MULTISYSTEM INFLAMMATORY SYNDROME IN CHILDREN:LITERATURE REVIEW

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ABSTRACT

The COVID-19 pandemic is yet to be over. Although the number of pediatric patients is relatively small, their clinical manifestations differ from the adult group. Multisystem Inflammatory Syndrome in Children (MIS-C) is one of the most recently discussed clinical manifestations. The clinical features of this case resemble those of Kawasaki disease or toxic shock syndrome with limited diagnostic methods. Patients experience gastrointestinal, mucocutaneous, cardiovascular, hematological, and neurological symptoms. There was also an increase in inflammatory parameters and cardiac disorders, which will also be confirmed by electrophysiological and radiological examinations. Management consists of the administration of immunoglobulins, steroids, and some anti-cytokines. When the patient goes into shock, fluid resuscitation is the mainstay of therapy. Until now, the number of MIS-C patients is relatively small compared to the number of COVID-19 cases, and the number of deaths is very minimal as well.

Keywords: *Multisystem Inflammatory Syndrome, Children, COVID-19, SARS-Cov-2, Kawasaki Disease*

ABSTRAK

Pandemi COVID-19 belum berlalu. Sekalipun jumlah pasien anak relatif sedikit, manifestasi klinik banyak berbeda dengan kelompok dewasa. Salah satu bentuk yang menyerang anak adalah *Multisystem inflammatory syndrome* yang menyerupai penyakit Kawasaki maupun Sindroma Syok Toksik. Anak yang terkena akan menunjukkan gejala dan tanda gastrointestinal, mukokutaneus, kardiovaskular, hematologi, dan neurologi. Pada anak akan dijumpai peningkatan parameter inflamasi serta kelainan jantung yang akan terkonfirmasi dengan pemeriksaan elektrofisiologi dan radiologi. Tatalaksana mencakup imunoglobulin, steroid, dan beberapa antisitokin. Bila pasien dalam keadaan syok, resusitasi cairan adalah tindakan utama. Hingga saat ini jumlah penderita MIS-C relatif kecil dengan angka kematian yang juga kecil.

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INTRODUCTION

The COVID-19 outbreak was first reported towards the end of 2019 in Wuhan, China.[1,2] As of August 2020, no effective medicines and vaccines have been discovered, and the pandemic is yet to be under control.[3,4] While there are relatively few pediatric patients worldwide compared to the number of adult patients, the two age groups have some significant differences.[1,2,5,6] One of the differences concerns clinical manifestations. In children, the manifestations of the disease are more diverse than in adults.[2,5-7] The dominance of respiratory symptoms and signs, for example, is not as dominant in the adult group.[2,6,7] Children also obtained a specific clinical spectrum that resembles Kawasaki disease (KD) and Toxic Shock Syndrome (TSS).[8-10] This unique spectrum is reported from many publications.[11]

The disease that occurs after SARS-CoV-2 infection can be of several types, all of which are immunological and inflammatory manifestations. These conditions include Kawasaki-like disease, Kawasaki disease shock syndrome (KDSS), TSS, myocarditis, and macrophage activation syndrome (MAS). The entire spectrum is then grouped and is called the Multisystem Inflammatory Syndrome in Children (MIS-C) or Pediatric Inflammatory Multisystem Syndrome (PIMS).[9,12-16] Some clinicians also consider MIS-C as consisting of 3 major groups, namely the group characterized by shock, the Kawasaki disease group, and the fever group with inflammation.[8,17] KD itself has been known since 1960s. Dr. Tomisaku Kawasaki carried out the first publication based on observations of 50 children in Japan. He mentioned “acute febrile mucocutaneous lymph node syndrome”.[18] This disease is common in East Asia. Until now, the cause of the disease is not clear, and none of the suspected causal microorganisms have yet been found.[11,19-21]

By the end of June 2020, there were more than 1400 publications regarding MIS-C in several world data sources, including preprints.[20] This large number shows cases of MIS-C were observed in several places in the world and provoked the concern of many clinicians.

THE NAME OF DISEASE

There are several names used to describe the diagnosis of this disease. The Royal College of Paediatrics and Child Health (RCPCH) in the UK named it the Pediatric Multisystem Inflammatory Syndrome temporarily associated with COVID-19.[22] The Center for Disease Control and Prevention (CDC) and the American College of Rheumatology (ACR) in the US call it the Multisystem Inflammatory Syndrome in Children Associated with COVID-19 (MIS-C),[23,24] while the European CDC (ECDC) referred to it as Pediatric Inflammatory Multisystem Syndrome temporally associated with SARS-CoV-2 (PIMS-TS).[16] Those names are intended for the same clinical spectrum. The WHO published the name Multisystem Inflammatory Disorder in Children and Adolescents on May 15, 2020.[25]

Given that the spectrum of disease is not uniform and is relatively complex, the correct name is very important so that its interpretation is the same by everyone.[26] In this paper, for uniformity, the name used is MIS-C.

FIRST REPORTS

The first report of MIS-C was published in the UK on 25 April 2020 when the National Health Service (NHS) alerted its staff to critical cases with depictions of TSS, atypical Kawasaki, and severe COVID-19 infection.[20,21,27] The RCPCH officially issued guidelines on May 1, 2020, specifically addressing this disease. A report followed the UK publication in the journal named Lancet on May 6, 2020, which discussed 8 cases of MIS-C. [13] A report was published in Bergamo, one of the epicenters of COVID-19 in northern Italy, at the same time as when about 10 cases arose that showed symptoms similar to KD and/or TSS.[9] Eight of the children had tested positive for the SARS-CoV-2 immunoglobulin. In the two months of observation since February 2020, the number of KD-like diseases in that area was 30 times higher than the same period in previous years. Patients in 2020 are also relatively older and more likely to experience shock.[9] The ECDC report on the same was published on 12 May 2020, in France.[16] This report mentions 125 cases in children. A publication from Paris listed 17 cases in the initial report.[14] The CDC report in the United States on May 14, 2020, stated that the first detection occurred on April 7, 2020, in a 6-month-old baby. There were three deaths in one month of monitoring. From 17 April to 4 May of 2020, 15 cases were detected, with 4 cases still showing

positive PCR results. Six out of 10 cases with negative PCR results had SARS-CoV-2 antibodies. On 10 May 2020, the number of cases had reached 85 with three deaths. On 12 May 2020, a total of 102 cases were reported, with 29% being in the age group of 5–9 years and 28% in the age group of 10–14 years.[23] The ECDC report dated 15 May 2020, mentioned 224 cases throughout Europe and Great Britain with two deaths (1 in England and 1 in France).[16] Until that date, there were no cases in other countries such as Japan, Greece, and Sweden. By the end of June, it was estimated that 1000 cases of MIS-C had been reported in various countries. These reports use a variety of case definitions.[28]

EPIDEMIOLOGY UP TO MID-AUGUST, 2020

There have been various case reports from many countries.[11] All of Western Europe arguably identified this case. In the US, reports came from various states across the country, with New York as the main epicenter. Many publications have also emerged from the Middle East. Interestingly, there have been no reports from Australia, New Zealand, or East Asia.[11] The majority of cases of MIS-C, in contrast to cases of KD, were mostly in those with African, African-American, and Afro-Caribbean backgrounds.[8,10,20,29-32] In the US, the Hispanic group is the most affected.[10,30,33] These racial differences can be caused by genetic or social factors such as economic conditions and degree of exposure.[24,31]

In the systematic review written by Abrams et al., from the end of April to the end of June 2020, there were at least 440 cases reported in 8 publications. Two publications came from the US while the remaining six were from Europe.[8-10,13-15,20,30,31] Only reports of more than 5 cases were included in this study.[20] Patients with KD are relatively younger than those with MIS-C. If KD attacks children less than 2 two years old, MIS-C patients' average age is ten years.[8,9,15,20,31,32,34-37] Being five years of age or older is a risk factor for a severe condition, as shown in the cohort from Paris.[34] In comparison, there are relatively few reports from outside Europe and the US.[21]

Cheung estimates the incidence of MIS-C as being 2 per 100,000 individuals aged 21 years and under.[35] From Queens, New York, the publication by Capone et al. mentions 33 children in one hospital alone.[38] In a larger US cohort study involving 186 children, no children under the age of 1 showed positive IgG results.[10] An MMWR

publication collected data from all US regions up to July 29, 2020, and identified 570 cases with a median age of 8 years, predominantly male, from the Hispanic or Latino group.[39]

Data as of the end of May 2020, in France, had 156 cases of MIS-C. All cases can be grouped into four parts, namely, confirmed SARS-CoV-2 cases (79), probable (16), possible (13), and unrelated/inconclusive (48). Positive serology test results were found in 42 out of the156 cases. Positive PCR results were present in 28 cases. The median age was eight years.[40]

In Asia, reports have mainly come from Iran. The first reports were known since late May 2020.[41] In Peru, the first reports were known since June 1, 2020, in a child of 3 years of age.[42]

PATHOGENESIS

Similar to KD, the pathogenesis of MIS-C is not fully known. Patients had previously been infected with SARS-CoV-2; this was proved by mostly positive immunoglobulin tests.[8,9,14,20,30,38,43,44] Even so, none of them had ever experienced severe symptoms before the episode. This indicates that the previous SARS-CoV-2 infection was asymptomatic or with mild symptoms that the children and the parents did not realize. The results of PCR examinations for all MIS-C patients were mostly negative, even though there were publications that reported a positive rate of 69% in the body. The time between the virus's presence and the onset of symptoms and signs is about four weeks.[14,30,38,45,46] Feldstein found an interval of 22 days.[10] In publications with many positive PCR results, all patients showed low viral loads.[34] A British cohort study (8 cases) of those who underwent an IgG isotype examination turned out to have detectable levels of IgG1 and three but not IgG2 and 4. This was different from the results of examinations in adults.[47]

The process in MIS-C is relatively severe and is considered as a manifestation of a delayed immune response with uncontrolled inflammation. The result is damage to the host tissue.[48]

The infection has long been known to be one of the triggers for inflammatory and autoimmune diseases, mainly suspected through molecular mimicry pathways.[12] The ECDC report mentions that microorganisms found in patients with MIS-C may occur later and are a trigger for MIS-C without direct relation to SARS-CoV-2 infection.[16] Until now, it is not clear which mechanism occurs.

SARS-CoV-2 infection is thought to trigger the emergence of antibodies against virus surface epitopes. Low levels of non-neutralizing antibodies can increase the stimulation of the immune response triggered by the virus so that the risk of worsening disease becomes even greater.[8,49] Antibodies that block the ACE-receptor binding region are believed to be protective, but antibodies to nucleocapsids and other epitopes in proteins S is not.[50] The virus coated with weak antibodies then undergoes internalization through the Fc receptor, followed by endosomal release from the virion. After that, the TLR and cytosolic-RNA sensors will trigger an IFN_{γ} response. This antibody-dependent enhancement (ADE) mechanism determines the immunological injury triggered by SARS-CoV-2. This has been proven in COVID-19[51], but in MIS-C, it has not been fully revealed.[52]

Coronaviruses could block the response to interferon types I and III by delaying cytokine storms in patients whose immune responses cannot control viral replication and are characterized by high viral loads.[53,54] This may also occur in cases with MIS-C.

In both KD and MIS-C, infection-induced vasculitis was found.[8] All inflammatory processes in MIS-C are more severe than those seen in KD.[8,9,13,14,24]

The phenomenon of cytokine storms in COVID-19 is characterized by an increase in proinflammatory cytokines and macrophages' activation. In KD, an increase in proinflammatory cytokines is also seen as in other autoimmune diseases.[21]

The immunological profiles of 8 patients in New York showed exposure to SARS-CoV-2 antibodies with normal isotype-switching and neutralization abilities. There were also increases in IL-8 and IL-16, which indicate inflammatory activation, increased chemotaxis, and activation of lymphocytic and myeloid (CCL3, CCL4, and CDCP1), and dysregulation of the mucosal immune system (IL-17A, CCL20, and CCL28). In addition, extravasation to the affected tissue was also shown, and increased ICAM1 and $Fc_{\gamma}R1$ in neutrophils and monocytes.[55] The composition of the cytokines in KD and MIS-C was different.[56,57]

Genetic aspects are thought to play a role in MIS-C, as is seen in KD patients.[8,58,59] From this genetic aspect, the *TMEM173* gene's role that regulates STING function in humans might be similar to that in bats and herpes viruses. STING is also overexpressed in arterial aneurysms.

Overactivation of STING will then cause hypercoagulability through the release of IFNβ and tissue factors by macrophage monocytes.[60] The effect of genetic aspects is also seen in family clusters of KD. Some of the symptoms and signs of COVID-19 may also be familial.[61]

The question is whether SARS-CoV-2 directly triggers MIS-C or if it is just a primary, intermediate, or co-stimulatory agent, or whether SARS-CoV-2 provides an entry point for the true trigger.[62]

Nakra argues that MIS-C is stage II of the course of COVID-19 or a delayed immunological phenomenon associated with inflammation. Phases I and II in the course of COVID-19 are the acute and pulmonary phases.[63] Direct infection by SARS-CoV-2 does not play a role in MIS-C.[63] Some of the differences between MIS-C and KD still require further exploration.[64]

CLINICAL SYMPTOMS AND SIGNS

Symptoms and clinical signs of MIS-C are mostly similar to KD or TSS or unusual gastrointestinal symptoms accompanied by very high inflammatory markers.[8,9,11,14,20,38,63] The ACR mentions that the clinical symptoms are fever, mucocutaneous symptoms (rash, conjunctivitis, palm edema, dry and cracked lips, and strawberry tongue), myocardial disorders, heart conduction disorders, gastrointestinal symptoms, and enlarged glands.[24] Other manifestations include neurological aspects of headache, cranial nerve palsy, altered mental status, or meningismus.[24] The Presbyterian Children's Hospital in New York mentions five things that can be found in MIS-C patients, namely, systemic inflammation (fever, myalgia, tachycardia, hypofusion or hyperfusion, and lymphadenopathy), cardiopulmonary symptoms (respiratory distress, chest pain), neurological symptoms (headache, change in status, mental, meningismus, focal deficits, and convulsions), mucocutaneous (rash, swollen lips, chapped lips, strawberry tongue, swelling of the extremities, conjunctivitis, and blisters or erosions), and gastrointestinal symptoms (nausea, vomiting, diarrhea, or abdominal pain). The hospital also divided clinical degrees into 3, namely, mild, moderate, and severe. The bases for this classification were vasoactive needs, support for breathing, and the presence of organ injury.[65] The RCPCH guidelines stated that all cases presented with a 38.5°C fever or more, and a majority had hypoxia and hypotension. The clinical features include the following: abdominal pain, conjunctivitis, cough, diarrhea, headache,

confusion, enlarged glands, mucosal changes, swelling of the neck, rash, respiratory symptoms, sore throat, swelling of hands and feet, and vomiting.[22] The systematic review by Abrams et al. described 87% of cases as having gastrointestinal signs and symptoms, 73% with dermatological/mucocutaneous, and 71% with cardiovascular symptoms.[20] Only 47% of patients have respiratory symptoms and signs. Several recent case reports also mentioned common psychiatric and neurological manifestations (21%).[20]

A publication from France in 35 children with MIS-C with acute heart failure has a predominance of gastrointestinal symptoms (80%).[15] In another publication reporting about 156 children in France, about two-thirds showed Kawasaki-like features and had myocarditis.[40]

The report by Loke et al. regarding 130 children with MIS-C in 5 countries (Italy, France, Switzerland, the USA, and the UK), and publications by Capone et al. from New York, USA, also found a predominance of gastrointestinal symptoms and signs.[21,38] This is different from what is seen in KD.[15,21]

Gastrointestinal disorders can include vomiting, diarrhea, or abdominal pain.[13] Pancreatitis has also been reported.[66] Abdominal pain in MIS-C cannot be ignored because in the publication by Tullie et al., most of the children were suspected of having appendicitis when they arrived at the hospital. The radiological examination makes clinicians more aware of this.[67] Several cases have undergone surgery because of this initial suspicion, and clinicians found mesenteric lymphadenitis and appendicitis.[63]

Rowley suggested that the focus of exploration should always be more intensive on gastrointestinal and cardiovascular aspects.[64] A New York cohort study had 44 children with MIS-C who showed predominant gastrointestinal system symptoms, apart from fever (100%) and rash (70%).[68] A similar condition with gastrointestinal predominance was also seen in a cohort study of 78 cases admitted to various PICUs in the UK. The number of people suffering from shock in this group was 87%.[31]

In the Whittaker report, which included 58 children who presented with fever, abdominal pain was present in about half of the cases. Diarrhea and rashes were also in the same proportion.[8] There were three groups observed in the publication: those with fever and increased markers of inflammation but without a complete picture

of KD, TSS, or organ failure, a group with shock and left heart disorders, and groups that meet the KD criteria.[8]

Cardiovascular disorders can be in the form of left-heart dysfunction, coronary artery dilatation, and conduction disorders.[15,24] What distinguishes KD is the fact that cardiac dysfunction was not too dominant.[15,21,24,38,69]

A British cohort study that examined several modalities and at least two devices for the heart alone (20 patients) showed different things. From the beginning, abnormal Doppler results were detected. The ejection fraction is less than 55% in half of the cases and continues to worsen during treatment-until it finally gets better when the patient is discharged. The left coronary artery's diameter was greater when the patient went home than when he was admitted to the hospital. More widening was seen in the left coronary artery (9 out of 12 cases).[70]

Neurological symptoms and shock that are also found in MIS-C are not the principal phenomena in KD.[24] Neurological symptoms can be status epilepticus.[71,72] In the case described by Schupper, the patient also exhibited multifocal echogenicity and infarction of several parts of the cerebral arteries.[72] Another report stated that patients were restless, agitated, and confused.[73] In other cases, diffuse brain hemosiderosis and clonus were found.[74] There were also headaches, irritability, and encephalopathy.[63]

US data shows that 490 out of 570 cases involving at least four organs. There were 99/570 cases involving at least six organ systems (with a proportion of 100% cardiovascular system and 97.5% gastrointestinal system). About 98% of this group had positive SARS-CoV-2 serology results. About two-thirds of cases do not have co-morbidities. The organs involved are gastrointestinal (90%), cardiovascular (86.5%), and mucocutaneous (70.9%). The most common symptoms and clinical signs are abdominal pain, vomiting, rash, diarrhea, hypotension, and red-eye.[39] The group with obvious respiratory symptoms may still be partly due to COVID-19. The patient has a cough, shortness of breath, pneumonia, and respiratory failure syndrome. Most of this group still showed positive PCR results with negative serology results. Mortality in this group was higher.[39] The group dominated by rash and mucocutaneous symptoms was lower in age and had more coronary artery dilatation. This group was more suitable with a complete KD.[39]

A US cohort with 191 cases in New York was mostly male and Hispanic.[30] All patients presented with fever, 97% with tachycardia, 80% with gastrointestinal signs, and 60% with rashes.[30] A separate publication of 15 of the first cases at a referral hospital in New York showed substantially interesting results.[75]

The New York cohort (33 cases) had fever and mutation as the chief complaints,[32] while the Paris cohort of 21 children and adolescents had 12 presenting with KDSS, 16 with myocarditis, and all of them had gastrointestinal complaints at the early phase.[14]

A New York cohort of 17 patients found all cases had fever and 14 children had gastrointestinal complaints. Mucocutaneous symptoms were common, with 12 patients exhibiting rashes, 11 with conjunctivitis, and 9 with lip swelling. Eight cases met the KD criteria and five as incomplete KD.[35] Feldstein et al. reported a US cohort with 186 cases that experienced involvement of gastrointestinal, cardiovascular, hematologic, mucocutaneous, and respiratory organs in 92%, 80%, 76%, 74%, and 70% of the total cases, respectively. Two of the patients died.[10]

LABORATORY ASPECT

As with KD, there is no definitive test for MIS-C.[16,20,22-24] Some guidelines state that all cases show fibrinogen abnormalities, high CRP/D-Dimer/Ferritin, hypoalbumin, lymphopenia, usually low neutrophils, and no evidence of infection with specific microorganisms. Some of them also have laboratory features such as acute kidney injury, anemia, coagulopathy, elevated IL-10 and IL-6, neutrophilia, proteinuria, elevated CK and LDH, thrombocytopenia, and transaminitis. Various publications mentioned these results.[16,20,22-24,31,46,63,64,68] ACR recommends a 2-stage laboratory examination to show priority scale and time considerations.[24] Reports from Italy, France, England, and the US also mentioned that children with MIS-C showed significant lymphopenia and thrombocytopenia, coagulopathy, increased cardiac enzymes such as troponin, hyponatremia, hypoalbuminemia, and increased lactate dehydrogenase and ferritin. This phenomenon is only slightly found in people with KD.[8,9,14,15,31,38,46,68,76] Abrams said that at least 75% of patients had high CRP levels, IL-6, and fibrinogen.[20] The descriptions of 5 cytokines (IFN-γ, IL-10, IL-6, IL-8, and TNF-α) have been analyzed to differentiate MIS-C and KD, and the

significant differences were only in TNF-α and IL-10.[76]

Laboratory data of US patients show different results between groups. The group with six or more organ involvement predominantly of gastrointestinal and cardiovascular symptoms and signs showed higher D-dimer, troponin, BNP, proBNP, and ferritin. This group has lower lymphocytes. The group with dominant mucocutaneous symptoms had the lowest D-dimer levels, troponin, BNP, proBNP, CRP, and ferritin, but the highest lymphocyte levels.[39] A New York cohort of 191 cases had increased CRP, D-dimer, and troponin in 100%, 91%, and 71% of cases.[30]

A US cohort with 186 cases had increased four or more inflammation markers in 92% of patients.[10] A New York cohort of 17 children had increased inflammation markers in all cases, predominantly lymphopenia, bandemia, elevated troponin T, and proBNP. IL-2R, IL-18, and CXCL 9 were elevated in all cases. IFN_{γ} and IL-8 increased in only a few cases.[35]

Ferritin and D-dimer increased in half of the patients. CRP, IL-6, and fibrinogen are even increased in 75% of patients. The increase in heart damage markers such as troponin and brain natriuretic peptide (BNP) has reached 100% in several publications.[20,46]

Verdoni reported that MIS-C patients had lower levels of leukocytes and platelets than Kawasaki patients, but with higher CRP and ferritin.[9] Whittaker et al. reported that MIS-C patients had higher levels of neutrophils, CRP, ferritin, troponin, and D-dimer but with lower lymphocytes and platelets levels.[8] The same results were demonstrated in the study of Belhajer et al.[15] A New York cohort of 33 children showed increased CRP, procalcitonin, D-Dimer, and proBNP.[32]

Examination of heart markers is highly recommended considering the proportion of heart problems in cases with MIS-C.[15,17,24,38,46,76,77] A UK cohort of 15 cases with cardiovascular symptoms and signs showed increased CRP, ferritin, troponin, creatine kinase, and proBNP.[78] There were 10 cases with valve regurgitation, and 12 showed decreased left ventricular ejection. A total of 14 out of the 15 cases showed coronary artery abnormalities, but ECG abnormalities were only found on 6 out of 15.[78] Radiological features may include patchy infiltrates and pleural effusions (Plain chest radiograph, CT scan for the thorax). Abdominal ultrasound may show colitis, ileitis, lymphadenopathy,

ascites, and hepatosplenomegaly. The results of echocardiography and ECG include myocarditis, valvulitis, pericardial effusion, and coronary artery dilatation.[16,22-24] Some earlier patients did not show a specific ECG pattern. Later, these children got worse, and some had to be admitted into the PICU.[15,38] Plain chest radiographs and CT scans are required not only for the MIS-C but also to detect COVID-19.[24] Of the 16 children in the US, the most common chest radiological images include cardiomegaly, pulmonary edema or congestive heart failure, atelectasis, pleural effusion, and pneumonia.[79] The results of echocardiography examinations in the US, in addition to coronary artery aneurysms, also show much left or right heart valve dysfunction, pericardial effusion, and mitral regurgitation.[77]

A UK cohort of 35 children has airway inflammation and pulmonary edema (which can be seen rapidly on chest radiology), and coronary artery aneurysms. The most common results of chest radiographs are peribronchial cuffing and perihilar interstitial thickening. For a chest CT scan, the most common result was basal consolidation and pleural effusion. A cardiac CT scan also shows decreased myocardial function, myocarditis, pancarditis, and pericardial effusion. The abdominal radiology results showed that there was an excessive inflammatory change in the right quadrant of the iliac fossa.[80]

In France, cardiac MRI images of the cohort in Paris showed a mixed picture, whereas echocardiography revealed low or normal low left heart function.[81] In the 33 cases reported by Capone et al. in New York, USA, hemodynamic instability and cardiac dysfunction were the main features. All cases improved quickly after receiving anti-inflammatory therapy.[38] Meanwhile, in the 33 cases reported by Kaushik et al., about 63% showed a decreased left ventricular ejection fraction.[32]

Of 44 children in New York, some abnormalities were mesenteric adenitis, acalculous cholecystitis or biliary sludge, and ascites.[68] For abdominal radiology, the results are ascites, hepatomegaly, thickening of the intestinal wall and bladder, echogenic kidneys, mesenteric lymphadenopathy, and splenomegaly.[79]

Laboratory examinations at Mount Sinai, New York, found that 87% out of 15 children had gastrointestinal manifestations, including vomiting, abdominal pain, and diarrhea. Only less than half showed a picture of KD. Tachycardia and hypotension were present in 87% of cases.[75] Cardiac

involvement was found in 87% of cases that involved elevated serum troponin or proBNP. Lymphopenia is present in 87% of patients, while thrombocytopenia and hypoalbuminemia are present in only about half of cases. Fibrinogen increases in 93% of cases.[75]

DIAGNOSIS

There is no definitive test to diagnose MIS-C. Inclusion criteria or case definitions may vary depending on the guidelines followed. Laboratory examination results can also vary.[20,63] The diagnosis of MIS-C is more of a syndromic diagnosis.

Inclusion criteria for case definitions according to the RCPCH 2020 guidelines are children with fever, inflammation (neutrophilia, increased CRP, and lymphopenia), and evidence of dysfunction of one or more organs (shock, cardiac, respiratory, renal, gastrointestinal, or nervous system disorders) plus multiple additional manifestations (clinical, laboratory, imaging, electrocardiogram). These guidelines also mention "including a complete and partial picture of Kawasaki Disease". MIS-C cases should be screened to exclude cases of bacterial infections, including Staphylococcus and streptococcus that also cause TSS, as well as cases of viral infections associated with myocarditis, such as those caused by enteroviruses. The RCPCH does not mandate a negative PCR examination.[22]

On the other hand, the CDC sets the following case boundaries: individuals under 21 years of age with fever, laboratory evidence showing inflammation, and evidence of serious clinical conditions requiring hospitalization, with more than two organs involved (cardiac, renal, respiratory, hematological, gastrointestinal, dermatological, and neurological), as well as the absence of other possible diagnoses, and the presence of evidence of SARS-CoV-2 infection with RT-PCR, serology, antigen testing, or exposure within four weeks before the appearance of clinical signs or symptoms.[23]

The WHO statement on 15 May 2020 stated the following criteria: children aged less than 19 years with a history of fever for more than three days, accompanied by at least 2 of the following signs:[25]

(1) Rash or bilateral non-purulent conjunctivitis or signs of mucocutaneous inflammation (in the mouth, hands, or legs)
(2) Hypotension or shock
(3) Myocardial dysfunction, pericarditis, valvulitis, or coronary abnormalities

(including echocardiography results or elevated troponin/NT-proBNP)

(4) Evidence of coagulopathy (PT, PTT, elevated D-dimers)

(5) Acute gastrointestinal problems (diarrhea, vomiting, or abdominal pain)

(6) An increase in inflammatory markers such as sedimentation rate, CRP, or procalcitonin

(7) No clear evidence of microbes causing inflammation (including bacterial and staphylococcal sepsis or streptococcal shock syndrome)

(8) Evidence of SARS-CoV-2 infection (RT-PCR, antigen or serology testing) or exposure to a COVID-19 patient

Both the CDC and the WHO require evidence of SARS-CoV-2 infection or previous exposure to patients. This, of course, is quite problematic considering the number of asymptomatic cases and the limitations of diagnostic methods.[28]

MANAGEMENT

During the pandemic, the treatment of cases with heart problems has become somewhat neglected because heart patients are afraid to come to the hospital and because doctors may be so concentrated on COVID-19 cases that they are somewhat "forgetting" other cases.[27,82]

The goals of MIS-C management are to reduce systemic inflammation and restore organ function, and reduce the risk of death and long-term sequelae (such as cardiac disorders).[63] Some experts suggest that treatment is given according to clinical manifestations. The largest group, which resembled KD, was given treatment similar to that in KD management, while the TSS-like group was given the TSS-like procedure, and in some places, empiric antibiotics (preceded by sampling for blood cultures) are mentioned. In all cases, it must be considered that there is a presence of SARS-CoV-2 infection, so personal protective equipment is compulsory.

As the situation deteriorates rapidly, close surveillance of the cardiorespiratory system includes continuous saturation and ECG with blood pressure monitoring. EKG examination is initiated from the time the patient arrives.[22,23,63]

Administration of Remdesivir can be done, but there is no strong evidence to support it. Antibiotics can be understood because clinical manifestations also resemble a severe bacterial infection.[63] In conditions similar to KD, intravenous immunoglobulin at a dose of 2 g/kg of

weight can be given. Immunoglobulins are given slowly under adequate supervision of the conditions. Aspirin at a dose of 30 mg/kg BW is also given and maintained until the patient is discharged from the hospital or until the inflammatory picture has improved.[16,19,22-24,46] Administration of immunoglobulins in MIS-C often requires repetition.[20,21,34] A Paris cohort, for example, found that 10 out of 16 children require repeat therapy.[34]

Other therapies given are steroids (52% of cases) and immunomodulators.[20,63] The report by Belhajer et al. mentions that 25 out of 35 children received immunoglobulins, and half of them also received steroids.[15] A Harvard cohort study in Boston, USA, reported that 71% are receiving immunoglobulins, 61% are receiving steroids, and 18% are receiving anakinra.[46] In New York, out of 44 children, steroids were given in 95%, immunoglobulins in 81%, and 90% received anticoagulants.[68] The British cohort study found the use of immunoglobulins and steroids in more than 70% of patients.[31]

Of the US cohort, 80.5% received immunoglobulins, and 62.8% received steroids. About 40% of cases received anticoagulants and vasoactive drugs.[39] Of the 33 children in New York, half received immunoglobulins, half also received steroids, and around half also received vasopressors. Five people received mechanical ventilation.[32] Of the 21 children in Paris, all received immunoglobulins, and 10/21 also received steroids.[14] All patients improved. In a cohort of 17 children in New York, 13 received immunoglobulins, and 14 received steroids.[35]

Some publications also mention IL-1 receptor antagonist (anakinra), TNF-α antagonist (infliximab), and IL-6 antagonist (tocilizumab) as adjuncts to therapy.[20,31,36,46,63,83] Heparin can be given for severely impaired ventricular function. Low doses of heparin can be considered in a non-severe situation because of the thromboembolism risks.[83]

A New York cohort of 191 cases showed that 62% of patients received vasopressors, and 80% had to be admitted to the PICU. Two patients died.[30] Another US cohort of 186 cases from 26 states showed that 80% of patients had to be admitted to the PICU, 48% received vasopressors, and only 20% required mechanical ventilation. Immunoglobulins were administered in 77%, steroids in 44%, and IL-6 or IL-1RA inhibitors in 20% of cases.[10]

In MIS-C shock, fluid resuscitation to treat circulatory collapse may be given.

Certain drugs also play a role when fluids do not work.[8,9,13,14] In conditions similar to TSS, intravenous immunoglobulin may also be given.

Multi-organ involvement should always be sought. If there is cardiological involvement (elevated troponin, ECG changes, echocardiographic abnormalities), prompt cardiological action and surveillance were needed.[22,23,63]

As many as 26% of patients had to be on a ventilator, and 6% even needed extracorporeal membrane oxygenation (ECMO).[20] Of the UK cohort, only 3 out of 78 children, needed ECMO.[31] Data on 156 cases in France found that 67% required treatment in the PICU. Of these, two-thirds received vasopressors, and half received mechanical ventilation.[40] In a cohort of 8 patients in the UK, six required treatment at the PICU.[47]

COMPLICATIONS

The main complication for both KD and MIS-C is the dilatation of the coronary arteries. The incidence of this complication ranges from 20%–25% in both diseases.[13] In a UK cohort study, there was an even 36% of cases with dilated coronary arteries.[31] Not many patients with MIS-C had large aneurysms. Most cases of MIS-C were resolved in a short period and rarely got worse.[8,9,11,13] Long-term side effects are not known.[11]

US data show the most complications are cardiac dysfunction (40.6%), shock (35.4%), myocarditis, coronary artery dilation, and acute kidney injury.[39] All children in Belhajer's study even had heart problems (35/35) but eventually improved.[15] Of the USA cohort studies above, about two-thirds of patients were admitted to the PICU. The incidence of complications was higher in the younger group and showed mucocutaneous signs and symptoms.[39]

PROGNOSIS

The prognosis for MIS-C patients is relatively good, and recovery occurs faster.[11,15,17,24,38,84,85] Of those who have dilated coronary arteries, most of them also heal as usual in a short time. Until now, it has not been confirmed whether MIS-C is a severe variant of KD triggered by SARS-CoV-2 infection or MIS-C is a separate disease that can be mild to severe and resembles KD, or TSS.[11,17,20] Clinicians suspect that the two diseases are distinct entities with some phenotypic aspects in common.[17,20,43,63,86]

The case fatality rate from various countries in children with MIS-C is relatively low.[9,10,14,20,30,35,87] Only two of the

78 children treated at the PICU in the UK have died. One of them had an arrhythmia that was due to cerebral infarction.[13,31,43] Two other reports came from New York.[8,21] Total deaths across the US 10 cases.[39] The group with higher mortality is which shows the symptoms and signs of the respiratory system.[39]

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