Chapter 46

Kawasaki Disease

Wanda C. Miller-Hance

Case Scenario

An 18-month-old toddler presents for cardiac magnetic resonance imaging. His medical history is significant for an acute febrile illness at the age of 9 months, requiring hospitalization and meeting diagnostic criteria for Kawasaki disease. His presentation in infancy, along with a delay in diagnosis and initial treatment, were thought to contribute to the development of large coronary artery aneurysms, which are still present at the time of the planned study. His current medications include aspirin and low molecular weight heparin. The imaging examination is being performed as part of his ongoing cardiology surveillance and will include inducible myocardial ischemia testing.

Key Objectives

- Define Kawasaki disease.
- Understand the clinical findings associated with Kawasaki disease.
- Describe the cardiac manifestations of this condition.
- Understand basic aspects of treatment in Kawasaki disease.
- Discuss the role of cardiac imaging modalities in Kawasaki disease.
- Describe the preanesthetic assessment of children affected with Kawasaki disease.
- Describe periprocedural and perioperative management considerations.

Pathophysiology

What is Kawasaki disease?

Kawasaki disease (KD), originally referred to as mucocutaneous lymph node syndrome, is an acute febrile illness affecting mostly infants and children, and, in particular, those under the age of 5 years. The condition, characterized by a systemic vasculitis, affects multiple organs and tissues.

Clinical Pearl

Kawasaki disease is an acute vasculitis of unknown etiology affecting mostly children under the age of 5 years.

What is the epidemiology of KD?

Kawasaki disease has been reported in children of all ethnic origins worldwide. In North America, the condition is estimated to affect nearly 25 out of 100,000 children under 5 years of age per year. In Asian countries, particularly Japan, the disease is substantially more prevalent, with an annual incidence approximately 10 times that of North America. There is a seasonal variation in the incidence of KD, with known peaks during the winter months and early spring.

What causes KD?

The etiology and pathogenesis of KD remain poorly understood despite its initial description many decades ago, an extensive clinical experience, and many years of research. Although no single infectious agent has been identified, an infectious cause has been strongly implicated. The current notion is that of a complex etiology likely influenced by an autoimmune process as well as genetic susceptibility.

What are the diagnostic features of KD?

The diagnosis of KD is established based on a constellation of clinical findings. The ***classic or complete form*** of KD is characterized by the presence of fever of five or more days in duration and at least four of the following five principal features as listed in Table 46.1.

The diagnosis of ***incomplete or atypical KD*** is considered in the presence of prolonged unexplained fever, fewer than four of the main clinical features, and compatible laboratory or echocardiographic findings.

https://doi.org/10.1017/9781108657341.047 Published online by Cambridge University Press

Table 46.1 Diagnostic Clinical Features in Classic Kawasaki Disease

- Polymorphous generalized rash
- Cervical lymphadenopathy (at least 1.5 cm in diameter)
- Bilateral conjunctivitis without exudate
- Oral mucosal changes (erythematous mouth and pharynx, strawberry tongue, and red, cracked lips)
- Peripheral extremity changes (erythema of the palms and soles and firm induration of the hands and feet, often with subsequent periungal desquamation in the subacute phase)

What laboratory values are consistent with KD?

Laboratory tests in KD are nonspecific but may support the diagnosis. Most studies reflect systemic inflammation, particularly during the acute phase of the disease. Common findings include leukocytosis, anemia for age, thrombocytosis, and elevation of acute-phase reactants (erythrocyte sedimentation rate and C-reactive protein). Elevated D-dimer levels can reflect endothelial damage and fibrinolysis. Reported laboratory abnormalities also include hyponatremia, hypoalbuminemia, elevated transaminases, and sterile pyuria. Certain laboratory values can serve to monitor the effectiveness of therapy during early stages of the illness.

What are the known phases of the disease?

The clinical course in KD has been divided into three phases, reflecting the variable clinical features of the illness over time. The ***acute*** phase begins with fever and usually lasts approximately 7–14 days; the ***subacute*** phase begins from the end of fever until symptoms and signs resolve, usually until weeks 4–6. The ***convalescent*** phase is characterized by complete resolution of clinical signs, typically within 3 months of initial presentation. A fourth ***chronic*** phase has been described to focus on the cardiac complications of the disease.

What sequelae are associated with KD?

In most cases, KD is a self-limited condition, with signs and symptoms that resolve after the acute illness, even without treatment. However, serious cardiovascular manifestations and sequelae can develop, representing major contributors to morbidity and mortality in affected patients. The most common and threatening complication during the acute phase of the disease is the development of coronary artery abnormalities. This occurs in up to 25% of untreated children and a small proportion (3%–5%) of those who receive what is considered appropriate acute therapy. The proximal left anterior descending and right coronary arteries are the vessels most frequently involved, followed by the left main and left circumflex coronary arteries. Involvement of the coronary arteries can lead to myocardial ischemia, infarction, and sudden death.

Clinical Pearl

Coronary artery abnormalities occur in up to 25% of untreated children and a small proportion (3%–5%) of those who receive what is considered appropriate acute therapy. Kawasaki disease can lead to coronary artery ectasia and the formation of coronary aneurysms. The coronary pathology can result in myocardial ischemia or infarction, and in some cases, even death.

What is the pathophysiology of KD?

The vasculitis that characterizes KD affects mostly medium-sized muscular arteries, with a predilection for the coronary arteries. The pathology involving the coronary arteries ranges significantly in severity from minimal vessel dilation to the formation of giant aneurysms. The affected vessels may be at risk for thrombosis, calcification, progressive stenosis, occlusion, and rupture. Children with large or giant aneurysms, such as the toddler in this scenario, are at particularly high risk for coronary artery thrombosis.

What is the relevance of KD?

Kawasaki disease is the leading cause of acquired heart disease among children in the United States and other industrialized countries. In the developing world, rheumatic heart disease remains the main cause of cardiac-related morbidity and mortality.

Clinical Pearl

Kawasaki disease is the leading cause of acquired heart disease among children in the United States and other industrialized countries.

What are the recommendations for treatment in KD?

In a scientific statement published in 2017, the American Heart Association (AHA) provided detailed recommendations regarding diagnosis, management, and guidelines for treatment in KD. In the acute phase of the disease, the timely administration of intravenous (IV) immunoglobulin together with aspirin is the mainstay of therapy to reduce inflammation and arterial damage to the coronary vasculature and prevent cardiac sequelae. Adjunctive or

https://doi.org/10.1017/9781108657341.047 Published online by Cambridge University Press

alternate therapies for primary treatment that may be considered depending on the particular clinical setting include corticosteroids (more likely to be used in Japan), antibody therapy against cytokines (e.g., tumor necrosis factor-α), calcineurin inhibitors (cyclosporine), interleukin-1β receptor antagonists, cytotoxic agents, and plasma exchange. For prevention and treatment of thrombosis in patients with coronary artery aneurysms, drug therapy may include antiplatelet agents and anticoagulants. In some cases, thrombolytic drugs have also been used. Other drugs that may be considered for long-term treatment include β-blockers and statins.

What determines the prognosis in KD?

The prognosis in KD is dependent solely on the severity of the coronary artery involvement. Most of the morbidity and mortality is seen in patients with giant aneurysms. However, even in those patients considered to be low-risk survivors of KD, vascular abnormalities and serum markers have been identified, suggesting a potential increased risk for cardiac morbidity, such as the accelerated development of atherosclerotic coronary heart disease.

What information does echocardiography provide in KD?

Transthoracic echocardiography is highly sensitive and specific for the diagnosis of coronary artery involvement in KD. The study is considered essential during the acute phase of the disease and is key during long-term follow-up. Echocardiography can evaluate the coronary arteries for abnormalities (dilation, presence of aneurysms, and thrombosis) and serves to monitor for other cardiovascular manifestations during the acute episode such as myocardial dysfunction, valvular abnormalities, or pericardial effusion.

What is the role of other cardiovascular imaging modalities in these patients?

The need for additional cardiac imaging in KD is highly dependent on the severity of the coronary artery involvement and the expert opinion of specialists that routinely care for these patients. Imaging modalities that may be considered include transesophageal echocardiography, cardiac catheterization and angiography, computed tomographic angiography, cardiac magnetic resonance imaging (CMRI), and myocardial perfusion imaging. The selection of imaging technique considers factors such as the necessary information to be obtained, invasive versus noninvasive nature of the examination, radiation exposure, and need for sedation or anesthesia.

What information does CMRI provide? What are some of the risks associated with newer applications of the technique?

Cardiac magnetic resonance imaging represents an important noninvasive diagnostic technique in children with heart disease as it overcomes many limitations of alternate imaging modalities. Specific to KD, CMRI provides anatomic evaluation of the coronary arteries (see Figure 46.1), enables the measurement of cardiac chamber dimensions, and allows for estimates of ventricular function. In addition, the ability to provide detailed myocardial characterization offers clinically relevant information regarding the presence of inflammation, ischemia, and fibrosis.

Stress perfusion CMRI imaging facilitates the detection of vulnerable myocardium and hemodynamic reserve. This technology is increasingly being applied in children with KD and coronary artery involvement for surveillance, risk stratification, and to aid in decisions regarding the need for coronary interventions. Stress imaging involves the administration of a pharmacologic agent that causes coronary hyperemia or vasodilation, exaggerating the differences between healthy and diseased or obstructed arteries, so that flow differences can be assessed. Although the selection of these agents considers their safety profile, their use can be associated with side effects such as flushing,

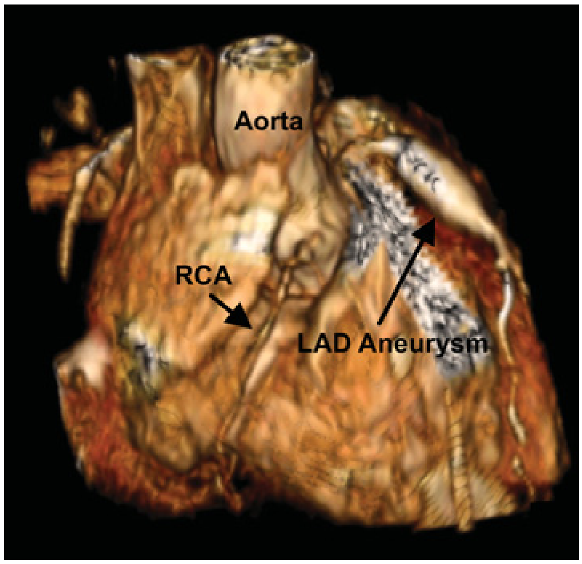

Figure 46.1 Left anterior descending coronary aneurysm in Kawasaki disease. Three-dimensional volume-rendered magnetic resonance image of the coronary arteries in a child with Kawasaki disease depicting a large fusiform aneurysm involving the left anterior descending (LAD) coronary artery. Note the normal appearing right coronary artery (RCA).

https://doi.org/10.1017/9781108657341.047 Published online by Cambridge University Press

diaphoresis, nausea, and vomiting that may disrupt the study in a lightly sedated patient. Even more concerning is the fact that these drugs can trigger rhythm disturbances, alter hemodynamics (increase heart rate and lower systemic arterial blood pressure), and cause bronchospasm. Adequate preparation and a high level of vigilance are of utmost importance during these examinations.

Clinical Pearl

Stress imaging involves the administration of a pharmacologic agent that causes coronary hyperemia or vasodilation, exaggerating the differences between healthy and diseased/obstructed arteries, so that flow differences can be assessed. These drugs can trigger rhythm disturbances, alter hemodynamics, and cause bronchospasm.

Anesthetic Implications

What basic principles guide anesthetic care of children with KD?

In children with KD undergoing diagnostic testing or noncardiac procedures that require sedation or anesthesia, management plans should be formulated based on the following basic principles:

- Principles guiding sedation/anesthetic care in this age group in general
- Principles unique to the planned procedure
- Principles specifically related to the pathophysiology of the disease

The first set of principles should be familiar to most that provide sedation and/or anesthesia for infants and children on a regular basis. The second set, although well known to those acquainted with CMRI in children with heart disease, may present a challenge to those less accustomed to these types of studies, thus the need for communication and discussion with the radiologist, cardiologist, and/or technologist involved. The third set of principles requires individual assessment of the child, in particular a detailed appraisal of suspected or confirmed KD-associated cardiac manifestations and the extent of disease in order to identify patients with potential vulnerability for an acute coronary syndrome or cardiac decompensation.

What are key elements in the preprocedural assessment of patients with KD?

A detailed preprocedural/preoperative evaluation is critical for identifying and anticipating factors that may place a child with KD at potential increased risk during anesthesia care. The history and physical examination are essential components of this evaluation. During preanesthetic assessment specific information should be obtained regarding the clinical course of the illness and the nature and severity of cardiac disease, and most specifically, any involvement of the coronary arteries. Cardiac manifestations during the acute phase of the disease, such as myocardial dysfunction due to inflammation (i.e., myocardial edema, myocarditis, or heart failure), valvular regurgitation, or the presence of a pericardial effusion, can significantly impact the anesthetic plan, thus the relevance of ascertaining the phase of disease. In older children, exploration of signs and symptoms suggestive of myocardial ischemia is appropriate, but these are more difficult to investigate in young children. The preanesthetic evaluation should include a review of recent relevant studies such as a 12-lead electrocardiogram (ECG), echocardiogram, and any other relevant study. Recent cardiology evaluations should also be reviewed.

One of the initial steps in the preoperative assessment of this child, as with any patient with serious heart disease, is a consideration of the study indications and an appraisal of the risk-to-benefit ratio. In some cases, there may be a need for a multidisciplinary discussion in advance with appraisal of such factors as suitable study/procedural venue and appropriate area for patient recovery. The immediate preanesthetic evaluation will occasionally establish the need to delay or defer a diagnostic test, intervention, or elective noncardiac surgery in these children.

What issues exist regarding perioperative medication management in these patients?

It is well established that a number of regularly taken drugs can have perioperative effects or interact with anesthetic agents. This is relevant to patients with KD who may be receiving such medications on a daily basis. In most cases, there is no need to discontinue long-term medications prior to scheduled noninvasive cardiac imaging. There are, however, several unique issues in patients with KD to be considered. One is the fact that children may be taking medications that are unfamiliar to the anesthesia provider, and, in many cases, different than those regularly administered to children with other types of heart disease. A detailed review of all medications is suggested to assess for potential drug interactions. Even more important is the fact that some of these patients may be taking antiplatelet and anticoagulation agents routinely. Thus, the potential need exists for these drugs to be adjusted perioperatively. The patient may require preadmission to make changes in anticoagulation strategy, and preparation to manage

https://doi.org/10.1017/9781108657341.047 Published online by Cambridge University Press

potential bleeding complications may be necessary depending on the planned intervention or surgical procedure.

Would premedication be appropriate for this patient?

Premedication facilitates parental separation in children. Practical options include either oral or intranasal administration of these agents. Drugs most likely to be considered include midazolam, ketamine, and dexmedetomidine. In this toddler with KD and known coronary artery involvement, the use of premedication, in addition to allowing for smooth parental separation and anxiolysis, can also facilitate advanced placement of an IV catheter, enhancing the overall safety of anesthetic induction. The potential disadvantage of premedication in this setting is related to residual drug effects that could possibly result in delayed hospital discharge, if discharge is planned immediately after the procedure. Judicious dosing of premedication can circumvent some of these challenges and satisfy most needs.

Which procedural considerations influence anesthetic technique in this child?

Most infants and young children require sedation or general anesthesia for CMRI. A number of procedural factors can be taken into consideration when selecting the most appropriate anesthetic technique for these children as listed in Table 46.2.

Which anesthetic techniques are appropriate for children with KD undergoing CMRI?

Several different anesthetic agents and techniques have been safely utilized in children with heart disease undergoing CMRI, including children in high-risk groups. Selection should be guided by the patient pathophysiology and procedural requirements as mentioned. The patient's age and the length of the planned procedure are important factors to consider as well. In the specific case of this toddler undergoing CMRI with plans for inducible myocardial ischemia testing, potential advantages of general anesthesia with tracheal intubation, muscle paralysis, and controlled ventilation over deep sedation include the following:

1. Airway protection provided by endotracheal intubation, in contrast to potential airway obstruction and respiratory depression that may result from deep sedation in a setting of limited patient access
2. Reduced anesthetic depth requirements when neuromuscular blockade is part of a balanced technique, avoiding undesirable hemodynamic effects from higher doses of drugs needed for deep sedation
3. Ability to facilitate image acquisition through breath-holds when general anesthesia is used, reducing overall scanning time and increasing study efficiency

What monitors would be appropriate in this toddler?

As in all patients undergoing an anesthetic, oxygenation, ventilation, circulation, and temperature should be continually evaluated. In the care of this child, standard monitoring as recommended by the American Society of Anesthesiologists would be most appropriate and invasive monitors are likely not warranted. Reliable monitoring is essential, particularly in this toddler, in view of the cardiac disease implying potentially limited cardiovascular reserve. Given the MRI setting, suitable monitors should be utilized. There are several important considerations regarding CMRI and ECG monitoring worth highlighting.

Table 46.2 Procedural Considerations Influencing Selection of Anesthetic Technique for Cardiac Magnetic Resonance Imaging

• ***Need for patient immobility*** Although stimulation related to this type of study is minimal, the goal of any anesthetic technique should be avoidance of patient movement in order to facilitate the acquisition of high-quality diagnostic images and to avoid image distortion.
• ***Need for breath-holding sequences*** High spatial resolution coronary imaging may require respiratory pauses and periods of apnea to overcome artifacts related to respiratory motion. The combination of a respiratory navigator and availability of advanced software algorithms that integrate respiratory gating may circumvent the issue of lung excursion, allowing for free-breathing imaging techniques at some institutions.
• ***Duration of the examination*** The extent of the information to be acquired in the study (anatomic, functional, ischemia assessment), directly influences the length of the examination. In some instances, concurrent imaging of extracardiac structures is planned, further lengthening the scan time.
• ***Comfort level of the anesthesia provider*** Provider preferences are important in the selection of anesthetic technique given the particular type of study and unique issues associated with an MRI setting which can include a challenging environment, usually remote setting, limited access to the patient, and not uncommonly, monitoring and equipment issues.
• ***Institutional preference*** The standard or usual approach of the facility regarding the conduct of the studies also impacts the anesthetic management plan.

https://doi.org/10.1017/9781108657341.047 Published online by Cambridge University Press

- Sequence acquisition is synchronized to the cardiac cycle; therefore, reliable ECG monitoring that allows for gating is key.
- A number of obstacles within the magnetic environment prevent the acquisition of undistorted signals. Consequently, in most cases a special MRI-conditional ECG lead system is used with three or four electrodes placed at small distances from each other, with filters and settings adjustments primarily suitable for image acquisition synchronization but not for physiologic monitoring. This means that ECG-based ischemia detection, a highly desirable goal in this particular case, may not be feasible in most available CMRI systems.

What type of anesthetic induction and maintenance would be most suitable for this child?

The basic principles of anesthetic induction and maintenance for CMRI in this child do not differ significantly from those that guide care in infants and children with other types of severe heart disease. Minimizing acute changes in preload and afterload and preserving ventricular function are common themes. Maintaining a favorable myocardial supply to demand balance is an important goal in all patients, but particularly in those with a history of KD and coronary artery involvement due to their ischemic propensity. Similar management strategies to those that guide anesthetic care in adults with atherosclerotic coronary artery disease may be considered with the goal of preserving myocardial perfusion and ventricular function.

In general, the strategy for anesthesia induction (inhaled versus IV) in children with heart disease is primarily guided by their clinical status and the extent of cardiac reserve. In children with KD, the severity of cardiac involvement may be added to this appraisal. Inhalation induction with sevoflurane is usually favored in children considered to be at low risk. Conversely, an IV induction with carefully titrated drugs provides a larger margin of safety and is more appropriate in those with poor clinical status, significant cardiac manifestations or when there are concerns for hemodynamic instability during anesthetic induction. Given the presence of large coronary artery aneurysms in this child, options to be considered may include an IV induction with drugs such as etomidate, ketamine, or even carefully titrated very small doses of propofol (large doses are best avoided), or a combined inhaled/IV induction, with titrated doses of these agents. Both of these techniques assume the presence of IV access. Another less desirable option might be that of an inhalation induction, limiting the inspired concentration of the volatile agent, with early establishment of IV access. This may avoid the stress associated with IV placement, particularly in the setting of difficult access. In most children anesthesia can be maintained with sevoflurane or isoflurane in a mixture of air and oxygen. Small doses of benzodiazepines, narcotics, or adjuvants such as dexmedetomidine may be administered. However, depending on the particular drug and dose, this may impact recovery times and discharge preparedness.

Clinical Pearl

Maintaining an optimal myocardial supply to demand balance represents an important goal in the anesthetic management of the child with Kawasaki disease and coronary artery involvement due to their potential for myocardial ischemia.

What special preparation, if any, is required for this type of case?

Given the cardiac disease in this child and potential risk, resuscitation drugs and equipment should be immediately and readily available. In the case of an acute event or emergency, the child should be immediately removed from the MRI scanning room for stabilization or resuscitation as indicated by the situation.

Clinical Pearl

In children with a history of Kawasaki disease, advanced cardiovascular diagnostic imaging studies are usually performed for suspected or confirmed cardiac disease. In view of potential risks associated with anesthetic care, resuscitation drugs and equipment should be immediately available at all times.

What data is available regarding risk in patients with KD?

The AHA Scientific Statement on KD proposed a risk stratification system for the development of long-term myocardial ischemia in affected patients based on the severity of past and current coronary involvement, in addition to other factors. As would be expected, the more severe the coronary pathology the higher the predicted risk, and consequently the greater the need for closer surveillance and more aggressive thromboprophylaxis and medical therapy. A similar risk estimation scheme can be applied to anesthesia care, implying a minimal risk level in the absence of coronary artery involvement or in the presence of only coronary artery dilation, and

https://doi.org/10.1017/9781108657341.047 Published online by Cambridge University Press

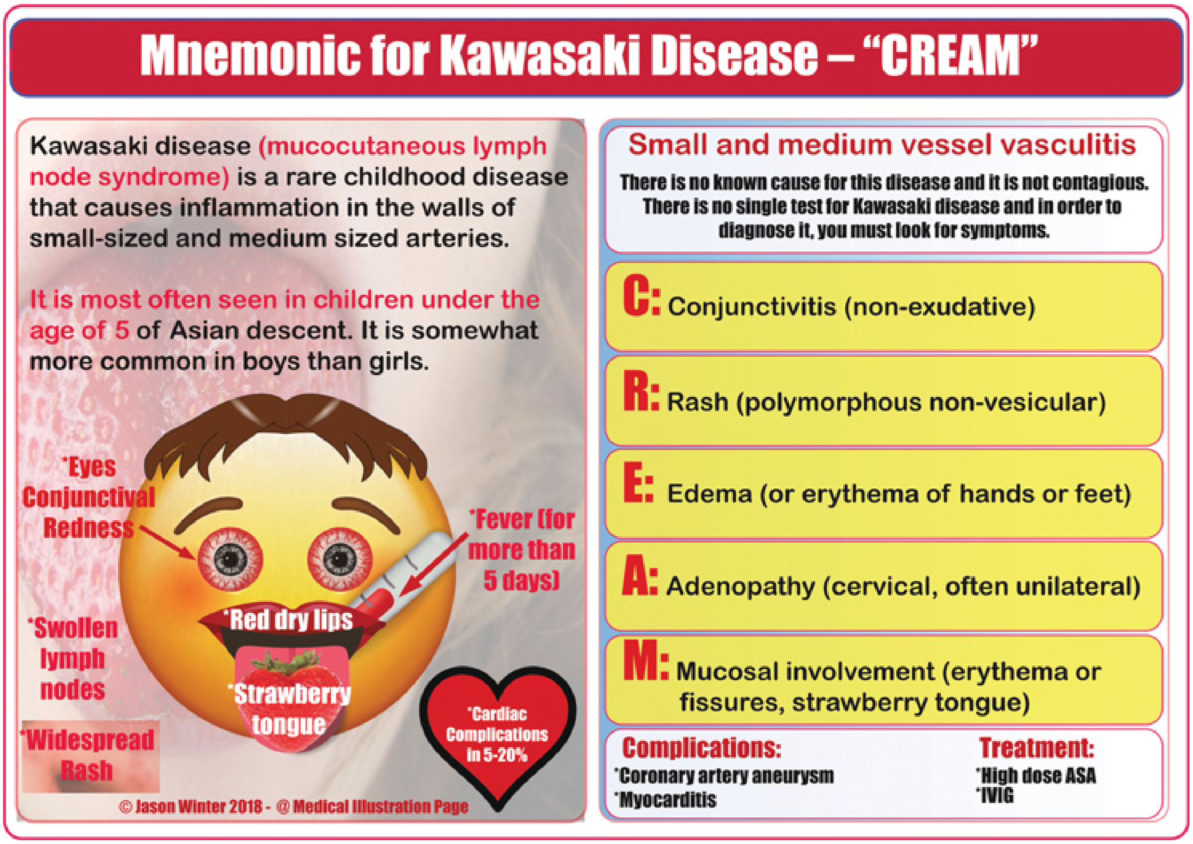

Figure 46.2 Mnemonic for Kawasaki disease: "CREAM." The graphic highlights the clinical features of Kawasaki disease and the diagnostic criteria utilized in an easy to remember mnemonic form. Illustration provided by Jason Winter and reproduced with permission.

greater risk for the development of myocardial ischemia if large or giant aneurysms are present or have persisted at the time that care is being provided.

Unlike the expanding literature addressing postoperative outcomes and risk assessment in the anesthetic care of patients with congenital heart disease undergoing noncardiac surgery, there is extremely limited data regarding anesthetic implications or outcomes in patients with KD. In fact, most of this literature is in the form of case reports. However, despite the small number of publications, the clinical experience to date has been favorable, indicating that despite potential risks, deep sedation or general anesthesia can be provided safely in most children with KD with a very low incidence of complications. An understanding of the disease process, as highlighted in Figure 46.2, and continued adherence to the basic principles discussed in this chapter will likely ensure the best possible outcomes in these children.

Suggested Reading

Daniels L. B., Gordon J. B., and Burns J. C. Kawasaki disease: late cardiovascular sequelae. *Curr Opin Cardiol* 2012; **27**: 572–7.

McCrindle B. W., Rowley A. H., Newburger J. W., et al. Diagnosis, treatment, and long-term management of Kawasaki disease: a scientific statement for health professionals from the American Heart Association. *Circulation* 2017; **135**: e927–99.

Odegard K. C., DiNardo J. A., Tsai-Goodman B., et al. Anaesthesia considerations for cardiac MRI in infants and small children. *Paediatr Anaesth* 2004; **14**: 471–6.

Son M. B. F. and Newburger J. W. Kawasaki disease. *Pediatr Rev* 2018; **39**: 78–90.

Sosa T., Brower L., and Divanovic A. Diagnosis and management of Kawasaki disease. *JAMA Pediatr* 2019; **173**: 278–9.

To L., Krazit S. T., and Kaye A. D. Perioperative considerations of Kawasaki disease. *Ochsner J* 2013; **13**: 208–13.

https://doi.org/10.1017/9781108657341.047 Published online by Cambridge University Press