

Cytokine cascade in Kawasaki disease versus Kawasaki-like syndrome

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Summary

Kawasaki disease (KD) is a medium vessel systemic vasculitis that predominantly occurs in children below five years of age. It is an acute febrile condition in which coronary artery aneurysms and myocarditis are the most common cardiovascular complications. It is most often characterized by hypercytokinemia. The etiopathogenesis of KD is not fully understood. The present review synthesizes the recent advances in the pathophysiology and treatment options of KD. According to different studies, the genetic, infections and autoimmunity factors play a major role in pathogenesis. Several susceptibility genes (e.g., *caspase 3*) and cytokines (e.g., IL-2, IL-4, IL-6, IL-10, IFN- γ and TNF- α) have been identified in KD. Patients with high cytokine levels are predisposed to KD shock syndrome. The importance of respiratory viruses in the pathogenesis of the disease is unclear. Coronavirus disease 2019 (COVID-19) caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) may induce in children and adults an abnormal systemic inflammatory response. This syndrome shares characteristics with KD. It has been called by many terms like MIS-C (Multisystem Inflammatory Syndrome in Children), PIMS-TS (pediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2), hyperinflammatory shock syndrome, cytokine storm (cytokine release syndrome) or simply,

Kawasaki-like syndrome. The cytokine's role in the development of KD or Kawasaki-like syndrome being triggered by COVID-19 is controversial. The presences of the antiendothelial cell autoantibodies (AECAs) together with the newly developed hypothesis of immunothrombosis are considered potential pathogenic mechanisms for KD. In consequence, the diagnosis and treatment of KD and Kawasaki-like syndrome, one of the most common causes of acquired heart disease in developed countries, are challenging without a clearly defined protocol.

Keywords: Cytokine storm, Kawasaki disease, diagnosis and treatment

Introduction

Kawasaki disease (KD) is an acute febrile medium vessel systemic vasculitis of unknown etiology. It's also known as mucocutaneous lymph node syndrome. Children younger than five years of age are more vulnerable to this pathological condition. In general, it is a self-limited disease. A small percentage of untreated or inadequately treated children may develop coronary artery aneurysms, myocarditis and other potentially lethal complications. Nowadays, it seems to be the most important leading cause of acquired heart disease in children in developed countries where rheumatic fever is less common [1,2].

The characteristic symptoms of KD are high fever that lasts for at least 5 days, bilateral conjunctival hyperemia, cervical lymphadenopathy, rash, oral mucositis (red lips and tongue-strawberry or raspberry tongue) and extremity changes (swollen hands and feet) [3,4]. The diagnosis is still based on clinical criteria with supportive laboratory evidence and imaging, 40 years after its discovery in 1967 by Tomisaku Kawasaki. None of these criteria is 100% specific for diagnosis. Only the presence of vascular complications is highly sensitive for the final diagnosis [5]. More concerning from the perspective of trying to prevent long

term complications is that many children who develop coronary heart disease never met the criteria for KD [6,7]. This clinical aspect is much more common nowadays being correlated, by different researchers, with Coronavirus disease 2019 (COVID-19) [8].

Regarding laboratory diagnosis, it is most often characterized by hypercytokinemia. The inflammatory markers are also elevated. Intravenous immunoglobulin (IVIG) with or without acetylsalicylic acid are the drugs of choice [9,10]. The disease etiopathogenesis is not fully understood. The genetic factors, viral infections, autoimmunity and immunothrombosis play a major role in the pathogenesis of KD. COVID-19 caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) may induce in children and adults an abnormal systemic inflammatory response. Recent evidence showed that severely ill patients tend to have a high concentration of pro-inflammatory cytokines, such as interleukin 6 (IL-6), compared to those who are moderately ill. The high level of cytokines also indicates a poor prognosis in COVID-19. This syndrome shares characteristics with KD and macrophage activation syndrome (MAS), especially in children. Most of the patients are previously healthy school-aged children. This syndrome has been called by many terms like MIS-C (Multisystem Inflammatory Syndrome in Children), PIMS-TS (pediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2), hyperinflammatory shock syndrome, cytokine storm (cytokine release syndrome) or simply, Kawasaki-like syndrome. The cytokine's role in the development of KD or Kawasaki-like syndrome/MIS-C being triggered by COVID-19 is controversial [11-13]. Dos Santos et al. have shown, in a case series of patients from 97 different original articles, diagnosed with COVID-19, that the association of KD to the new coronavirus appears to trigger a severe clinical condition of vasculitis in children called a cytokine storm. Although similar, the cytokine storm is not KD exactly. While KD and MIS-C are clinical conditions, cytokine (release) storm (syndrome) is a common laboratory and pathophysiological entity of both [14].

There are few discordances among these definitions. The common characteristics are fever, evidence of inflammation, multisystem organ involvement, likely contact or evidence of SARS-CoV-2 infection, and exclusion of other microbial causes. These definitions may include children fulfilling partial or complete criteria for KD. MIS-C is infrequent, but children might present as a life-threatening disease. Given the current hypotheses of the pathophysiology of MIS-C, viral infection versus a postinfectious disease, RT-PCR and serology for COVID-19 are important parts and clues of the laboratory diagnosis. There are some recent clinical evidences of the fact that these clinical syndromes are also present in non-SARS-CoV-2 coronaviruses. Thus, the clusters of MIS-C observed may be secondary to massive exposure to a trigger in a susceptible population [11,12].

KD versus Kawasaki-like syndrome

Patients with MIS-C/Kawasaki-like syndrome usually develop fever, lymphopenia, gastrointestinal symptoms, rash and mucositis. Respiratory and neurological symptoms and acute kidney injury are generally mild. Left ventricular dysfunction and coronary abnormalities have been reported in most of the patients, explaining the high frequency of shock and vasoactive support requirements. Cases of MIS-C fulfilling criteria for KD and myocarditis are not frequently reported. Regarding laboratory diagnosis, all inflammatory markers are elevated, being the most consistent C-reactive protein (CRP). CRP is unspecific, but it is disproportionately elevated approximately 20 times the normal value. There are a high number of patients with shock criteria explaining the frequent requirement of intensive care unit admissions. Regarding treatments, most MIS-C/Kawasaki-like syndrome patients received IVIG or steroids and Interleukin Inhibitors. Despite the severity of cases, antiviral therapy, ECMO (Extracorporeal membrane oxygenation) and continuous renal replacement therapy are very uncommon. The overall prognosis of MIS-C is generally good [11-13].

Epidemiology

The epidemiology of KD varies by geographic region. Ethnic variation and seasonality are characteristics. The incidence rates of KD in Asian countries, especially in Japan, are significantly higher than those in the USA and Europe [15]. In Japan, the annual incidence rates varied between 243.1 and 264.8 per 100,000 in children younger than 5 years in the last decade (2010-2020) [16]. In South Korea and Taiwan, the disease prevalence is also higher than in different other parts of the world [17]. In contrast, the incidence of KD in the USA is estimated to be between 17.5 and 20.8 per 100,000 children <5 years in the same period. Average annual incidence rates per 100,000 children aged <5 years in Europe were constant over the same decade and much lower than in Japan (e.g. Finland, 11.4; Norway, 5.4; and Sweden, 7.4) [18].

According to CDC, the overall incidence of Kawasaki-like syndrome/MIS-C is around 5 persons per 1 000 000 SARS-CoV-2 infections in persons younger than 21 years. Different data suggest a seasonal exposure to a KD agent. During the winter months, the disease is more common. There is a consistent peak in the number of cases reported in January, with another gradual increase in spring to summer (March–June). The seasonal fluctuation is related to infectious agents, especially viral infections. PIMS-TS is infrequent. KD is the most common vasculitis in children worldwide, but MIS-C is much rarer [18,19].

Etiopathogenesis

Recent findings support a genetic component to KD susceptibility, including, an increased incidence in children whose parents have a history of KD. Several single-nucleotide polymorphisms (*SNPs*) in different genes and gene regions have been implicated in family linkage such as caspase 3 (*CASP3*), inositol 1,4,5-trisphosphate kinase-C (*ITPKC*), *CD40*, *FCGR2a* (Fc Fragment Of IgG Receptor IIa), *ORAI 1* (Calcium Release-Activated Calcium Modulator 1), a Ca^{2+} -release activated Ca^{2+} (*CRAC*) channel mediating store-operated Ca^{2+} -entry (*SOCE*) on the plasma membrane, located in chromosome 12q24) and B- cell

lymphoid kinase (*BLK*) [20,21]. Some of these *SNPs* associated with KD have been identified in other inflammatory diseases including ulcerative colitis, systemic lupus erythematosus or systemic sclerosis. These findings may indicate a common pathway in the inflammatory immune response. Knowledge of susceptibility genes involved in pathogenesis may provide new insights into diagnosis and treatment [22,23]. Some of these can predict the course, propensity to develop coronary artery sequelae, IVIG resistance and the severity of the illness in a patient with KD. The commonly used inflammatory markers e.g. erythrocyte sedimentation rate (ESR), CRP and total leucocyte counts (TLC) can be detected but none of these has reasonably high sensitivity and specificity in predicting the course of the disease [24,25].

Recent studies have been evaluated the importance of vaccination in the pathogenesis of KD. Vaccine exposure theory emphasized that vaccination may play a role in triggering KD through powerful stimulation of the innate and adaptive arms of the immune system. However, there is no clear evidence to suggest that vaccine administration is associated with the development of KD [26,27]. In contrast, other studies highlight that viral infections including COVID-19 are considered the most plausible stones in the mosaic of etiopathogenesis of KD. In consequence, vaccination could be an important way to prevent cytokine storms [12,13].

The role of the respiratory viruses in the pathogenesis of the disease is unclear. Until nowadays, no infectious causes have been identified as potential underlying etiologies, despite many investigations. The viral pathogens seem to be more implicated than other microorganisms: bacterial toxins, super-antigens or fungi. According to different studies, an unknown stimulus triggers an inflammatory cascade with activation of both the innate and adaptive arms of the immune system. The innate immune system may be activated through the detection of either pathogen-associated molecular patterns (PAMPs) or damage-

associated molecular patterns (DAMPs). The *NLRP3* inflammasome (*NLR* family pyrin domain containing 3) recognizes these abnormal molecular patterns in the body. The *NLRP3* inflammasome is a critical component of the innate immune system that mediates caspase-1 activation and the secretion of proinflammatory cytokines in response to microbial infection and cellular damage. At the same time, the aberrant activation of the *NLRP3* inflammasome has been linked with several inflammatory disorders, including KD, Alzheimer's disease, diabetes or atherosclerosis [28].

IL-1, IL-2, IL-4, IL-6, IL-10, IFN- γ and TNF- α are the most important cytokines identified in KD. IL-1 has a major inflammatory effect on coronary artery endothelial cells. It is well-known that IL-6 plays a major role in KD pathophysiology via megakaryocyte maturation, thereby leading to thrombocytosis. It also potentially causes vasculitis by triggering a cascade that stimulates polyclonal B cell autoantibody production, resulting in acute inflammation and antibody-mediated endothelial damage. Recent evidence suggested that IL-6 may be culpable for myocardial injury in COVID-19 patients. Recent studies have found IL-6 levels to be significantly elevated in MIS-C patients [12,13,28]. Patients with hypercytokinemia are predisposed to Kawasaki disease shock syndrome (KDSS). KDSS is associated with more severe laboratory markers of inflammation and greater risk of coronary artery abnormalities, mitral regurgitation and prolonged myocardial dysfunction [29,30]. Serum levels of IL-6, ferritin, CRP, lactate dehydrogenase, D-dimer and count of lymphocytes and neutrophils in COVID-19 patients are correlated to the disease severity. Hyperferritinemia and serum levels of IL-6 are associated with a multitude of clinical conditions, including MAS and with worse prognosis in critically ill patients. These patients may be also resistant to immunoglobulin therapy and require additional therapy [31,32].

There are new findings that are related to tropospheric wind patterns. Recent reports suggest that winds arising from certain regions may carry viruses to another one [33,34]. It

was found that some patients diagnosed with KD had positive titer adenovirus infection [35,36]. J. L. Turnier et al. have shown, in a case series of 222 patients that the most important viruses associated with KD are rhinovirus and enterovirus based on RT-PCR test [37], but at the same time, no statistically significant differences were found in the clinical characteristics and laboratory values between the patients with and without positive results [34]. Recent articles have reported children with Kawasaki-like syndrome/MIS-C associated with COVID-19 [38,39]. The literature review revealed many articles describing over 500 children with Kawasaki-like syndrome associated with COVID-19. Pediatric COVID-19 cases usually present incomplete Kawasaki-like syndrome. Thus, pediatricians need to be aware of such incomplete presentations resembling KD for early diagnosis of COVID-19 [40,41].

The best therapeutic options for COVID-positive patients with atypical symptoms of KD were: IVIG, acetylsalicylic acid, tocilizumab, anakinra, enoxaparin and methylprednisolone [41]. Y Sakurai in his recent study on KD revealed severe endothelial damages related to B-cells activation [42]. Antiendothelial cell autoantibodies (AECAs) have been identified in patients with KD. The binding of AECAs to endothelial cells would cause endothelial damages, followed by proinflammatory cytokine released. This binding together with leukocyte activation by proinflammatory cytokines leads to a hypercoagulable state. In time, a hypercoagulable state would conduct to coronary artery lesions. Sakurai demonstrated that simple binding of AECAs to the vasa vasorum can lead to panvasculitis and the presence of a vulnerable vessel wall may result in an aneurysm. Further, platelets activated by shear stress, along with von Willebrand factor (VWF) released by endothelial cells, would cause platelet-driven arterial thrombosis. This concept is called immunothrombosis. Autoimmunity-associated thrombosis seems to play a major role in the pathogenesis of KD [42,43].

Recent studies have been demonstrated that serum titres of IgM AECA in the KD patients were positively correlated with cytotoxicity. Findings suggest that IgM AECA can also mediate complement-dependent cytotoxicity against endothelial cells and gammaglobulin may reduce complement-dependent cytotoxicity of AECA against endothelial cells [41-43]. *Understanding* the disease pathogenesis is important for the development of *improved treatment* strategies.

Diagnosis/Imaging

The characteristics symptoms of KD are high fever that lasts for at least 5 days, bilateral conjunctival hyperemia, cervical lymphadenopathy, rash, oral mucositis (red lips and tongue- strawberry or raspberry tongue) and extremity changes (swollen hands and feet). These clinical features tend to appear sequentially, which helps to differentiate KD from other medical conditions. In the acute phase, conjunctival hyperemia occurs soon after the fever and is usually bilateral, nonpurulent and painless. Oral mucositis may include cracking and erythema of the lips associated sometimes with a strawberry tongue. Unilateral cervical lymphadenopathy is characteristics and includes at least one lymph node greater than 1.5 cm in diameter. The polymorphous rash usually occurs within five days after fever onset and may present as generalized maculopapular erythema or scarlatiniform rash. Extremity changes with induration and erythema of the hands and feet usually occurred two to three weeks after the fever onset. There are as well, a variety of less common features, including gastrointestinal (diarrhea, emesis, and abdominal pain), respiratory (cough and rhinorrhea) and rheumatologic (joint pain and swelling) symptoms [3-5].

More common in younger infants, the atypical disease is suspected when patients have a fever for at least five days with only two or three of the principal clinical features [44,45]. Patients with Kawasaki-like syndrome or MIS-C usually develop fever, lymphopenia, gastrointestinal symptoms, rash and mucositis. Left ventricular dysfunction and

coronary abnormalities have been reported in most patients while myocarditis is an infrequent condition. Cases of MIS-C fulfilling criteria for KD are relatively common [46,47].

The American Heart Association (AHA) and Japanese Circulation Society published diagnostic criteria for classic (typical) and incomplete (atypical) KD (Table 1).

Table 1. Clinical criteria with supportive laboratory evidence and imaging for KD (an update to the 2004 American Heart Association guidelines and Japanese Circulation Society)

Clinical criteria (2004)	Clinical criteria (2017)
<p>Typical KD is diagnosed in patients with a fever of five days or more with at least four of five features such as bilateral conjunctival hyperemia, oral mucositis, cervical lymphadenopathy, extremity changes and polymorphous rash.</p>	<p>Infants ≤ 6 months old with persistent fever (≥ 7 days) without other explanation should undergo laboratory testing and, if evidence of systemic inflammation is found, an echocardiogram is recommended, even if the infants have no clinical criteria (incomplete KD). A CRP ≥ 3.0 mg/dl and an ESR \geq of 40 mm/h are supportive of KD. Other laboratory findings are anemia for age, platelet count of $\geq 450,000$ after the 7th day of fever, albumin ≤ 3.0 g/dl, elevated alanine aminotransferase, white blood cell count $\geq 15,000/\text{mm}^3$ and urine with ≥ 10 white blood cell/hpf.</p>
<p>The Echocardiography should be performed as soon as KD is suspected to evaluate the risk</p>	<p>The Echocardiography should be performed when the diagnosis of KD is considered and</p>

<p>for coronary artery aneurysms. Can treat before performing echocardiogram.</p>	<p>repeated at 1-2 and 4-6 weeks after treatment.</p>
<p>The corticosteroids may be helpful as adjunctive therapy to IVIG for preventing coronary abnormalities.</p>	<p>Single-dose pulse methylprednisolone should not be administered with IVIG as primary therapy. Administration of a longer course of corticosteroids, together with IVIG and aspirin, may be considered for the treatment of high-risk patients with acute KD.</p>
<p>Patients with acute KD should be given IVIG, 2 g per kg in a single dose, to prevent coronary artery abnormalities</p>	<p>Patients should be treated with IVIG 2 g/kg as a single infusion, usually given over 10-12 hours. Administration of moderate (30-50 mg/kg/day) to high (80-100 mg/kg/day) dose of aspirin should be continued until the patient is afebrile.</p>
<p>Patients with acute KD should be given high-dose aspirin, 80 to 100 mg per kg per day in four divided doses, until afebrile for 48 to 72 hours.</p>	<p>Approximately 20% of patients with KD have a persistent or recurrent fever after primary therapy with IVIG and aspirin. The statement details the role of additional therapeutic options, including a second dose of IVIG, high-dose pulse steroids, a longer course of steroids, infliximab, cyclosporine and immunomodulatory monoclonal antibody therapy.</p>

All patients who have had KD should have, at a minimum, periodic cardiovascular risk assessment; those with persistent aneurysms should have more intensive screening.	The management of the patients with aneurysms required biannual follow-up with echocardiogram and ECG. Annual stress test and evaluation of myocardial perfusion scan are also indicated
[48]	[49]

The World Health Organization published on www.who.int site the case definition of **Kawasaki-like syndrome/MIS-C** (Table 2).

Table 2.WHO criteria for case definitions of Kawasaki-like syndrome/MIS-C:

WHO case definition
All 6 criteria must be met:
1. Age 0 to 19 years
2. Fever for ≥ 3 days
3. Clinical signs of multisystem involvement (at least 2 of the following):
<ul style="list-style-type: none"> ▪ Rash, bilateral nonpurulent conjunctivitis, or mucocutaneous inflammation signs (oral, hands, or feet)
<ul style="list-style-type: none"> ▪ Hypotension or shock
<ul style="list-style-type: none"> ▪ Cardiac dysfunction, pericarditis, valvulitis, or coronary abnormalities (including echocardiographic findings or elevated troponin/BNP)

<ul style="list-style-type: none"> ▪ Evidence of coagulopathy (prolonged PT or PTT; elevated D-dimer)
<ul style="list-style-type: none"> ▪ Acute gastrointestinal symptoms (diarrhea, vomiting, or abdominal pain)
4. Elevated markers of inflammation (eg, ESR, CRP, or procalcitonin)
5. No other obvious microbial cause of inflammation, including bacterial sepsis and staphylococcal/streptococcal toxic shock syndromes
6. Evidence of SARS-CoV-2 infection
<ul style="list-style-type: none"> ▪ Any of the following: <ul style="list-style-type: none"> • Positive SARS-CoV-2 RT-PCR • Positive serology • Positive antigen test • Contact with an individual with COVID-19

Differential diagnosis of KD may include scarlet fever, toxic shock syndrome, staphylococcal scalded skin syndrome, juvenile arthritis, viral infections, Steven-Johnson syndrome or drug hypersensitivity. Regarding laboratory diagnosis, supplemental laboratory criteria are: anemia for age, elevated CRP level and ERS, elevated liver enzyme levels and platelet count of $\geq 450,000$ after the 7th day of fever and leucocytosis. According to different studies, the usefulness of ESR is doubtful [50-52].

Transthoracic echocardiography is the imaging modality of choice to detect coronary aneurysms and other cardiac artery abnormalities in KD. Magnetic resonance coronary angiography is helpful after treatment for the acute disease to visualize coronary artery stenosis, presence of thrombi and intimal hyperplasia in difficult-to-image locations like the circumflex and more distal arteries. [53-55] KD shock syndrome is associated with more severe laboratory markers of inflammation and greater risk of coronary artery abnormalities,

mitral regurgitation and prolonged myocardial dysfunction. These patients may be resistant to immunoglobulin therapy and require additional anti-inflammatory treatment [53,54].

Treatment

Early diagnosis, as well as, timely administration of treatment has successfully reduced the incidence of coronary artery lesions. IVIG are the drugs of choice when administered within 10 days of the onset of the disease, which usually starts with fever. The proper administration of IVIG decreases the risk of coronary artery aneurysm formation. The initial treatment consists of a single infusion of high-dose IVIG at 2 g/kg together with acetylsalicylic acid (ASA). Single-dose pulse methylprednisolone should not be administered with IVIG as primary therapy. The use of corticosteroids in KD is still for discussion since several studies showed that this treatment could increase the risk of coronary aneurysm development [55-57].

Even with prompt IVIG therapy, up to 25% of patients will develop recurrent or persistent fevers. These patients are termed IVIG-resistant. Some risk factors for IVIG-resistant KD have been identified. The most important are: improper IVIG administration, increased ESR, hypercytokinemia, hyperferritinemia, decreased hemoglobin and platelet levels, oral mucositis, cervical lymphadenopathy, extremity swelling and presence of a polymorphous rash. In this case administration of a second dose of IVIG to help prevent coronary sequelae is recommended. The major effects induced by IVIG are the modulation of cytokine production and the influence on T-cell activity. The final result is the suppression of antibody synthesis [58,59].

Moderate-dose (30–50 mg/kg/day) to high-dose (80 to 100 mg/kg/day) of ASA are recommended until the patient is afebrile. There is also no clear evidence that any dose of ASA will decrease the development of coronary artery lesions. ASA is used to modify the

inflammatory state and to prevent thrombosis. In KW and Kawasaki-like syndrome/MIS-C is ASA the treatment of choice regardless of the Reye syndrome risk [52,53].

After the acute phase, low doses (3–5 mg/kg) of ASA are used for the antiplatelet effect. In consequence, patients remain on low-dose ASA into the convalescent phase. The decision to continue or discontinue therapy is made around 6–8 weeks pending any coronary artery lesions on echocardiogram. The patients who are at high risk of treatment resistance or patients with coronary sequelae may benefit from adjunctive treatments. Because of concern for Reye syndrome, patients on long-term aspirin should receive the influenza vaccine and varicella vaccination status should be checked [60,61].

Administration of a longer course of corticosteroids, together with IVIG and aspirin, may be considered for the treatment of high-risk patients with acute KD. Resistant KD is defined by the American Heart Association as failure to respond within 36 h following the first dose of IVIG. The optimal management of resistant KD is still unclear. American Heart Association guideline states that the relative roles of repeated use of IVIG and other adjunctive therapies (e.g., corticosteroids, TNF- α antagonists, plasma exchange) are unclear. Different studies suggested that TNF- α antagonists such as Infliximab are involved in the faster resolution of fever. They may reduce also the level of some inflammatory markers. TNF- α antagonists did not improve treatment response over IVIG and aspirin alone. Corticosteroids and plasma exchange may reduce the risk of coronary artery abnormalities at one month [62,63].

- The therapeutic approach and guidelines for MIS-C is a little bit different and currently, the guidelines were published in several studies.
- Currently, biologicals could be beneficial for the treatment of cytokine storms. From this group, the blockade of IL-1 or IL-6 is in the middle of interest. Anakinra and Tocilizumab, in the context of cytokine storm, are the drugs of choice.

It is well-known that IL-6 plays a major role in KD. Therefore, IL-6 inhibitors may prove to be a valuable treatment option in Kawasaki-like syndrome/MIS-C. Tocilizumab, a monoclonal antibody that serves as an IL-6 inhibitor, is used to treat systemic-onset juvenile idiopathic arthritis, which shares many features with MIS-C, such as skin rash, major inflammatory syndrome, MAS and fever. Also, Tocilizumab is already undergoing clinical trials to be used in severely ill COVID-19 adult patients. 4 mg/kg IV q4 weeks initially is the safe starting dose. You may increase to 8 mg/kg q4 weeks based on clinical response. Not to exceed 800 mg/dose q4 week [64].

- Anakinra is an IL-1 receptor antagonist that is commonly used to treat systemic juvenile arthritis induced cytokine release syndrome and is currently undergoing a Phase 2 clinical trial for its use in KD. The physicians recommend Anakinra for MIS-C patients who have initially failed IVIG and/or methylprednisolone treatment. In infants, children and adolescents/adults the initial dose is 1 to 2 mg/kg/dose once daily. You may adjust the dose in 0.5 to 1 mg/kg increments as needed to a maximum of 8 mg/kg daily to achieve control of active inflammation [64].

Long-Term Management

Patients with aneurysms are treated with aspirin in combination with other antiplatelet agents. Heparin and warfarin are reserved for treating larger aneurysms. Coronary thrombosis is treated with thrombolytic agents in association with aspirin and heparin. The management of the patients with aneurysms required biannual follow-up with echocardiogram and ECG. Annual stress tests and evaluations of myocardial perfusion scans are also indicated. The first angiography is indicated at 6–12 months or sooner if clinically recommended. After that, angiography is used to address therapeutic options [54-56].

In consequence, the diagnosis and treatment of KD are challenging without a clearly defined protocol. Due to this fact, the prevalence of KD and Kawasaki-like syndrome/MIS-C

seems to be underestimated. More concerning from the perspective of trying to prevent long term complications is that many children who develop coronary heart disease never met the criteria for KD, especially COVID-19 positive children. At the same time, the association of KD to the new coronavirus appears to trigger a severe clinical condition of vasculitis with a strong cytokine storm. Anakinra and Tocilizumab, in the context of cytokine storm, seems to be the best drugs of choice since these cytokines are the common pathway in the inflammatory immune response.

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