Introduction and Pathophysiology

Kawasaki disease (KD) is an acute systemic vasculitis syndrome of unknown etiology occurring in infants and children. It primarily affects small-medium sized arteries, especially coronary arteries [1] and was originally described in Japan by Dr. Tomisaki Kawasaki in 1967 [2]. It is one of the leading causes of ischemic heart disease in infants and children from thrombosis in coronary artery aneurysms secondary to coronary arteritis. Although, several theories including role of pathogens, genetic markers, environmental factors have shown to be associated with KD, the true cause of KD still remains unknown.

Epidemiology

KD is markedly more prevalent in Japan with an annual incidence of 264.8 per 100,000 in 2012. The estimated incidence of KD in North America is 25 cases per 100,000 children who are less than 5 years of age per year [3]. Although KD has
been well described in developed countries, it is increasingly recognized in many developing or resource limited countries. The incidence in Europe and Australia is approximately 6–9/100,000 [4–6]. The global incidence of KD is shown in Fig. 12.1 [7].

KD is more common during winter and early spring in the extratropical northern hemisphere, with the lowest number of cases in late summer and fall. However, there is a lack of seasonal variation in the tropics and the extratropical southern hemisphere [8]. The highest relative risk is seen in Asian children, especially those of Japanese ancestry. Boys are slightly more affected than girls with ratio of 1.5–1.7:1 of affected children <5 y [9–11]. The recurrence rate of KD is ~3.5% in Japan, Asians, Pacific Islanders. In United States, the rate of recurrence is quite low at 1.7% [11] occurring at a median age of 1.5 y after initial episode [12], increasing

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**Fig. 12.1** Histogram showing incidence of KD across the globe
the risk for development of coronary artery sequelae [13]. After a first case in the family, the incidence of KD in a sibling has approximately ten-fold higher relative risk and of these, 50% will develop within 10 days of the first case [14]. This risk is higher in identical twins, which could likely be secondary to genetic predisposition that interacts with exposure to similar pathogenic agent in the environment [15, 16]. It is important to note that the peak mortality usually occurs 15–45 days after the onset of fever, this is secondary to coronary vasculitis, elevation in platelet count and hypercoagulable state [17]. Sudden death in children and adults occur later in life and has been shown to be secondary to myocardial infarction from aneurysm and stenosis of the coronary arteries [18].

**Pathology**

KD causes systemic vasculitis of medium sized arteries and inflammation of various organs during the acute febrile phase. Apart from coronary artery involvement, it can also cause myocarditis, pericarditis, valvulitis and extracardiac involvement leading to hepatitis, interstitial pneumonitis, abdominal pain, vomiting, diarrhea, gall bladder hydrops, aseptic meningitis, irritability, pyuria, pancreatitis and lymphadenopathy.

The primary pathology involves following three process:

1. **Necrotizing arteritis:** Self-limiting neutrophilic process leading to progressive destruction of arterial wall into adventitia, causing aneurysms, vasculitis and perivasculitis of microvessels causing edema and inflammation. This lasts for 2 weeks after fever onset.

2. **Subacute/chronic vasculitis:** Subacute process beginning 2 weeks after fever onset leading to infiltration of lymphocytes, plasma cells, eosinophils and may continue for several months.

3. **Luminal myofibroblastic proliferation (LMP):** This is an active proliferative process that begins in first few weeks after fever onset and leads to arterial stenosis of the coronary arteries [19–23]. This stage is characterized myofibroblastic proliferation process consisting of myoblasts and inflammatory cells which may persist for months to years.

The pathological outcomes of involvement of coronary artery damage depends on the severity of lesions. Mildly dilated arteries usually return to normal size soon. Large sized aneurysms usually lose their intima, media and elastica which cannot be regenerated. Fusiform aneurysms can thrombose or develop progressive stenosis. Large aneurysms may resolve when the lumen size decreases because of layered mural thrombi or myofibroblastic proliferation. Giant aneurysms generally lose all the media, with only a rim of adventitia remaining that leads to successive layers of thrombi, with organization and calcification of the oldest thrombi. Giant aneurysms may rupture in the first 2 to 3 weeks after fever onset but rarely do so thereafter. Myocardial infarction can occur from acute or progressive thrombosis or from stenosis [24].
**Etiology**

Etiological factors for KD have not been well confirmed, although several factors have been described including preceding respiratory illness, or an autoimmune process. Other epidemiological studies have correlated the incidence of KD cases in Japan, Hawaii and western United States with tropospheric wind currents originating in Northeastern China suggesting a wind-borne agent trigger. The high incidence of KD in Asian children especially in Japan, China, Korea and Taiwan strongly supports the hypothesis that genetic susceptibility determines host response to the KD pathogen. Several genes and signaling pathways have been shown to have association with aneurysm formation and host susceptibility [25, 26].

KD also has clinical similarities to scarlet fever and Staphylococcus toxic shock syndrome (SSS), both of which are caused by toxin producing bacteria, causing release of superantigens. However, KD differs markedly from SSS, in that there is a lack of acute vasculitis in SSS [27–30].

**Clinical Features and Diagnosis**

The clinical features and diagnosis of KD is made based on clinical criteria (Table 12.1, Fig. 12.2). Patients who meet the definition based on the primary findings are said to have complete KD or typical KD or classical KD. Patients who do not have sufficient clinical findings are known to have incomplete or atypical KD. In the absence of a specific diagnostic test, other clinical, laboratory and echocardiographic findings can support the diagnosis of incomplete KD without meeting the classical definition [3].

The principal diagnostic criteria used for classical/typical KD are:

- Persistent fever >5 days
- Conjunctival injection
- Oropharynx changes
- Peripheral extremity changes
- Diffuse erythematous rash
- Cervical lymphadenopathy

The diagnosis of classical KD can be made based on the presence of ≥5 days of fever and presence of ≥4 of the 5 principal clinical features (Table 12.1 and Fig. 12.3). In the presence of >4 principal clinical criteria, particularly when redness and swelling of the hands and feet are present, the diagnosis may be made with only 4 days of fever.

Fever is typically high spiking (>39 °C – 40 °C) and continues for 1–3 weeks. After the IVIG infusion, the fever usually resolves within 36 hours. However, if the fever does not resolve in that time frame, the patient is considered to have resistance to IVIG (discussed later in the chapter).
In the early phase, painful erythema of the palms and soles may occur. Within 2–3 weeks after the onset of fever, desquamation of the fingers and toes occurs, which may extend into palms and soles in about two thirds of all patients.

A diffuse erythematous maculopapular rash usually appears within 5 days of fever onset and is extensive, primarily involving the trunk and extremities with early development of a diffuse erythematous maculopapular rash. This rash is usually present within 5 days of fever onset and may be extensive, particularly involving the trunk and extremities. It may be present in about two thirds of all patients. Patients may also develop unilateral cervical lymphadenopathy that is ≥1.5 cm in diameter.

Table 12.1 Diagnosis of classical Kawasaki disease

| Feature                                                                 | Description                                                                 |
|-------------------------------------------------------------------------|-----------------------------------------------------------------------------|
| Classical or typical KD is diagnosed by presence of fever for at least 5 days (the day of fever onset is taken to be the first day of fever) along with at least 4 of 5 principal clinical features: |
| 1. Erythema and cracking of lips, strawberry tongue, and/or erythema of oral and pharyngeal mucosa |                                                                                   |
| 2. Bilateral bulbar conjunctival injection without exudate               |                                                                                   |
| 3. Rash: Any of the following form: Maculopapular, diffuse erythroderma, erythema multiforme-like |                                                                                   |
| 4. Erythema and edema of the hands and feet in acute phase and/or periungual desquamation in subacute phase (usually after 1–2 weeks of fever onset) |                                                                                   |
| 5. Unilateral cervical lymphadenopathy ≥1.5 cm diameter                  |                                                                                   |

Patients who lack full clinical features of classical KD, may be diagnosed as incomplete or atypical KD

Laboratory test findings in such cases:

| Finding                                                   | Description                                                                 |
|----------------------------------------------------------|-----------------------------------------------------------------------------|
| 1. Normal or elevated white blood cell count             |                                                                             |
| (a) Neutrophil predominance                              |                                                                             |
| 2. Elevated acute phase reactants – during acute phase   |                                                                             |
| (a) C-reactive protein                                   |                                                                             |
| (b) Erythrocyte sedimentation rate (ESR)                 |                                                                             |
| 3. Low serum sodium                                      |                                                                             |
| 4. Low albumin level                                     |                                                                             |
| 5. Elevated liver enzymes                                |                                                                             |
| 6. Sterile pyuria                                         |                                                                             |
| 7. In the second week after fever onset, thrombocytosis is common |                                                                             |

Fig. 12.2 Clinical features of classic Kawasaki disease. (a) Diffuse maculopapular rash on the trunk or erythema multiforme-like, (b) Bulbar conjunctival injection without exudate, (c) Erythema and cracking of lips, (d) Palmar erythema with swelling in acute phase

In the early phase, painful erythema of the palms and soles may occur. Within 2–3 weeks after the onset of fever, desquamation of the fingers and toes occurs, which may extend into palms and soles in about two thirds of all patients. A diffuse erythematous maculopapular rash usually appears within 5 days of fever onset and is extensive, primarily involving the trunk and extremities with early development of a diffuse erythematous maculopapular rash. This rash is usually present within 5 days of fever onset and may be extensive, particularly involving the trunk and extremities. It may be present in about two thirds of all patients. Patients may also develop unilateral cervical lymphadenopathy that is ≥1.5 cm in diameter.

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A diffuse erythematous maculopapular rash usually appears within 5 days of fever onset and is extensive, primarily involving the trunk and extremities with early
desquamation. Other common findings include scarlatiniform erythroderma and erythema multiforme-like lesions. Bullous, vesicular and petechial rashes are not consistent with KD; hence the doctor should search for alternative diagnosis. Bilateral non-exudative bulbar conjunctivitis begins shortly after fever onset and is limbus sparing. Changes of lips and oral cavity including erythema, dryness, fissuring, peeling, cracking and bleeding of the lips, strawberry tongue and diffuse erythema of the oropharyngeal mucosa are classical for KD. Presence of oral ulcers and pharyngeal exudates usually rules out KD.

Cervical lymphadenopathy is usually unilateral and is ≥1.5 cm in diameter and is usually noted in the anterior cervical triangle. Occasionally cervical lymphadenopathy may be confused with bacterial lymphadenitis. It is very important to be cautious in misdiagnosing and delaying the appropriate treatment. In such situations, imaging studies including ultrasound or CT scan neck may be helpful in differentiating KD lymphadenopathy from bacterial lymphadenitis which may lead to complications such as parapharyngeal and retropharyngeal edema and non-suppurative phlegmon [31, 32].

The presence of exudative conjunctivitis, exudative pharyngitis, oral ulcerations, splenomegaly and vesiculobullous or petechial rashes should prompt consideration of another diagnosis [33]. In a nonimmunized child who presents with clinical features, measles should always be considered as one of the diagnoses. Detection of a virus such as respiratory syncytial virus, metapneumovirus, coronavirus, parainfluenza or influenza virus doesn’t necessarily exclude the diagnosis of KD as there may be concurrent viral infections during the winter seasons [34–36]. In children with clinical features of KD and a positive rapid test or culture for group-A streptococcus without improvement after 24–48 hours of effective antibiotic therapy, the diagnosis of KD should be reconsidered.
Incomplete/Atypical KD

The diagnosis of incomplete KD should be considered in any infant or child with prolonged, unexplained fever and have less than 4 of the principal clinical criteria along with lab and echo findings (Fig. 12.3) [37].

Hence it is important to include KD as one of the differential diagnosis in infants <6 months of age who present with prolonged fever and irritability, and unresponsive to antibiotic therapy.

Other Clinical and Lab Findings

Other than involvement of coronary arteries, KD may also cause features of neurological irritability, diarrhea, vomiting, abdominal pain, gallbladder hydrops, urethritis, arthritis or interstitial pneumonia.

Lab findings include leukocytosis during acute stage of illness, with a predominance of immature and mature granulocytes. Leukopenia and lymphocyte predominance usually suggest an alternate diagnosis. Presence of normocytic normochromic anemia is common and usually resolves with resolution of inflammation. Acute phase reactants such as ESR and CRP are elevated during the acute phase and is universal in the diagnosis of KD. The CRP usually normalizes more quickly than the ESR during resolution of inflammation, however, the ESR is elevated with IVIG therapy as well. Hence, monitoring of CRP trend is a useful marker of inflammation after treatment of acute inflammation.

Thrombocytosis is an important finding and it generally doesn’t occur until the second week, peaking in the third week and normalizing by 4–6 weeks after its onset. Thrombocytopenia is rare but may occur in the first 1–2 weeks of illness. Other lab findings may include elevation in serum transaminases or gamma glutamyl transpeptidase (GGT) [38, 39], hypoalbuminemia, and B-type natriuretic peptide (NT-pro-B-NP; which is indicative of myocardial involvement may be elevated in some patients with KD but may non-specific in diagnosing KD [40, 41].

Cardiovascular Manifestation

During the acute phase, most importantly, coronary arteries may be inflamed due to arteritis. However, in certain cases, the whole heart may be affected including pericardium, myocardium, endocardium and the valves. The clinical manifestation during acute phase may include tachycardia, hyperdynamic precordium, innocent murmur, gallop rhythm. Presence of pericardial effusion is a common echocardiographic finding, but a precordial rub or tamponade may be rarely found. Most
commonly mitral valve may be involved in up to 25% of patients. Aortic root dilation may be noticed in ~10% of patients during the acute illness [42]. Involvement of the sinus node and AV node can lead to arrhythmias and prolonged PR interval. Non-specific ST-T changes with abnormal ventricular repolarization may also be noted.

Since the introduction of gamma globulin in 1992, there has been a significant decline in the incidence of transient dilation and aneurysm formation of the coronary arteries. Historically, most of these patients received Aspirin as a part of anti-platelet therapy. Use of IVIG has significantly reduced the prevalence of coronary artery abnormalities [43, 44]. These landmark studies have led to the initiation of IVIG therapy as a primary standard of therapy for KD.

Occasionally myocarditis may be seen and can be transient in nature leading to myocardial dysfunction in a few children. They respond well to anti-inflammatory therapy. Certain subsets of patients may develop Kawasaki disease shock syndrome (KDSSS) associated with shock like presentation requiring inotropic support and may develop greater risk for coronary artery abnormalities, mitral regurgitation and have prolonged course of myocardial dysfunction [45].

**Involvement of Coronary Arteries**

Coronary artery involvement may lead to mild dilation to giant aneurysms in both proximal and distal arteries. Most of the patients with significant coronary artery dilatation may have baseline dilatation within the first 10 days of illness. Up to 50% of patients may develop mild dilatation of coronary arteries that will resolve within 4–8 weeks, patients with extensive or giant aneurysm may be asymptomatic unless they present with myocardial ischemia. Rarely, patients may develop aneurysms of other medium sized blood vessels such as axillary, subclavian, brachial, femoral, iliac, splanchic and mesenteric arteries usually near the branching points [24, 46] with similar pathology as the involvement of coronary arteries during acute phase of illness.

Resolution of acute inflammatory process may be followed by chronic vasculitis and luminal myofibroblastic proliferation (LMP) which may normalize eventually but this may eventually increase the risk for stenosis of the arteries.

Echocardiography is considered as the primary imaging modality in the assessment of KD both during acute phase of illness as well as during follow-up period. It is non-invasive and has high sensitivity and specificity to detect abnormalities of proximal coronary artery segments. In the acute phase of illness, echo should be performed for diagnosis of KD. However, unavailability of echocardiography or technical limitations should not delay the treatment for patients. Presence of normal initial echocardiogram during the first week of illness does not completely rule out diagnosis of KD. The initial echocardiogram establishes a baseline for long-term follow-up for many patients, hence in an uncooperative or irritable patient, sedation may be needed.
In addition to standard anatomic and physiological imaging windows, the 2D imaging should focus on left main coronary artery, left circumflex, left anterior descending, right coronary artery and posterior descending artery. Maximal efforts must be made to visualise complete coronary arteries from multiple imaging planes (Fig. 12.4). The most common sites of coronary artery aneurysms are proximal left anterior descending, proximal right coronary artery, left main coronary artery and left circumflex coronary artery.

Coronaries may show diffuse ectasia or aneurysms (Figs. 12.5 and 12.6). The aneurysms may be described based on the morphology as saccular or fusiform. The use of z-score is shown to better evaluate the coronary artery dimension by correcting for body surface area (BSA). The coronary artery luminal dimensions are

![Fig. 12.4](image1.png) Multiplanar reconstruction of a normal right and left anterior descending coronary artery

![Fig. 12.5](image2.png) Follow-up cardiac CT in patient with Kawasaki disease presenting with areas of calcification within the aneurysm of the right coronary artery
classified based on the z-score and relative or absolute dimension of coronary lumen as follows [47]:

Following z-score classification is broadly used for assessment of coronary abnormalities:

1. **No involvement:** Always <2
2. **Dilation only:** 2 to <2.5; or if initially <2, a decrease in Z score during follow-up ≥1
3. **Small aneurysm:** ≥2.5 to <5
4. **Medium aneurysm:** ≥5 to <10, and absolute dimension <8 mm
5. **Large or giant aneurysm:** ≥10, or absolute dimension ≥8 mm

Echocardiography is an excellent tool for diagnosis and follow up of the size, thrombus, stenosis or aneurysm as well, it is also helpful in assessment of the aortic root, detection of ventricular wall motion abnormalities, pericardial effusion, valvar regurgitation. Use of other advance imaging modalities such as computed tomographic angiography (CTA), cardiac magnetic resonance imaging (MRI) or invasive angiography may be helpful in making decisions in further management of these patients over long-term course of the disease process.

In uncomplicated patients, echo should be repeated within 1 to 2 weeks, and 4–6 weeks after the initial treatment. For those patients who have coronary artery involvement with z-score > 2.5, at least weekly echocardiography should be performed until luminal dimensions have stopped progressing. To detect coronary artery thrombosis, it may be reasonable to perform echo in rapidly expanding large or giant aneurysms at least twice a week (or more frequently while the dimension is increasing) until 3 months after the illness onset.
Treatment

Acute Treatment

The primary goal of starting immediate therapy is to reduce the coronary artery inflammation and arterial damage to prevent thrombosis in the coronary artery abnormalities. The mainstay of therapy for both complete and incomplete KD is a single high dose of IVIG along with acetyl salicylic acid (ASA) (Table 12.2).

Table 12.2 Medications used in Kawasaki disease

| Initial management                                                                 | Additional dose of IVIG 2 gm/kg may be given 24 hours after first dose if fever doesn’t subside |
|-----------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------|
| IVIG 2 gm/kg                                                                       | Given as single IV dose for 10–12 hours within first 10 days of onset                           |
| Aspirin 80–100 mg/kg/day divided every 6 hours                                     | Given until the child is afebrile for 48–72 hours                                               |
| Clopidogrel 0.2–1.0 mg/kg/day                                                      | Thromboprophylaxis given together with ASA for complex coronary artery aneurysms including giant aneurysms where dual antiplatelet therapy is warranted |

Adjunct therapies

IVIG + Prednisolone:
2 mg/kg/day divided every 8 hours followed by oral taper over 2–3 weeks

Infliximab: IV 3 mg/kg/day divided every 12 hours
Or
Oral 4–8 mg/kg/day divided every 12 hours

Alternative therapies

Cyclosporine:
IV: 3 mg/kg/day divided every 12 hours
Oral: 4–8 mg/kg/day divided every 12 hours

Anakinra: 2–6 mg/kg/day given subcutaneous

Cyclophosphamide:
2 mg/kg/day IV

Plasma exchange

(continued)
All patients meeting the AHA diagnostic criteria for KD should be treated as soon as possible in the course of illness. IVIG should be started as early as possible within first 10 days of onset of fever. IVIG should also be started in patients with delayed diagnosis (>10 days of fever) if they have ongoing elevation in the ESR, CRP along with associated coronary artery aneurysms (z-score > 2.5).

IVIG has been shown to reduce new coronary artery abnormalities in several studies. All patients should be started treatment with IVIG 2 gm/kg as a single infusion given over 10–12 hours period along with ASA [48]. As IVIG is a biological product made from pooled donor plasma, rare complications may develop such as aseptic meningitis without any neurological sequelae. Children receiving IVIG should defer measles, mumps, varicella immunizations after receiving high dose IVIG. However, children in whom risk of exposure to measles is high may receive vaccination earlier and then be reimmunized at least 11 months after IVIG administration if they have inadequate serological response.

Standard treatment during the acute phase of illness consists of administering high dose ASA of 80–100 mg/kg/day every 6 hours in North America, 50 mg/kg/day in Japan and western Europe. The high dose is transitioned to low dose aspirin

**Table 12.2 (continued)**

| Initial management |
|--------------------|
| **Antithrombotic therapy** |
| Low Molecular Weight Heparin (LMWH) | Monitored by Anti-factor Xa level 0.5–1.0 U/ml |
| Enoxaparin: Given every 12 hours subcutaneous | Titrate to anti-factor Xa target range |
| <2 mo. age: 1.5 mg/kg per dose | |
| >2 mo. age: 1.0 mg/kg/dose | |
| Warfarin: Load with 0.2 mg/kg/day, followed by 0.1 mg/kg/day, titrate the dose to INR target level | INR target level 2–3 |

| Thrombolytic therapy |
|----------------------|
| Tissue plasminogen activator – Alteplase: Following dosing regimen may be used: 0.1–0.6 mg/kg/hr. IV for 6 hours |
| Or 0.2 mg/kg IV bolus (max 15 mg), followed by 0.75 mg/kg over 30 min (max 50 mg), followed by 0.5 mg/kg over 60 min (max 35 mg) for total max dose of 100 mg |
| Monitor closely for bleeding |
| Reassess for thrombus after completion of the infusion by echocardiogram |
of 3–5 mg/kg/day after the patient is afebrile for 48–72 hours. The low dose aspirin is continued until the patient has no evidence of coronary artery changes by 6–8 weeks after the onset of illness.

Use of high dose ASA for prolonged period of time when there is active influenza or varicella infection is associated with Reye’s syndrome [49–51]. Hence in patients presenting with active influenza and KD, in addition to starting IVIG, alternative antipyretics such as acetaminophen should be considered for a minimum of 2 weeks. Ibuprofen antagonizes the irreversible platelet inhibition by ASA, hence ibuprofen should be avoided in patients with coronary aneurysms for the antiplatelet effects [52].

7% of patients develop KD shock syndrome (KDSS) [45, 53] defined by the presence of shock, hypotension requiring initiation of volume expanders, infusion of vasoactive agents or transfer to intensive care unit for the management. It is critical to recognize early signs of KD during KDSS presentation so that IVIG therapy can be initiated promptly to reduce coronary complications.

Adjunct Therapy for KD

A combination of corticosteroids along with IVIG as an initial treatment in high risk KD patients is associated with reduction in the coronary artery abnormalities [54]. Another drug, Infliximab which is a chimeric monoclonal antibody that binds with high affinity to TNF-alpha may be used as a rescue therapy in patients resistant to IVIG therapy [55, 56]. Adding infliximab to the initial therapy along with IVIG does not necessarily prevent recrudescent fever.

IVIG Resistance

Although most of the patients are responsive to IVIG within first 24–48 hours, ~10—20% of patients with KD develop recrudescence or persistence of fever [57–59]. The presence of fever at least 36 hours after the end of IVIG infusion is known as IVIG resistant KD. The mechanism of resistance is poorly understood and may be associated with host genetic factors or polymorphisms in the receptors. Patients who are resistant to initial IVIG dose are at a higher risk of developing coronary artery abnormalities [60–62].

In case of resistance to IVIG treatment, a second dose or retreatment with IVIG 2 gm/kg may be given. Administration of high-dose pulse steroids such as IV methylprednisolone 20–30 mg/kg IV for 3 days with or without a subsequent course and taper of oral prednisone may be considered as an alternative to second infusion of IVIG. Other adjunct therapies including infliximab (5 mg/kg) may be used as an alternative to a secondary infusion of IVIG or corticosteroids for this subset of patients. Patients who do not respond either to second dose of IVIG, steroids or infliximab, will require additional therapy to control inflammation. Plasma exchange or Cyclosporine may also be used as another adjunct therapy.
A newer drug, Anakinra is a recombinant, non-glycosylated form of human IL-1 receptor antagonist and may be used for treatment of highly refractory KD [63, 64].

**Thrombus Management**

Antiplatelet therapy is considered as the standard therapy for patients with coronary artery aneurysms. For patients with small coronary artery aneurysms, monotherapy with low dose ASA therapy is sufficient for prophylaxis of thrombosis. In patients with moderate size aneurysms, ASA therapy along with a Thienopyridine such as Clopidogrel may be used, due to the superior efficacy of this regimen when compared to ASA alone [65–68].

Patients with large or giant aneurysms, with internal luminal diameter z-score $\geq 10$ or absolute dimension $\geq 8$ mm, are at particularly high risk for coronary artery thrombosis and eventually development of stenosis. In such patients, treatment should be initiated with an antiplatelet and anticoagulant therapy, most commonly low-dose ASA together with warfarin therapy (to maintain INR ratio target 2.0–3.0) or with low molecular weight heparin (LMWH).

Transition from LMWH to warfarin may be considered once aneurysms have stopped expanding and the patient is stable. More aggressive therapies may be used in patients with exceptionally high risk for coronary artery thrombosis. Infants and children requiring thrombolysis for coronary artery thrombosis may be maintained for a limited time on 3 agents such as ASA, Clopidogrel and an anticoagulant therapy. Ibuprofen and other NSAIDs with known or potential involvement of cyclooxygenase pathway may be harmful in patients taking ASA for its antiplatelet actions.

For the therapy of acute coronary syndrome with thrombosis, the goal is to reestablish coronary artery flow, patency, salvage the myocardium and overall reduce morbidity and mortality. The coronary artery thrombosis of adult coronary artery disease is caused by plaque rupture or inflammation, with exposure of lipids and extracellular matrix to the coagulation system. However, this is different in KD as the pathology is due to abnormal flow characteristics leading to thrombus formation. Therapy for coronary thrombus rarely requires use of thrombolytic therapy such as tissue-type plasminogen activator (t-PA). It is used in acute occlusive or near-occlusive thrombosis in infants and children.

**Long-term Outcomes and Management**

Long term management begins at the end of acute illness which is 4–6 weeks after fever onset. The primary goals of long-term management are to prevent thrombosis and myocardial ischemia which can be achieved by thromboprophylaxis and careful surveillance of coronary artery stenosis and myocardial ischemia respectively along with maintenance of optimal long-term cardiovascular health.
KD can also lead to long term vascular changes including systemic arterial dysfunction and increasing arterial stiffness and intima-media thickness and thus overall vascular health is affected.

The long-term risk stratification is assessed by the use of echocardiographic coronary artery body surface area (BSA) adjusted z-score measurements. Risk stratification may help in specific recommendations for medical therapy, thromboprophylaxis, physical activity and reproductive health.

Only in patients without coronary artery involvement, ASA is stopped after 6–8 weeks. However, those with coronary artery involvement, low dose ASA (3–5 mg/kg) is continued. Addition of anticoagulation including warfarin or LMWH along with dual antiplatelet therapy (ASA + Clopidogrel) may be used depending on the extent of coronary artery aneurysm involvement. Additional therapies including statin and beta-blocker may be use in those with higher risk including small-medium aneurysms.

**Long Term Follow-up**

Assessment of patients during follow-up period includes history and physical examination, electrocardiography, echocardiography. Patients without coronary artery involvement and those with z-score < 2 are discharged from the cardiology care after echo surveillance at 4–6 weeks. It is unlikely to develop new coronary artery dilation after 4–6 weeks after acute treatment [69–72].

Ongoing cardiology follow-up is recommended in patients with aneurysm of any size (Table 12.3). Patients with small to medium size aneurysms often regress

| Coronary artery involvement | ASA low dose (3–5 mg/kg/day) | Dual antiplatelet therapy (ASA + Clopidogrel) | Warfarin or LMWH | Statin |
|----------------------------|-------------------------------|---------------------------------------------|-----------------|-------|
| No involvement (z-score < 2) | 6–8 weeks, then discontinue | Not indicated | Not indicated | Not indicated |
| Dilatation only (z-score 2 to <2.5) | May continue after 6–8 weeks | Not indicated | Not indicated | Not indicated |
| Small aneurysm (≥2.5 to <5) | Continue | Not indicated | Usually not indicated | Empiric therapy may be considered |
| Medium aneurysm (≥5 to <10, or < 8 mm diameter) | Continue | May be considered | Usually not indicated | Empiric therapy may be considered |
| Large and giant aneurysm (≥10, or ≥ 8 mm diameter) | Continue | May be considered | Indicated | Empiric therapy may be considered |
towards normal luminal dimensions most quickly during first year after acute treat-
ment. However, large or giant aneurysms take longer and fewer of them regress
back to normal luminal dimension. As this slow regression happens over a period
of time, these aneurysms are associated with increased risk of stenosis and obstruction.
For routine surveillance, historically, only invasive coronary angiography was used
for follow-up. However, other modalities are currently being used such as use of
physiological and pharmacological stress imaging including nuclear medicine
(NM) scintigraphy stress imaging, Positron Emission Tomography (PET) and car-
diac MRI for assessment of myocardial perfusion imaging (MPI). Physiological
exercise stress echocardiography is found to be superior to exercise stress electro-
cardiography alone in the detection of ischemia, the major limitation is the rapid
return of the heart rate back to normal rate in young patients and that younger chil-
dren cannot optimally perform on treadmills. Hence alternatives include Dobutamine
stress echocardiography. Patients with inducible myocardial ischemia on testing
should eventually undergo invasive coronary angiography.

Cardiac MRI considered as a useful for the assessment in long term imaging of
KD patients and has an advantage of avoiding radiation exposure [73]. Myocardial
stress cardiac MRI is a promising new technique where it can be used for risk strati-
fication of patients. In a recent study by Bratis et al., the authors demonstrated an
inducible perfusion defect and myocardial scar in patients and they showed signifi-
cant impaired myocardial perfusion reserve when compared to control subjects sug-
gest the presence of microvascular dysfunction in these patients [74].

Cardiac CT angiogram can provide 3-D visualization of the coronary artery tree
and may identify regions of stenosis more optimally than cardiac MRI. It can also
provide detailed view of the presence of thrombus in the coronary arteries as well.
However, the radiation exposure may be significant and may limit its use. Newer CT
scan systems with lower levels of radiation exposure could increase the utility and
safety of this modality.

Invasive angiography is considered as the “gold standard” for coronary artery
assessment, although it is invasive. It provides detail coronary anatomy, luminal
diameter and structure. Fractional flow reserve (FFR) measured during angiography
is useful in determination of ischemia causing areas in patients affected by
KD. Intravascular ultrasound (IVUS) has also been used to demonstrate vascular
pathology in patients where coronary artery abnormalities are noted.

Important Long-term Cardiovascular Health

Patients with KD has a different pattern or susceptibility to CVD risk factors than
general population. Due to their increased risk for coronary artery disease (CAD) in
KD patients, it warrants more aggressive management and lifestyle modifications to
reduce CVD risk factors such as cholesterol levels, adiposity, vascular health.

Empiric use of hydroxy methylglutaryl coenzyme-A (HMG-CoA) reductase
inhibitors (Statins) is the cornerstone of therapy for the primary and secondary pre-
vention of atherosclerotic cardiovascular events in adults [75, 76]. Statins have
shown to lower the low-density lipoprotein (LDL) cholesterol and have potential benefits by its pleotropic effects on inflammation, endothelial function, oxidative stress, platelet aggregation and coagulation. Hence empiric therapy with low-dose statin may be considered in KD patients with past or current aneurysms, regardless of age or sex as a long-term therapy.

For antiplatelet action, most commonly Aspirin is used. However, in patients with Aspirin allergy, other types of antiplatelet therapy may be considered. For anticoagulation, most common medication used is Warfarin. However, dosing based on the levels may be problematic especially for monitoring levels for few patients and in such cases, LMWH may be an alternative.

Since KD is an illness of childhood, most of the early education and care is directed towards parents. Hence it is important to educate and involve the child (patient) during the transition of care discussion starting as early as 12 years [77]. Patients who never had coronary artery involvement or aneurysms, long term cardiology follow-up is not recommended in such cases. Due to the ongoing need for long term management, both pediatric and adult cardiologist should collaborate together for optimal transition and long-term care of these patients.

**Effect of COVID-19 Pandemic**

A special emphasis is deserved during the COVID-19 pandemic era caused by the virus, SARS-CoV-2. Several pediatric cases of a Kawasaki-like disease have been reported, with clusters of children and adolescents requiring admission to intensive care units who are presenting with atypical Kawasaki disease or acute toxic shock like syndrome. This Multisystem Inflammatory Syndrome in children (MIS-C) is been reported across the world, predominantly in Europe [78] and other countries [79–82]. The proposed hypothesis and mechanism for lung and myocardial injury from SARS-CoV-2 is due to a "cytokine storm" from the proinflammatory and regulatory T cells [83].

The World Health Organization (WHO) currently has a preliminary case definition which is similar to atypical KD criteria, which includes: fever for ≥3 days and a constellation of clinical and lab features of KD in addition to positive COVID-19 testing or contact with a COVID-19 positive patient [84]. Although the WHO clinical data platform is being updated constantly, of the reported cases, almost all patients present with significant myocardial dysfunction leading to hypotension or shock requiring inotropic support in the ICU setting. Coronary artery involvement is seen in 17% of cases in one of the multiinstitutional studies [78] as opposed to 50% in classical KD. Gastrointestinal symptoms such as diarrhea and vomiting is in several children in addition to a -purulent bilateral conjunctivitis, lymphadenopathy, skin rash, and cracked lips have been described. Due to the overlap with atypical KD symptoms, several children are being treated with IVIG in addition to inotropic support (as indicated). Although several children have had relatively short hospital stays with near recovery [78], the long-term implications of MIS-C needs to be studied in children post-discharge.
Global recognition of MIS-C is imperative during this time period, since the early recognition of these clinical findings is important to avoid delaying treatment with IVIG and other KD related adjunctive therapies.

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