medical practice for STEMIs in children with Kawasaki disease, we offer a practical approach to children at risk for this potentially devastating event.

General Considerations

- Parents and caregivers of a child with giant aneurysms should have training in cardiopulmonary resuscitation and should have a written emergency action plan in place. Day care centers, schools, and other caretakers should also be aware of the plan. Patients should be encouraged to wear a medical alert bracelet that identifies their condition, medications, and risk for MI.
- If there is concern that a child with known giant aneurysms might be having symptoms of myocardial ischemia, parents or caregivers should call 911, as well as their Kawasaki disease physician, that is, their pediatrician and/or pediatric cardiologist. Parents should be instructed to administer 81 mg aspirin, even if the child is already taking aspirin. For infants, signs and symptoms of a MI could include tachypnea with diaphoresis, pallor, vomiting, lethargy, or distressed cry.[17] For older children, symptoms often additionally include a complaint of chest pain.
- The Kawasaki disease physician should contact the supervising physician in their emergency department or, if the patient lives at a distance, the closest emergency department, to provide a patient history and concern for myocardial ischemia.
- Immediate evaluation in the emergency department should include the following: vital signs, 12-lead ECG, laboratory studies: troponin T (high-sensitivity cTnT assay; upper limit of normal, 0.01 ng/mL), international normalized ratio if on warfarin, anti-factor Xa if on enoxaparin, fibrinogen, brain natriuretic peptide, complete blood count, and chemistry panel. Staff should obtain intravenous (IV) access and an echocardiogram if feasible.
- As soon as the diagnosis of an acute coronary syndrome is strongly suspected or confirmed, the designated MI team at the primary center should be alerted and a management plan instituted that is tailored to the specific local hospital setting and the patient's age and medical circumstances. Caregivers on the MI team

generally include the cardiac intensive care attending, interventional cardiology team (pediatric and/or adult cardiologists, anesthesia), and, if not routinely available, the extracorporeal membrane oxygenation team on standby. It is highly recommended that an adult interventional cardiologist be involved in decisions regarding percutaneous (catheter-based) revascularization and medical management.

Management of STEMI

If STEMI is evident on ECG, 3 different scenarios may arise.

1. PCI not possible owing to small patient size or inexperience of available invasive cardiology personnel. This circumstance is likely to be the most common scenario for children presenting with a STEMI. Initiate thrombolytic therapy and anticoagulation as follows:
   - Start tissue plasminogen activator (tPA). Pediatric dosing for a low-dose tPA protocol is 0.03-0.10 mg/kg/h IV for 6-12 hours, with a maximum dose of 2 mg/h.[18,19] Fibrinogen must be >150 mg/dL to avoid bleeding complications. If fibrinogen is <150 mg/dL, give fresh frozen plasma 10-20 mg/kg IV and recheck. Standard adult tPA dosing (0.3-0.5 mg/kg/h, with a maximum dose of 2 mg/h) may be considered, but is associated with a higher risk of bleeding.
   - While infusing low-dose tPA, start unfractionated heparin in a separate line at a maintenance dose of 10 U/kg/h. Because tPA and heparin are not compatible in the same IV, if a second IV cannot be established then priority should be for tPA with the heparin to start after the 6 hours are completed.
   - Check the antithrombin III level and replace to maintain a level of 80%-120% of normal activity. If there is a delay in getting antithrombin III level results, administer 1 vial.
   - Once tPA is stopped, increase heparin to achieve the target activated clotting time of 200-250 seconds or comparable measure. A 50 U/kg bolus may be needed, as well as an increased dose of heparin to achieve that goal.
   - Repeating tPA infusion on subsequent days and redosing antithrombin III if heparin continued may be considered.
   - To inhibit platelet aggregation, a IIb/IIIa receptor antagonist may be considered. For example, eptifibitide (Integrilin) 180 μg/kg IV bolus may be given, then 2 μg/kg/min infusion for 12 hours. The dose is based on data from adults; no specific pediatric dosing information is available.
   - For patients complaining of chest pain, administration of sublingual or IV nitroglycerin 0.5-1.0 μg/kg/min may be considered, although caution must be exercised to avoid hypotension.
2. The expected time to the catheterization laboratory of >90 minutes and PCI will be possible based on patient size and catheterization laboratory staffing:
   - While awaiting transfer to catheterization laboratory, start tPA: Pediatric dosing for a low-dose tPA protocol is 0.03-0.10 mg/kg/h IV for 6-12 hours with a maximum dose of 2 mg/h.[18,19] Fibrinogen must be >150 mg/dL to avoid bleeding complications. If fibrinogen is <150 mg/dL, give fresh frozen plasma 10-20 mg/kg IV and recheck. The tPA should be stopped 10 minutes before starting the catheterization procedure (the half-life of tPA is 5-10 minutes).
   - Start low-dose heparin at 10 U/kg/h in a separate IV and continue the heparin after the 6 hours of tPA are complete. Because tPA and heparin are not compatible in the same IV, if a second IV cannot be established then priority should be for tPA with the heparin to start after the 6 hours are completed.
   - The patient should be urgently transferred to a pediatric center catheterization laboratory.
3. The expected time to catheterization laboratory <90 minutes and PCI is possible based on patient size and catheterization laboratory staffing: Go directly to the cardiac catheterization laboratory, which must be stocked with appropriate guides and catheters/balloons.
   - The management of coronary occlusion must be tailored to size of aneurysm and thrombus burden.[11,20,21] Modifications may be necessary based on patient size.
   - Antiplatelet agents should be administered as soon as is practical. For infants, give clopidogrel 0.2 mg/kg/d by mouth. For children, give clopidogrel 1 mg/kg by mouth. For teenagers, give ticagrelor 180 mg by mouth or prasugrel 60 mg by mouth.
   - Once vascular access has been established, administer unfractionated heparin as initial IV bolus of 75 U/kg, which should achieve therapeutic anti-factor Xa in 90% of children, followed by 20 U/kg/h.[22]
   - In cases of large thrombus burden, consider IIb/IIIa receptor antagonist to inhibit platelet aggregation: eptifibitide 180 μg/kg IV bolus, then 2 μg/kg/min. infusion for 12 hours. Administer beta-blocker and angiotensin-converting enzyme inhibitor within first 24 hours.
   - Aspiration of thrombus not recommended (level of evidence A, Class III).[20]

Management of Non-STEMI

If ST depression is evident on ECG and serial troponin levels are rising (ie, there is a non-STEMI):

- Administer unfractionated heparin (initial IV bolus of 75 U/kg), which should achieve therapeutic anti-factor Xa in 90% of children, followed by 20 U/kg/h.
- Continue aspirin at 3-5 mg/kg with a maximum of 81 mg/d and clopidogrel loading dose 2-3 mg/kg followed by 1 mg/kg/d with a maximum of 75 mg/d.
- Computed tomography angiogram or diagnostic cardiac catheterization in collaboration with adult interventional cardiologist should be performed.
- Consider tPA as for the STEMI protocol based on imaging findings.

Therapy and Prognosis after AMI in Kawasaki Disease

Patients with Kawasaki disease who have had an AMI are at significant risk for future cardiovascular events, including recurrent MI, death, and heart failure. In the largest series from Japan, among those who suffered an MI, 1 in 5 patients subsequently died.[23] In general, the management of the child who has had a MI should follow adult guidelines.[11] At hospital discharge, anticoagulation and antiplatelet therapy should be tightly controlled. Therapy with beta-blockers and angiotensin-converting enzyme inhibitors is standard. Despite the differing etiology of STEMI in adults and in children with Kawasaki disease, statin use should be considered in children based on adult guidelines and the evidence-based improved outcomes in AMI likely owing to the pleotropic effects of this class of drugs.[24] A phase I/IIa trial demonstrated the safety of a dose of 0.75 mg/kg/d of atorvastatin in pediatric patients with acute Kawasaki disease ≥2 years of age.[25] The safety and dosing of any statin in patients <2 years of age has not been established.

The guidance in this document is based solely of the experience of a small group of expert clinicians who care for patients with Kawasaki disease with giant aneurysms. Ultimately, management decisions must be individualized to a patient's specific circumstances and the available medical resources. Given the small number of patients at risk, robust evidence from randomized clinical trials will likely never be available. Nonetheless, treatment strategies and outcomes for this high-risk patient population could be improved in the future by systematic data collection using a registry approach. ■

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