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Kawasaki Disease: Etiopathogenesis and Novel Treatment Strategies

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Abstract

Introduction—Kawasaki disease is an acute febrile systemic vasculitis that predominantly occurs in children below five years of age. Its etiopathogenesis is still not clear, but it is thought to be a complex interplay of genetic factors, infections and immunity.

Areas covered—This review article discusses in detail Kawasaki disease, with particular emphasis on the recent updates on its pathogenesis and upcoming alternate treatment options. Though self-limiting in many cases, it can lead to severe complications like coronary artery aneurysms and thrombo-embolic occlusions, and hence requires early diagnosis and urgent attention to avoid them. Intravenous immunoglobulin (IVIG) with or without aspirin has remained the sole treatment option for these cases, but 10-15% cases develop resistance to this treatment.

Expert Commentary—There is a need to develop additional treatment strategies for children with Kawasaki disease. Targeting different steps of pathogenesis could provide us with alternate therapeutic options.

Keywords

Coronary artery aneurysm; Intravenous immunoglobulin; Kawasaki Disease; Refractory Kawasaki disease; Thrombo-embolic occlusion

1 Introduction

Kawasaki disease (KD), also called mucocutaneous lymph node syndrome, was first described by a Japanese pediatrician, Dr. Tomisaku Kawasaki in 1967 [1]. It is a febrile vasculitis disorder which is usually diagnosed by a cluster of signs and symptoms along with supporting laboratory findings. It is a multisystem disorder, with predilection for small and medium sized arteries, especially coronary arteries [2]. If left untreated, it can lead to various complications like coronary artery aneurysm, thrombosis, stenosis and even sudden

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death [3]. In fact, KD is considered as the leading cause of acquired heart diseases in developed countries [4]. KD has, therefore, remained an interesting subject of investigation to determine its exact etiology and pathogenesis, and warrants the development of other treatment options apart from intravenous immunoglobulin (IVIG) therapy. There has been considerable research done in this regard and in this article, we have critically reviewed the recent findings on the etiopathogenesis of KD and therapeutic alternatives.

2 Epidemiology

Kawasaki disease predominantly affects young children, mostly below 5 years of age, with 1.5-times higher risk in boys than girls [5]. The epidemiological patterns are quite distinct in different geographical locations, with variations in incidence based on ethnicities and season. Worldwide, the highest incidence has been found in Japan (239/100,000 below 5 years of age), followed by Korea (113.1/100,000) and Taiwan (69/100,000) [6]. In these countries robust nationwide epidemiological surveys for KD are conducted every 2-3 years. Three epidemics of KD have occurred in Japan each in the year 1979, 1982, and 1986 [4]. Epidemiological surveys in Japan have also reported higher incidence in children with parental or sibling with history of KD compared to the general population [7].

In the United States of America (USA), the incidence of KD hospitalizations has been reported to be 19/100,000 in children below 5 years of age [4]. However, clear variation has been noted in different ethnicities. Incidence is 2.5-times more in Asians and Pacific Islanders and 1.5-times more in blacks compared to Caucasians [4]. This is also supported by the fact that Hawaii, which has the highest Asian population in USA, has the highest incidence of KD in the USA with an average of 50.4/100,000 cases over a period of 1996-2006 in children below 5 years of age [8]. In Europe, United Kingdom reported an annual incidence of 8.4/100,000 in children below 5 years of age, while in Denmark and Netherlands it was found to be around 4-5/100,000 in children below 5 years [8].

Interestingly, seasonal variation has also been noted in the trends of KD incidence. While in Japan incidence is higher in January (winters) and July (summer), as also seen in Korea, USA has higher incidence during winter and spring season, with no variation noted in areas like Hawaii possibly due to the tropical climate throughout the year [9-11]. In Europe, incidence is highest in the winters. One hypothesis for this variation was suggested by Singh et al. [5]. These researchers hypothesized that KD might be triggered by an airborne agent in Central Asia which is then blown to different geographical locations to cause KD by gaining entry in the body through the respiratory tract. Therefore, the wind patterns might determine the incidence of KD in different parts of the world. But, this association has to be confirmed by conducting more epidemiological studies across the globe.

3 Diagnosis

Diagnosis of KD is a clinical challenge, given the wide variety of clinical presentations and the similarity to many viral and bacterial illnesses. The clinical sequel occurs in three phases: acute, subacute and convalescent phase [12]. Diagnosis of typical KD is made on the basis of the evidence of fever along with 4 out of the 5 other symptoms (Table 1). All the

clinical features might not appear simultaneously, hence it is important to enquire about all the possible symptoms while taking history [13]. Kuo et al [14] have established a mnemonic to aid in memorizing these clinical symptoms. It is described as 1-2-3-4-5, with 1 for one 'mouth' (strawberry tongue and fissured lips); 2 for two 'eyes' (bilateral conjunctivitis); 3 for three fingers palpation of neck lymph nodes (cervical lymphadenopathy); 4 for limb changes (swelling of hands and feet) and 5 for multiple skin rash throughout the body. This is a simple yet effective way of remembering the variety of symptoms to look in suspicious Kawasaki cases.

Acute phase usually lasts for up to 14 days and is characterized by high grade fever ($> 38.5^{\circ}\text{C}$), with no response to antipyretics or antibiotics. Conjunctival injection is another common finding, which is usually bilateral, painless, non-exudative with limited involvement of limbic area [13]. Apart from conjunctivitis, patients may also present with other eye symptoms like subconjunctival hemorrhages, uveitis and papilledema. Oropharyngeal mucosal changes include dry and cracked lips, strawberry tongue and non-exudative inflammation of the tongue [15]. Some children can present with cervical adenopathy, which is usually unilateral, mostly involving anterior cervical chain [12]. Rash of KD is non-pruritic, with macular lesions on trunk and extremities. Perineal desquamation is common in the acute phase while periungual desquamation is seen in the subacute phase [16]. Diffuse erythema of the palms and soles with clear distinction from the uninvolved skin and painful swelling of hands and feet is also noticed in the acute phase [13]. Other uncommon symptoms found to be associated with KD in few cases include diarrhea, vomiting, sterile pyuria, dysuria, arthritis, aseptic meningitis [17]. However, these symptoms are not a part of the diagnostic criteria for KD. In patients who have received *Bacillus Calmette-Guerin* vaccine, erythema, crusting and induration of the skin at the site of vaccination are considered strong specific indicators of KD [13]. Tseng et al [18] recently attempted to correlate the grade of BCG reaction to the severity of systemic involvement in Kawasaki disease. They reported that severe induration in the form of target lesions was associated with highest elevation of liver enzymes, and the risk of coronary artery dilatations and milder induration in the form of a faint rash or a homogenous white area were associated with lesser degree of systemic inflammation in KD. These investigators also indicated that the target lesions could, therefore, even serve as biomarkers of clinical severity of KD [18].

KD has a predilection for cardiovascular complications. During acute phase, valvulitis, myocarditis, pericarditis and KD shock syndrome are commonly seen [12]. Coronary artery aneurysms (CAAs) and dilatation are most often in the subacute to convalescent phase. Almost 20% of the untreated children develop aneurysms [12]. Risk factors for developing aneurysms include: male sex, extremes of age, prolonged fever, delay in diagnosis and treatment [16]. Though involvement of coronary arteries is most common in KD, other arteries that might be affected include axillary, renal and iliac arteries [16].

According to the American Heart Association (AHA) guidelines outlined in 2004, Incomplete KD is the term used for patients with less than 4 positive symptoms along with fever and abnormal lab values, while atypical KD refers to patients with KD who present with rare symptoms like renal impairment [19]. These variations are usually common in

younger infants, less than 6 months of age and are at higher risk of CAAs and other complications [13]. Accordingly, AHA recommends that infants less than 6 months of age with fever lasting for more than 7 days, at least 2 classical symptoms of KD and lab values showing systemic inflammation with no apparent alternate explanation should be evaluated by an echocardiograph for incomplete KD [19].

No lab studies are specific for KD, but they can help to rule out KD and predict the outcomes. In majority of the cases, signs of systemic inflammation like high erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) are noticed in the acute phase [16]. Other findings include neutrophilic leukocytosis, normocytic normochromic anemia and thrombocytosis [15]. Echocardiography is useful to study in detail the coronary abnormalities. Hyponatremia is reported to predict adverse coronary outcomes [15]. Neutrophils are considered a marker of ongoing inflammation, whereas lymphocytes are markers of immune response. Hence, high neutrophil-to-lymphocyte ratio (NLR) could mean an imbalance between inflammatory and immune response. Ha et al. [20] studied the usefulness of neutrophil to lymphocyte ratio in predicting KD outcomes in 587 patients with KD. They reported that NLR after 2 days of IVIG (Intravenous immunoglobulin) treatment could be helpful in predicting the occurrence of CAAs ($p=0.03$) and resistance to IVIG ($p<0.001$). They concluded that NLR above 1 after 2 days of IVIG treatment indicated higher risk of CAAs and IVIG resistance. But this relationship still needs to be evaluated in larger prospective studies.

Given the high rate of cardiac complications in KD, usefulness of cardiac biomarkers in KD is also being evaluated. One such biomarker that appears to be highly promising is N-terminal pro-B-type natriuretic peptide (NT-proBNP) [21]. This biomarker is synthesized by ventricular cardiomyocytes and is an indicator of cardiomyocyte stress [22]. Elevated levels of NT-proBNP are found to be associated with diastolic dysfunction. A recent meta-analysis to determine the usefulness of proBNP in the diagnosis of KD by Lin et al [22] concluded that it is a specific (pooled specificity 0.72) and moderately sensitive (pooled sensitivity 0.89) diagnostic tool for KD, which could be helpful for recognizing KD in patients with undifferentiated febrile illness. Another study by Ye et al [23] found it to be highly useful for establishing response to IVIG treatment with higher levels noticed in patients who were unresponsive to IVIG treatment (area under the curve 0.73).

For patients with coronary artery lesions, regular monitoring is performed by conventional techniques like myocardial perfusion imaging and CT angiography [24]. Cardiac MRI is a newer technique that has been studied in recent for following up the patients and has the advantage of being radiation-free and non-invasive imaging technique [25]. It can provide information about both structure and function of cardiac tissue [23]. Tacke et al [24] performed a comprehensive MRI in sixty-three patients with KD and compared the findings to echocardiography results in these patients and reported favorable performance of cardiac MRI. Mavrogeni et al [26] similarly reported that cardiac MRI could be useful in acute phase of KD for identifying myocardial inflammation, left ventricular function, lesions of coronary artery lumen and vessel wall, while in chronic phase it might be helpful in risk stratification and treatment guidance.

4 Etiopathogenesis

The etiopathogenesis of KD has been studied extensively but is still not fully understood. It appears to be an interplay of genetic susceptibility and infectious trigger followed by an abnormal immune response.

4.1 Genetic susceptibility

Genetic susceptibility is one of the areas of ongoing investigation in KD given the specific patterns of occurrence of this condition in different ethnic groups and races. Epidemiological studies have shown highest incidence in Japan, Korea and Taiwan [8] and Asian races in the USA [4]. In Japan, it has been reported that there is ten-times more risk of KD in siblings of patients with KD than general population and two-times higher risk in children with parental history of KD [7]. These differences in the family and races suggest that genetic factors could play a strong role in the pathogenesis of KD.

Initial studies on the genetic basis of KD were focused on Human Leukocyte Antigen (HLA) and found HLA-DRB1, HLA B5, Bw51 and Bw44 to be associated with KD susceptibility [27]. There are many ongoing investigations to detect candidate genes for KD. These studies are being conducted not only to identify the genetic relationship of KD but also to provide insight to its etiopathogenesis [28]. With the beginning of Genome Wide Association studies, considerable progress has been achieved to identify potential loci of susceptibility. Some of the most widely studied genes to be found consistently associated with KD include inositol 1,4,5-triphosphate 3-kinase (ITPKC), caspase-3 (CASP3), B lymphocyte kinase (BLK), CD40, and HLA.

The ITPKC gene codes for one of the three isoenzymes of inositol 1,4,5-triphosphate 3-kinase that is involved in the Ca^{2+} /nuclear factors of activated T- cells (NFAT) signaling pathway in T cells [29]. It functions as a negative regulator of T cell activation [29]. Onouchi et al in 2008 reported that single nucleotide polymorphisms (SNPs) in ITPKC on chromosome 19q13.2 were associated with susceptibility to KD and risk of coronary artery abnormalities in Japanese and American children (rs28493229) [30]. Other variants found to be associated with KD were SNP rs2720378 and rs2290692 [31]. Polymorphism of ITPKC might result in increased activation of T cells and consequently increased release of interleukin-2 (IL-2). This could lead to prolonged expression of T cells during acute phase of KD and cause vascular endothelial cell injury and subsequently, increase the severity of KD as well risk of coronary artery lesions [21, 23].

Caspase3 (CASP3) is a part of Activation Induced Cell Death (AICD) pathway of apoptosis. It carries out apoptosis of immature cells [31]. It cleaves Inositol 1,4,5 triphosphate receptor, type 1 in apoptotic T cells and thereby serves as the positive regulator of Ca^{2+} /NFAT pathway [28]. Onouchi et al carried out a potential candidate gene study and reported a SNP within CASP3 gene (rs113420705) located on 4q34-35 to be associated with KD [32]. This finding was again consistent in both Japanese and American population. It has been suggested that the G to A substitution within exon1 of CASP3 reduces the binding of NFAT to DNA around the SNP, decreasing the transcription of CASP3 mRNA. This inhibits T cell apoptosis and causes prolonged activation of immune cells which in turn, might increase the

susceptibility to KD. But, this CASP3 polymorphism was not found to be associated with the risk of CAAs or response to IVIG treatment [29, 31].

Another gene found to be strongly associated with KD is the Fc fragment of IgG, low affinity IIa, receptor (FCGR2A) gene [29]. It is expressed on the surface of immune cells like, dendritic cells, macrophages, monocytes and neutrophils and transduces activation signals into cells on binding with immune complexes [27]. The A to G substitution of the SNP in FGR2A (rs1801274) alters the translation of the 131st amino acid from histidine (H) to arginine (R) [33]. This polymorphic form now has lower binding affinity to IgG2, that could be related to more immune activation during the acute phase of KD [33].

B-lymphocyte kinase (BLK) SNPs have also been implicated in KD based on studies in Japanese, Taiwanese, Korean and Asian population [29]. BLK is a tyrosine kinase expressed mainly on the B cells where it is involved in signal transduction [27]. Two GWAS studies carried out independently in Japan and Taiwan reported considerable association of KD with FAM167A-BLK region on chromosome 8p23-p22. This suggests that the involvement of B cell might be in the pathogenesis of KD. Also, in animal studies it was found that BLK is required for maturation of IL 17 producing $\gamma\delta$ T cells in mice [27]. In acute phase of KD, high levels of IL-17 are reportedly which might be related to BLK polymorphism [27]. However, function of FAM167A still remains unclear [33].

The involvement of the Transforming growth factor- β (TGF- β) signaling pathway in KD susceptibility, disease outcome and response to treatment was shown by Shizimu et al [34]. TGF- β is involved in maintaining a balance of pro- and anti-inflammatory T cells and therefore, genetic variation in TGF- β pathway could lead to an imbalance between inflammatory and regulatory T cells by influencing Foxp3 expression mediated by SMAD3 and NFAT [6, 7, 21]. KD susceptibility was associated with one SNP each in TGF- β 2 (rs 2796817) and TGF β R2 (rs 11466480) and 5 in SMAD3 [29].

Other genes found to be associated with KD susceptibility include CD40L, HLA DQB2, HLA DOB, KCNN2, DEL1, COB2 [27, 29].

4.2 Infections

Though the exact etiology of KD is unknown, it is considered to have an infectious trigger followed by the activation of immune system in a genetically susceptible individual [35]. This theory is also supported by results from epidemiological studies. Firstly, similar to viral infections, incidence of KD is higher in winter and spring seasons [17]. Like infections, there is occurrence of epidemics and clusters of cases [36]. KD is also self-resolving in 1-3 weeks and the most common age of acquiring KD is 6 months to 5 years when the susceptibility of the child to infections is also the highest [36]. Cases are rarely seen below 6 months of age which could be attributed to the passive transmission of maternal immunoglobulins providing protection to the child at an early age, which gradually decreases over the time [37]. Recently, Nagao et al also reported that KD has a similar mode of transmission to infections upon close contact with infected persons [38].

Recent studies have shown that bacterial superantigens might be related to the causation of KD. This is based on the similarity of clinical presentations in the two groups like strawberry tongue and desquamation of hands and feet [36]. It has been proposed that Staphylococcal Toxic Shock Syndrome toxin (TSST-1) and Streptococcal pyogenic toxins might act as superantigens that initiate an immune response which could lead to the occurrence of KD [2]. Another study also reported increased IgM antibodies to these superantigens in KD that further supports the hypothesis [39]. It has been suggested that superantigens bind to V β region of T cell receptor, and induce the release of immunological mediators like IL-6, TNF- α , TGF- β that are found to be elevated in KD [40]. But, it is still not clear whether these bacterial antigens activate immune system and cause KD by T cells directly or indirectly by T cell-mediated B cell differentiation [2].

Viral etiology has also been considered for KD pathogenesis. It has been found that in acute phase, there is infiltration of CD8⁺ T lymphocytes, IgA plasma cells and macrophages in the coronary arteries, which is similar to the observations in any acute viral infection [2]. However, in peripheral blood there is predominance of CD4⁺ T lymphocytes which could be possibly explained by the transmission of CD8⁺ T lymphocytes to the infected tissues [2]. Apart from this, in autopsy specimens of KD cases, electron microscopy studies have shown cytoplasmic inclusion bodies in ciliated bronchial epithelium with aggregates of RNA and viral protein [2]. This suggests that KD could be initiated by an acute viral infection of the respiratory system which later on leads to dysregulated immune response resulting in KD [2,27].

Till now, no specific infectious agent has been found to be consistently associated with KD. However, many case reports have linked KD with many viral agents like *Mycoplasma pneumoniae* [41], Cytomegalovirus [42], adenovirus, rhinovirus, enterovirus [43], bocavirus [44].

4.3 Immunity

KD is classically believed to occur as a consequence of dysregulated immune system. It has been proposed that KD is similar to autoimmune diseases in pathogenesis [3]. T cells have been primarily implicated in the immunopathogenesis of KD with involvement of inositol 1,4,5-triphosphate 3-kinase (ITPKC) as the main mediator [17]. ITPKC is a negative regulator of T cell activation and loss of its control leads to increased activation of T cells and production of cytokines, which has been shown in KD patients [17]. Onouchi et al [45] identified itpkc_3, a functional SNP in the ITPKC gene on chromosome 19q13.2 to be significantly associated with susceptibility to KD and increased risk of coronary artery lesions. They hypothesized that the C allele might be responsible for the immune hyper reactivity in KD. Wang et al [46] studied the serum samples of KD patients and analyzed the levels of cytokines of Th1 and Th2 cells. They found increased levels of IL-6, IL-20, IFN- γ (interferon γ) and TNF- α (Tumor necrosis factor- α) before IVIG treatment and reported rapid decrease in the serum levels of IL-6, IL-10 and IFN- γ after IVIG treatment [46]. Recently, studies have also shown an imbalance of Th (T helper cells) and Treg cells (regulatory T cells) in acute KD. Th17 cells are pro-inflammatory cells that secrete cytokines like IL-6, TNF- α , and IL-8 after activating neutrophils, monocytes, and fibroblasts

[47] while Treg cells are anti-inflammatory that work through secretion of cytokines like IL-10 and TGF- β to control the progression of inflammatory and autoimmune diseases. Jia et al [47] demonstrated that in children with acute KD, levels of Th17 cells and their cytokines (IL-17, IL-6 and IL-23) were significantly upregulated whereas Treg cells and the level of their transcription factor (FoxP3) were significantly downregulated. These investigators then proposed that this imbalance of Th17/ Treg cells might be involved in disturbing the immune homeostasis in KD. This relationship was also shown by Ni et al [48]. Kuo et al [49] performed a meta-analysis of the ITPKC studies carried out in Taiwanese population and reported a significant association between ITPKC allele rs28493229 and KD (Odd's ratio of 1.36 and 95% confidence interval: 1.12-1.66), especially with the risk of aneurysm formation (p=0.001).

NKG2D is expressed by immune cells like NK cells, cytotoxic T cells (CD8+ T cells) and plays a role in immunomodulation by enhancing the activity of these cells [50]. Therefore, its low levels in acute phase of KD might be associated with immune system dysregulation [50]. This association was shown by Ge et al [50]. They analyzed NKG2D expression on CD8+ T cells and CD3⁻CD56⁺ NK cells in acute KD cases, and found significantly lower levels than in controls. Additionally, the NKG2D expression was found to be lower in patients with coronary artery lesions compared to those without the coronary artery involvement [50].

Lee et al [51] showed the critical role of IL-1 in the pathogenesis of KD using mice knockout models and antibodies. This then led to clinical trials for the use of IL-1R (Anakinra) in children with KD and is currently in phase IIa of clinical trials [52].

Histological examination of the affected tissue shows both activation and damage of endothelial cells [36]. TNF- α , produced initially by the T lymphocytes and later released by the monocytes/macrophages, is one of the key inflammatory cytokines mediating this process [7]. It facilitates endothelial cell activation via increased expression of adhesion molecules and promotes the release of chemokines required for leukocytes-endothelial cell interaction [7]. TNF- α also stimulates the activity of MMP-9 (matrix metalloproteinase) which in turn leads to breakdown of elastin and aneurysm formation in vessel wall. Therefore, use of TNF- α blockers could be one of the therapeutic strategies in KD patients to prevent aneurysms formation and is undergoing clinical trials [17]. It has also been shown that nitric oxide (NO) production is increased in KD patients and goes down rapidly with IVIG treatment [52]. NO is known to maintain normal vascular tension. High NO concentrations could therefore lead to vessel wall dilatation and lesions [53]. This is mediated by the inducible nitric oxide synthase enzyme (iNOS) present in myocardial cells, vascular smooth muscle cells, leukocytes and inflammatory cells which is upregulated during inflammatory response and in turn, promotes elevation of NO [52,54]. IVIG treatment has been shown to decrease the levels of NO in KD [52,53,55]. The imbalance of various cytokines and other inflammatory markers in KD is summarized in Figure 1.

4.4 Perinatal exposure and KD

There has been recent interest to investigate if there are any perinatal factors that might increase the risk of acquiring KD in later life of the child. This hypothesis was recently

studied by Hayward et al [56]. They performed a retrospective, case control study and identified 1019 KD patients in the 21-year study period (1987-2007). After adjusting for confounding factors like gender, race and birth year, they found group B streptococcus (GBS) colonization (OR 0.51, 95% CI: 0.26-0.97), maternal age above 35 years (OR 1.65, 95% CI: 1.20-2.27) and early infant hospitalization (OR 1.42, 95% CI: 1.04-1.93) to be significantly associated with the risk of KD. In particular, early infancy bacterial infections were associated with 2.8-times increased relative risk of KD. One possible mechanism is that the early exposure to infections might weaken the developing immune system in a way that renders it susceptible to KD later in life. Alternatively, these children might be having some immune deficit that could predispose them to both infections in early life and KD at a later age. GBS colonization was associated with a lower risk of KD, which could possibly be explained by the trans-placental transfer of antibodies to the growing fetus that provides protection from KD at later age.

This raises the possibility of KD susceptibility with in utero and early infancy risk factors, but this is only a single study data. More studies should be performed to accurately establish the association between the two.

5 Treatment

5.1 Acute phase treatment

AHA and AAP (American Academy of Pediatrics) recommend a combination of aspirin and IVIG for treating acute KD [57].

5.1.1 IVIG—The first description of the use of IVIG in treating KD dates back to the 1980s by Furusho et al [58]. Since then it has been used successfully in treating majority of the cases of KD and has become the standard of treatment. The best response is seen if IVIG treatment is started within 10 days of the onset of symptoms at a single dose of 2g/kg infusion over 12 hours [59] as per AAP and AHA guidelines.

The mechanism of action of IVIG is still under investigation but the proposed possible mechanisms of action of IVIG include: neutralization of infectious antigens and superantigens, suppression of TNF- α , neutralization of pathogenic autoantibodies, inhibition of inflammatory cytokines release and modulation of B and T cells function [2, 59] (Figure 2).

A recent meta-analysis by Chen et al studied the dose-response relationship for IVIG treatment by comparing low dose IVIG (400 mg/kg) given over 4-5 days to a high dose (2g/kg) single infusion [60, 61]. They concluded that single infusion is more efficacious in preventing CAA. Studies have compared the various commercial preparations of IVIG available in the market and reported that using acidic conditions for preserving immunoglobulins has increased risk of CAAs and treatment failure [58]. The efficacy of treating patients with IVIG 10 days after the onset of symptoms is not well established, therefore, it is recommended to start IVIG treatment soon [14]. But, it is still recommended to administer IVIG to patients presenting even later than 10 days if they have ongoing fever or other signs of inflammation, including elevated CRP and ESR [14]. Muta et al reported

that IVIG treatment after 10 days is helpful in decreasing the inflammatory process, even though the risk of CAA still remains high [62].

However, in spite of adequate IVIG treatment, around 5% children develop transient coronary artery dilatation and 1% develop aneurysms [2,36].

5.1.2 Aspirin—Aspirin is used in conjunction with IVIG for its anti-inflammatory effect in the acute phase of KD and for its anti-platelet activity during the sub-acute phase [63][64]. The accepted dosage varies from country to country. While in the USA, it is given at a high dose of 80-100 mg/kg/day as per the AHA guidelines, in Japan it is recommended at a moderate dose of 30-50 mg/kg/day given the risk of hepatic toxicity at higher doses [59, 64]. Studies have reported similar efficacy of the two treatment regimen[65]. According to AHA recommendations, in the acute phase, patient is given 80-100 mg/kg/day in 4 divided doses, followed by 3-5 mg/kg/day during the sub-acute phase of KD for at least 6-8 weeks for its antithrombotic activity [19]. If the patient has coronary artery abnormalities, aspirin is continued at low dose till there is echocardiographic evidence of the resolution of coronary artery lesion, while it is continued for indefinite time if there is evidence of CAA [19]. Patients with giant aneurysms should be started on low molecular weight heparin or warfarin given the risk of thrombotic complications in these cases [59].

Children with KD on treatment with aspirin for prolonged periods have a risk of developing Reye's syndrome if they are also affected by influenza or varicella infections [2]. It is therefore, recommended to use clopidogrel as an alternative to aspirin in such cases [2].

Although it helps to reduce inflammation, aspirin has not been shown to play a role in reducing the frequency of CAA or IVIG resistance in KD [60]. Kuo et al [58] demonstrated that high dose aspirin impairs the decrease in hepcidin level, thereby resulting in lower availability of iron for erythropoiesis and in turn, anemia. They also noted that patients treated with high dose aspirin had persistently elevated CRP levels despite treatment, suggesting no improvement of inflammation with aspirin in KD. Wang et al [55] also reported similar findings. They both therefore, even suggested to completely stop the use of aspirin in the acute phase of KD, but there is a need to carry out more randomized controlled trials in this respect.

5.2 Refractory KD

AHA and AAP define refractory KD as the one where fever persists beyond 36 hours of treatment with IVIG [66]. These patients can then be treated with either a second dose of IVIG or steroids [66]. There are many other upcoming treatments aimed at decreasing inflammation which are discussed in detail below (Table 2).

5.2.1 Corticosteroids—Though steroids are one of the mainstay treatment for various conditions with vasculitis, it was initially avoided for the treatment of KD, based on findings of one report that concluded increased risk of cardiovascular complications with steroids monotherapy [67]. But later studies reported reduced CAA risk on use of steroids along with IVIG and aspirin [68]. One of the largest RCT (Randomized clinical trial) conducted in this regard was in Japan, named RAISE study, randomized controlled trial to Assess

Immunoglobulin plus Steroid Efficacy for Kawasaki Disease, which reported improvement in coronary artery outcomes in KD patients on giving prednisolone along with IVIG [69]. Steroids could be helpful in KD by down regulating inflammatory mediators, preventing leukocyte migration and decreasing capillary permeability [70]. Use of intravenous pulsed methylprednisolone (IVMP), 30 mg/kg for 2-3 hours once daily for 2-3 days is the most commonly used steroid regimen [36].

But, controversies still exist regarding the the indications for the use of steroids in KD. Some suggest use of steroids only in cases that fail to respond to >2 infusions of IVIG, while others recommend use of IVIG in cases where the first dose of IVIG itself is unable to bring down inflammation [36]. AHA recommends the use of steroids in patients that fail to respond to 2 or more infusions of IVIG [70]. Ogata et al reported better outcomes in refractory KD patients with combined IVIG and IVMP treatment [71]. Chen et al [72] performed a meta-analysis of clinical trials to compare the efficacy of IVIG plus steroid treatment compared to IVIG alone and concluded that their combined therapy as an initial treatment in KD is more useful in reducing the risk of CAA. IVMP through their anti-inflammatory functions suppress cytokine levels faster than IVIG alone [73]. The usefulness of second dose of IVIG versus steroids in IVIG resistant cases needs to be fully established [14].

The safety of steroids in KD patients was studied by Miura et al [74]. They reported higher incidence of sinus bradycardia and hyperglycemia in patients treated with IVMP compared to those treated with second dose of IVIG. Although these adverse effects were only transient, but indicate the need for monitoring of patients on steroid infusion [75]. Overall IVMP is considered safe as an adjuvant treatment to IVIG alone or along with aspirin [14].

Although with regards to the use of steroids in KD, most of the studies have investigated the use of IVMP, Lim et al [76] studied the use of dexamethasone, a longer acting steroid in KD in a retrospective study. They reported better clinical outcomes on combined use of dexamethasone and high dose IVIG in terms of shorter febrile periods, lesser need for IVIG second dose and shortened hospital stay without worsening of cardiovascular outcomes [76]. Further larger and prospective studies are required to establish the efficacy of steroids as initial or second line treatment and also comparative efficacy of IVMP versus dexamethasone.

5.2.2 TNF- α inhibitors—In view of the role of TNF- α in the pathogenesis of KD as well as coronary artery dilatations, it is plausible to use its inhibitors in the primary therapy for KD or in refractory cases. TNF- α antagonists can be subdivided into 2 categories: monoclonal antibodies (infliximab and adalimumab) and soluble receptors (Etanercept) [66].

Infliximab, a chimeric monoclonal antibody has been reported in many studies to be useful for the treatment of refractory KD. Mori et al [77] conducted an open labelled trial for infliximab in patients refractory to IVIG treatment. The 18 of the 20 patients were successfully treated with infliximab without any adverse effects. Tremoulet et al [78] have conducted a large randomized placebo controlled clinical trial for the use of infliximab in addition to the standard treatment in acute KD. They have completed phase III clinical trial

and reported that infliximab helped to reduce fever, markers of inflammation, IVIG reaction rates but had no effects on treatment resistance [78]. It was found to be safe and well tolerated [78]. Infliximab is usually administered at the dose of 5 mg/kg and response is seen within 24 hours of the treatment [59].

Abciximab, a monoclonal antibody against GpIIb-IIIa receptors has been used for the treatment of acute and sub-acute cases of KD with coronary artery aneurysms [79]. Williams et al [79] reported that addition of abciximab to standard therapy lead to greater reduction in the aneurysm diameter and hence, better outcomes. They also concluded that abciximab helps to promote vascular remodeling and hence decreases the risk of CAAs [79]. However, larger clinical trials are yet to be undertaken in this regard.

Etanercept, was used as an adjunctive therapy to IVIG for the first time in a clinical trial by Choueiter et al [80] where they reported favorable response in children at the dose of 0.4-0.8 mg/kg/week for 3 weeks. Based on these findings, a multicenter, double blinded, placebo controlled randomized clinical trial, named the EATAK trial, was initiated in 2011 to assess the efficacy of etanercept as an adjunctive treatment to IVIG in refractory KD [66].

5.2.3 Plasma exchange—In KD, inflammatory mediators are elevated and their elevation is a risk factor for developing CAAs. So, plasma exchange (PE), which removes various inflammatory cytokines could serve as a promising treatment option for preventing CAAs. It has been successfully used in many refractory KD cases. Mori et al [81] reported that early introduction of PE therapy, by 10th day, can help to reduce the risk of CAA in these patients based on their findings in 46 children treated with PE after failure of response to second dose of IVIG.

Fujimaro et al [64] used plasma exchange in 9 IVIG resistant cases, and reported decreased levels of IL-6, IL-17, G-CSF, TNF- α , TNFR1, TNFR2 after 4-5 days of plasma exchange therapy with no adverse effects in any case.

Duration of PE depends on many factors which includes resolution of symptoms like fever and normalization of inflammatory markers [64]. Generally, it is administered for 3-4 days although Fujimaro et al found it to be effective when given for 4-5 days [64].

Matsui et al [82] used a combination of IVMP and PE in a IVIG-resistant case. Two doses of IVIG followed by PE and IVMP from 10th to 14th day of illness resulted in considerable improvement in clinical symptoms as well as improvement of inflammatory markers, IL-6, sTNF α R type 1 and type 2 levels. Sonoda et al [83] used a stepwise treatment of IVIG, infliximab and PE to treat the KD patients. They selected 76 patients unresponsive to 2 doses of IVIG and treated them with infliximab first, followed by PE for those who did not even respond to infliximab (6 out of 76 patients). This resulted in the resolution of inflammation, with disappearance of fever and improvement of laboratory values [83]. Based on these findings, these investigators concluded that this stepwise protocol for refractory KD patients was highly effective. But, further large scale, multicenter, prospective studies are required to establish the success of the combination therapy.

5.2.4 Cyclosporine—Cyclosporine acts as a calcineurin inhibitor [84]. Since recent studies have shown the involvement of IPTKC/calcineurin pathway in the pathogenesis of KD, therefore, blocking of this pathway could be a useful treatment option for refractory KD patients. Cyclosporine would therefore, block the release of IL-2 which is a cytokine signaling molecule [70]. It is also postulated to inhibit T cell differentiation, thereby modulating the cell-mediated immunity and reducing inflammation in KD [70]. There have been conflicting results regarding the efficacy of cyclosporine in KD treatment. Kuijpers et al [85] reported no improvement in clinical outcomes in a 16-month old child with refractory KD. Suzuki et al demonstrated cyclosporine to be a safe and promising treatment option for refractory KD patients [86]. They conducted a prospective cases series in Japan and reported effective treatment of IVIG resistant cases with oral cyclosporine at the dose of 4-8 mg/kg/day in 18 of the 24 patients [86]. A phase III clinical trial of using IVIG and cyclosporine in severe KD (KAICA Trial) is also ongoing in Japan [87]. Patients are randomized to receive either oral cyclosporine (5mg/kg/day for 5 days) and high dose IVIG (2g/kg for 24 hours) plus aspirin 30 mg/kg/day, or high dose IVIG and aspirin at the same dose [87].

But, calcineurin inhibitors can be toxic to the endothelium and therefore should not be routinely administered but could be considered as a potential treatment option in certain cases [61, 88]. Further studies are required to find the optimal dose, safety and efficacy of cyclosporine in KD [14].

5.2.5 Cyclophosphamide—Cyclophosphamide is an immunosuppressive drug that is believed to reduce inflammation in KD. It inhibits DNA synthesis and cross linking of DNA strands, thereby preventing cell division [89]. This leads to cell death and is believed to involve cytokines. Inflammation is reduced when these immune cells are suppressed [70]. There have not been many studies with respect to cyclophosphamide use in KD. Wallace et al [90] performed a retrospective analysis of treatment of children with KD. Out of the 65 children in the study, 5 children had persistent KD even after 2 doses of IVIG. Four of these cases were treated with pulse IVMP (30 mg/kg/day) and 2 with cyclophosphamide (2 mg/kg/day). These patients did not have any progression of coronary artery aneurysms or mortality. No adverse effects of cyclophosphamide were reported. Further studies are required to establish the efficacy of this drug in KD treatment.

5.2.6 Methotrexate—Methotrexate (MTX) is primarily used as an anticancer drug. It is an antimetabolite that inhibits the enzyme Dihydrofolate reductase required for DNA synthesis and replication [91]. In KD, methotrexate (MTX) is believed to lower the C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and block the release of IL-1 and IL-6 [70]. Lee et al [92] first reported the successful use of methotrexate in a 6-year old child with refractory KD. This child did not respond to multiple courses of IVIG and was later started on methotrexate (10 mg/body surface area, weekly once) along with dexamethasone (0.6 mg/kg, daily) on day 38 of illness. This resulted in gradual subsiding of the inflammation. Lee et al [93] later performed a prospective study with 17 patients who were refractory to initial IVIG treatment. These patients were then treated with low dose methotrexate (10 mg/body surface area, once a week) till the CRP values were normalized. It was found that fever

dropped significantly within first week of treatment with MTX and even CRP was significantly lower after 1 week of treatment with MTX (8.9 mg/dl vs 1.2 mg/dl). No adverse effects were noted. Later few case reports have also reported successful resolution of KD with MTX without any adverse effects [94, 95].

6 Expert Commentary

Kawasaki disease has emerged as the major cause of acquired heart diseases in children in industrialized countries. The pathogenesis is still, however, unclear. Recent reports have associated genetic susceptibility to its causation. Many case reports have attributed its occurrence to different infectious agents but none of them have been found to be consistently associated and hence, requires further research. Dysregulation of the immune system is known to occur in Kawasaki disease but the underlying mechanisms warrants further investigation and currently is the subject of research for many investigators. As per treatment, aspirin and IVIG combined treatment has shown positive results in most of the acute cases. But, in refractory cases, IVIG is not of much use. In order to prevent coronary complications, multiple drugs are being examined and have shown positive results, but large scale prospective studies are still required to establish their safety and efficacy in the treatment of refractory KD.

7 Five-year view

With the ongoing research and clinical trials regarding the pathogenesis and effective drugs to be used in KD, in the upcoming years, we are expecting advancement in the field especially in regard to the role of genes, infections and immunity in the causation of KD. With a possibility of various multicenter, larger, prospective studies for the use of alternative drugs to IVIG and aspirin and also in refractory KD, more options for the treatment of KD would hopefully be available to the clinicians. Detailed information on potential adverse effects and safety of all these therapeutic alternatives would facilitate the decision process in the treatment plan depending on individual patient requirements. This will further be able to reduce the incidence of coronary and other complications associated with KD.

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Reference annotations

* Of interest

** Of considerable interest

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provides detailed information about the factors associated with pathogenesis and treatment of Kawasaki disease, as well as ongoing trials for the newer therapeutic options being explored

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Key issues

- Kawasaki disease is the leading cause of acquired heart diseases in children living in industrialized countries.
- The pathogenesis is still unclear, though there appears to be an interplay of genetic susceptibility, infections and immune dysregulation.
- Genome wide association studies have helped to recognize many genes that may confer susceptibility to Kawasaki disease.
- Perinatal factors might also influence the risk of occurrence of Kawasaki disease.
- IVIG and aspirin remain the mainstay therapy for acute phase treatment.
- There is no drug currently available to decrease the risk of coronary artery abnormalities or reverse the already occurred damage. Obviously, additional studies are urgently warranted in this area.

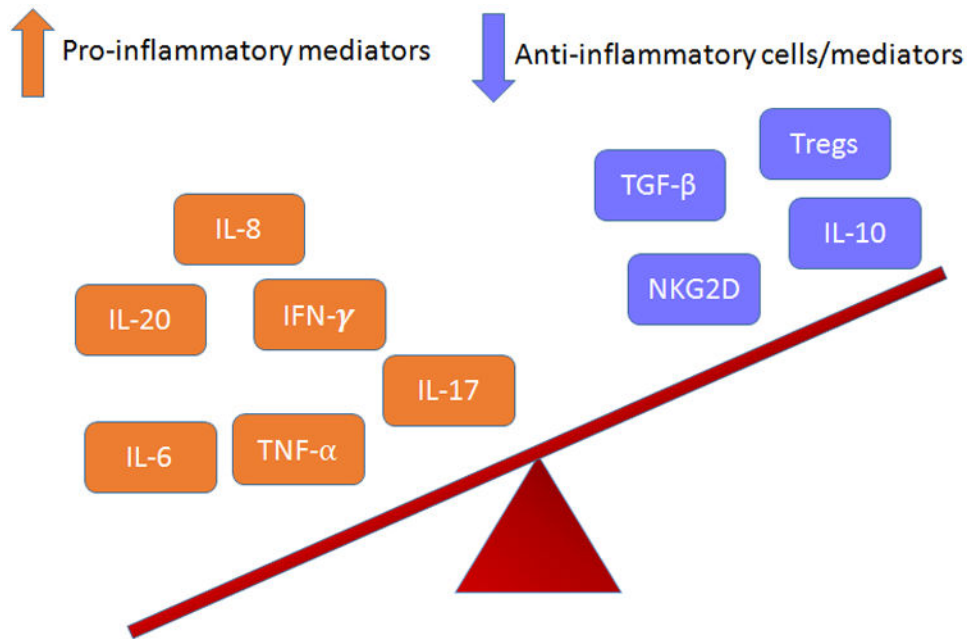


Figure 1. Diagrammatic depiction of the imbalance of the inflammatory markers in Kawasaki Disease. The pro-inflammatory markers are elevated along with downregulation of anti-inflammatory markers, leading to a state of inflammation and damage.

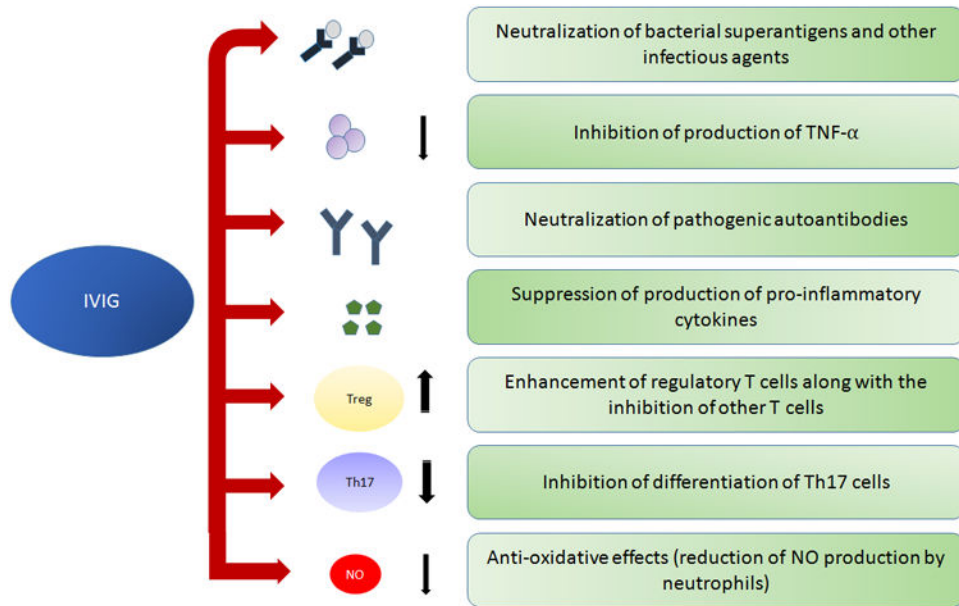


Figure 2.
Multiple functions of IVIG in the treatment of Kawasaki disease.

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Table 1

Clinical features of classical Kawasaki disease patient and the supporting laboratory findings.

Classical clinical case definition	Supportive laboratory findings
Persistent fever for 5 days with additional at least 4 of the 5 following symptoms: <ul style="list-style-type: none"> • Bilateral conjunctival injection • Changes in lips and oral mucosa • Polymorphous exanthema • Cervical lymphadenopathy, usually unilateral • Changes in hands and feet: erythema, edema and desquamation. 	<ul style="list-style-type: none"> • Elevated Erythrocyte sedimentation rate (ESR) • Elevated C Reactive Protein (CRP) • Leukocytosis with neutrophilia • Hyponatremia • Hypoalbuminemia • Anemia

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Table 2
Novel Therapeutics in the treatment of Refractory Kawasaki disease

Drug	Dosage	Mechanism of action (MOA)	Potential Side Effects	Evidence	Reference
Infliximab	5mg/kg IV	It binds to and inhibits TNF α , thereby preventing the release of pro-inflammatory cytokines and interleukins.	Infections, hepatomegaly, bradycardia, anemia, neutropenia, leukopenia	18 of the 20 patients were treated successfully with infliximab, 2 required additional plasma exchange therapy. In phase III RCT, it did not appear to reduce treatment, although it was helpful in reducing fever duration, few markers of inflammation and left anterior descending coronary artery Z scores [tr6].	[77] [78]
Etanercept	0.4-0.8 mg/kg/week for three weeks.	Soluble receptor blockade of TNF α receptors.	Headache, sinus infections, psoriasis, hepatitis B, allergic reactions.	Fifteen patients successfully completed the study. No serious adverse effects were noted. Though etanercept did not significantly improve the treatment outcome, but there was no case of prolonged or recurring fever requiring second dose of IVIG. None of the children developed coronary artery dilation or other abnormalities.	[80]
Steroids Methylprednisolone	Reduces inflammation by preventing the migration of leukocytes and decreasing capillary permeability.	30 mg/kg IV infused over 2 hrs for 3 days	Sinus bradycardia, hypothermia, hypertension, hypokalemia	Incidence of coronary artery abnormalities was significantly lower in IVIG plus steroids group compared to IVIG and aspirin alone (CI 0.12-0.28, p<0.0001). Meta-analysis of 9 clinical studies showed that IVMP and steroids combined treatment reduced the risk of coronary artery abnormalities significantly (OR 0.3, 95% CI 0.20-0.46).	[69] [72]
Dexamethasone	0.3mg/kg/day for 3 days			Patients receiving combined IVIG and dexamethasone treatment had shorter febrile period and hospital stay (p<0.001). Even the risk of coronary artery abnormalities was lower in this group, but it was not statistically significant (p=0.03).	[76]
Methotrexate	Inhibits the enzymes dihydrofolate reductase and thymidylate synthase, which play a role in folate synthesis. Might also reduce the release of IL-1 and IL-6 and leukotrienes.	10 mg/BSA weekly PO	Stomatitis, alopecia, bone marrow suppression, hepatotoxicity	Patients treated with methotrexate following IVIG had lower duration of fever (p=0.025), lower CRP (p<0.001) with no adverse effects. Case reports showing resolution of symptoms of KD with no adverse effects.	[93] [92,94,95]
Cyclosporine	Inhibits the assembly and release of IL-2, also inhibits the activation of T lymphocytes, thereby suppressing immune activation.	4 mg/kg/day IV or PO	Hyperkalemia, hypertension, hirsutism, infections, tremors and renal susceptibility	Out of 28 patients of refractory KD, 18 (64.3%) became afebrile within 3 days of cyclosporine treatment, while 6 (21.4%) failed to respond even after 5 days of treatment.	[79]

Drug	Dosage	Mechanism of action (MOA)	Potential Side Effects	Evidence	Reference
Cyclophosphamide	Inhibits DNA synthesis and prevents cell division by cross linking DNA strands	2 mg/kg/day IV	Hemorrhagic cystitis, alopecia, diarrhea, mucositis, bone marrow suppression	2 patients out of the 5 who developed refractory KD were treated with additional cyclophosphamide in addition to IVIG and reported no progression of coronary aneurysms and no adverse effects.	[82]
Plasma exchange	Centrifugation of blood, followed by discarding of filtered plasma containing the inflammatory cytokines and its replacement with another colloid such as donor plasma or albumin.	-	Transfusion allergic reactions, paresthesia, hypocalcemia, hypotension, bleeding.	Six patients unresponsive to IVIG and infliximab were treated with plasma exchange therapy and they reported complete resolution of symptoms. Even the patients who had coronary artery lesions, later reported suppression or reversal of abnormalities. 9 children with IVIG resistant KD were treated with plasma exchange and showed good response. Although three patients developed CAA, there was a resolution of these lesions by the end of a year.	[74] [54]