

# Atrioventricular Block in Children With Multisystem Inflammatory Syndrome

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abstract

**BACKGROUND:** Children are at risk for multisystem inflammatory syndrome in children (MIS-C) after infection with severe acute respiratory syndrome coronavirus 2. Cardiovascular complications, including ventricular dysfunction and coronary dilation, are frequent, but there are limited data on arrhythmic complications.

**METHODS:** Retrospective cohort study of children and young adults aged  $\leq 21$  years admitted with MIS-C. Demographic characteristics, electrocardiogram (ECG) and echocardiogram findings, and hospital course were described.

**RESULTS:** Among 25 patients admitted with MIS-C (60% male; median age 9.7 [interquartile range 2.7–15.0] years), ECG anomalies were found in 14 (56%). First-degree atrioventricular block (AVB) was seen in 5 (20%) patients a median of 6 (interquartile range 5–8) days after onset of fever and progressed to second- or third-degree AVB in 4 patients. No patient required intervention for AVB. All patients with AVB were admitted to the ICU (before onset of AVB) and had ventricular dysfunction on echocardiograms. All patients with second- or third-degree AVB had elevated brain natriuretic peptide levels, whereas the patient with first-degree AVB had a normal brain natriuretic peptide level. No patient with AVB had an elevated troponin level. QTc prolongation was seen in 7 patients (28%), and nonspecific ST segment changes were seen in 14 patients (56%). Ectopic atrial tachycardia was observed in 1 patient, and none developed ventricular arrhythmias.

**CONCLUSIONS:** Children with MIS-C are at risk for atrioventricular conduction disease, especially those who require ICU admission and have ventricular dysfunction. ECGs should be monitored for evidence of PR prolongation. Continuous telemetry may be required in patients with evidence of first-degree AVB because of risk of progression to high-grade AVB.



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**DOI:** <https://doi.org/10.1542/peds.2020-009704>

Accepted for publication Aug 21, 2020

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**WHAT'S KNOWN ON THIS SUBJECT:** Children with multisystem inflammatory syndrome are at risk for cardiovascular complication, including ventricular dysfunction and coronary artery dilation.

**WHAT THIS STUDY ADDS:** Patients with multisystem inflammatory syndrome are also at risk for atrioventricular conduction disease, especially those who present with hypotension or shock and ventricular dysfunction. PR prolongation on the electrocardiogram may be used to identify patients at risk for progression to high-grade atrioventricular block.

**To cite:** Dionne A, Mah DY, Son MBF, et al. Atrioventricular Block in Children With Multisystem Inflammatory Syndrome. *Pediatrics*. 2020;146(5):e2020009704

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the cause of the current worldwide coronavirus disease 2019 (COVID-19) pandemic, with >5 million confirmed cases in the United States. Children were initially thought to be largely spared from severe disease.<sup>1,2</sup> In April 2020, initial reports emerged from the United Kingdom of patients presenting with Kawasaki disease–like features and a severe inflammatory syndrome. Most cases occurred in children testing positive for current or recent infection with SARS-CoV-2. Children presented with fever, hypotension, multiorgan involvement, and markedly elevated inflammatory markers. Gastrointestinal and myocardial involvement was frequently observed, whereas respiratory symptoms were rarely seen.<sup>3</sup> Additional cases were reported throughout Europe<sup>4</sup> and America, leading to a health advisory from the US Centers for Disease Control and Prevention in May 2020 for multisystem inflammatory syndrome in children (MIS-C) associated with COVID-19.<sup>5</sup>

Cardiovascular complications, including shock, decreased left ventricular systolic function, coronary artery dilation, and aneurysms, were reported in a high proportion of patients in the initial European reports.<sup>3,6</sup> In our institutional experience, we also observed arrhythmias and electrocardiogram (ECG) changes in children with MIS-C. In this single-center series, we characterize the incidence of arrhythmias and ECG changes in patients with MIS-C.

## METHODS

### Population

We completed a retrospective cohort study of children and young adults aged 0 to 21 years who were admitted with a diagnosis of MIS-C between March 1, 2020, and May 30,

2020. Patients with previously diagnosed atrioventricular conduction disease were excluded from analysis. This included 1 patient with cardiac surgery complicated by complete heart block the week before MIS-C diagnosis. Because most of the cardiac and ECG findings described in this series were not applicable to this patient in the immediate postoperative period, he was excluded from analysis. This study was approved under exemption from informed consent by the Institutional Review Board at Boston Children's Hospital.

### Data Collection and Definitions

Data elements, including demographic characteristics, ECG and echocardiogram findings, and hospital course, were collected from the electronic medical record. The following criteria were used to define individuals with MIS-C on the basis of the Centers for Disease Control and Prevention case definition:

- aged <21 years;
- presenting with fever ( $\geq 38.0^{\circ}\text{C}$  for  $\geq 24$  hours);
- presenting with laboratory evidence of inflammation (including, but not limited to,  $\geq 1$  of the following: elevated values for C-reactive protein, the erythrocyte sedimentation rate, fibrinogen, procalcitonin, d-dimer, ferritin, lactic acid dehydrogenase, or interleukin 6; an elevated neutrophil count; a reduced lymphocyte count; and a low albumin level);
- presenting with evidence of clinically severe illness requiring hospitalization, with multisystem ( $\geq 2$ ) organ involvement (cardiac, renal, respiratory, hematologic, gastrointestinal, dermatologic, or neurologic), and no alternative plausible diagnosis;
- testing positive for current or recent SARS-CoV-2 infection by reverse transcription polymerase

chain reaction (RT-PCR), serology test, or antigen test; or exposed to COVID-19 within the 4 weeks before the onset of symptoms.<sup>5</sup>

Hypotension or shock was defined as requirement for fluid resuscitation ( $>20$  mL/kg) or inotropic support. An elevated troponin T level was defined as a troponin value  $>0.09$  ng/mL. An elevated brain natriuretic peptide (BNP) level was defined as a value  $>100$  pg/mL. Echocardiograms were reviewed during hospital admission and follow-up after discharge for ventricular function, valvar function, pericardial effusion, and coronary artery dimensions. Ventricular dysfunction was defined as a left ventricular ejection fraction  $<55\%$ . Coronary artery z scores were calculated for the left main coronary artery, proximal right coronary artery, and proximal left anterior descending artery by using the Boston formula.<sup>7</sup> Coronary artery dilation was defined as a coronary artery z score  $\geq 2$  but  $<2.5$ . On the basis of the American Heart Association guidelines, coronary artery aneurysm was defined as a coronary artery z score  $\geq 2.5$  and classified as small if the z score was  $\geq 2.5$  to  $<5$ , medium if the z score was  $\geq 5$  to  $<10$ , and large or giant if the z score was  $\geq 10$  or  $\geq 8$  mm absolute measurement in diameter.<sup>8</sup> On the basis of normal values for age, first-degree atrioventricular block (AVB) was defined as delayed conduction (prolonged PR interval) from the atrium to the ventricle without interruption in atrial to ventricular conduction.<sup>9</sup> Second-degree AVB was defined as intermittent atrial conduction to the ventricle and further classified as Mobitz type I (with progressive PR prolongation before the dropped beat) or Mobitz II (without progressive PR prolongation before the dropped beat). Third-degree AVB was defined as no atrial conduction to the ventricle. Prolonged QTc interval was defined

as a QTc interval in the >98th percentile for age and sex.<sup>9</sup> All ECGs were reviewed by the investigator (A.D.) blinded to patients' clinical course.

### Statistical Analysis

Descriptive statistics were obtained for all study variables. Quantitative variables were summarized as medians and interquartile ranges (IQRs), and categorical variables were summarized as frequencies and percentages. Because of the small sample size, no statistical tests were used to compare differences between groups.

## RESULTS

### Patient Characteristics

During the study period, 25 patients were admitted for management of MIS-C, of whom 15 (60%) were male, and the median age was 9.7 (IQR 2.7–15.0) years (Table 1). Forty percent of patients ( $n = 10$ ) had significant previous morbidities, including asthma ( $n = 3$ ; 15%), obesity ( $n = 3$ ; 15%), a previous episode of Kawasaki disease ( $n = 2$ ; 8%), sickle cell anemia ( $n = 1$ ), mitochondrial disease ( $n = 1$ ), and triploidy with prematurity and chronic respiratory failure status post tracheostomy ( $n = 1$ ).

Fever was present in all patients, followed in frequency by gastrointestinal symptoms ( $n = 18$ ; 72%), dermatologic manifestations ( $n = 14$ ; 56%), respiratory symptoms ( $n = 11$ ; 44%), hypotension or shock ( $n = 11$ ; 44%), hematologic anomalies ( $n = 7$ ; 28%), acute renal failure ( $n = 2$ ; 8%), and neurologic symptoms ( $n = 1$ ; 4%). All patients had documented SARS-CoV-2 infection (RT-PCR in 15 patients [60%], serology tests in 13 patients [52%]). Four patients had positive RT-PCR test results 2 to 8 days before MIS-C diagnosis, whereas the remainder had positive results at the time of hospital admission and MIS-C diagnosis.

**TABLE 1** Baseline Characteristics of Patients With MIS-C Based on Presence or Absence of Second- or Third-Degree AVB

	All Patients ( $N = 25$ )	AVB ( $n = 5$ )	No AVB ( $n = 20$ )
Age, y, median (IQR)	9.7 (2.7–15.0)	12.1 (10.3–16.2)	7.2 (2.2–13.7)
Male sex, $n$ (%)	15 (60)	2 (40)	13 (65)
Past medical history, $n$ (%)	10 (40)	1 (20)	9 (45)
Hospital course			
Duration of fever, d, median (IQR)	6 (4–8)	7 (6–9)	5 (4–6)
Hospital length of stay, d, median (IQR)	7 (3–11)	11 (9–12)	6 (3–9)
ICU admission, $n$ (%)	14 (56)	5 (100)	9 (45)
ICU length of stay, d, median (IQR)	7 (4–11)	6 (3–14)	7 (4–10)
Inotropic support, $n$ (%)	7 (28)	4 (80)	3 (15)
Noninvasive positive pressure ventilation, $n$ (%)	6 (24)	1 (20)	4 (20)
Intubation, $n$ (%)	1 (4)	1 (20)	1 (5)
Treatments received, $n$ (%)			
IVIg	16 (64)	5 (100)	11 (55)
Steroids	13 (52)	5 (100)	9 (45)
Anakinra	4 (16)	2 (40)	2 (10)
Aspirin	14 (56)	4 (80)	10 (50)
Enoxaparin	14 (56)	4 (80)	10 (50)
Remdesivir	9 (36)	3 (60)	6 (30)
SARS-CoV-2 testing, $n$ (%)			
PCR	15 (60)	3 (60)	12 (60)
Antibodies	13 (52)	2 (40)	11 (55)

IVIg, intravenous immunoglobulin; PCR, polymerase chain reaction.

ICU admission for monitoring and treatment was required in 14 patients (56%) for a median of 7 (IQR 4–11) days. Inotropic support was administered in 7 patients (28%), noninvasive positive pressure ventilation was administered in 6 patients (24%); and mechanical ventilation was administered in 1 patient (4%). The only patient requiring mechanical ventilation had a past medical history of chronic lung disease and had a previous tracheostomy.

Treatment received included intravenous immunoglobulin in 16 patients (64%), steroids in 13 patients (50%), anakinra in 4 patients (15%), and remdesivir in 9 patients (35%). A majority of patients were treated with aspirin (14 patients; 56%) and/or enoxaparin (14 patients; 56%).

At the time of publication, patients had a median follow-up of 51 (IQR 38–64) days after onset of illness, and all patients were discharged from the hospital.

### Echocardiographic Anomalies

All patients with a diagnosis of MIS-C had an echocardiogram performed during hospital admission, and 23 patients (92%) had at least 1 follow-up echocardiogram.

Left ventricular systolic dysfunction (left ventricular ejection fraction <55%) was found in 15 patients (60%) at a median of 5 (IQR 3–8) days after onset of fever (Table 2). The majority of patients had mild ventricular dysfunction, whereas 2 patients (8%) had moderate ventricular dysfunction or greater (left ventricular ejection fraction <40%). Of those with ventricular systolic dysfunction during the acute phase of illness, function normalized in 13 of 15 patients (87%) at a median of 5 (3–8) days after onset of dysfunction, with persistent mild ventricular dysfunction in 2 of 15 patients (13%).

New coronary artery enlargement was diagnosed in 5 patients (20%) at a median of 5 (IQR 2–5) days after

**TABLE 2** Cardiac Complications in Patients With MIS-C Based on Presence or Absence of Second- or Third-Degree AVB

	All Patients (N = 25)	AVB (n = 5)	No AVB (n = 20)
Ventricular dysfunction, n (%)			
EF <55%	15 (60)	5 (100)	10 (50)
EF <40%	2 (8)	1 (20)	1 (5)
Coronary artery dilation, n (%)			
Dilation (z score $\geq 2$ but <2.5)	3 (12)	1 (25)	2 (10)
Aneurysm (z score $\geq 2.5$ )	3 (12)	0 (0)	3 (15)
ECG changes, n (%)			
First-degree AVB	5 (20)	5 (100)	0 (0)
Second-degree AVB, Mobitz 1	2 (8)	2 (40)	0 (0)
Second-degree AVB, Mobitz 2	1 (4)	1 (20)	0 (0)
Third-degree AVB	1 (4)	1 (20)	0 (0)
QTc prolongation	7 (28)	4 (80)	3 (15)
QTc prolongation >500 ms	1 (4)	1 (25)	0 (0)
Nonspecific ST segment changes	14 (56)	5 (100)	9 (45)
Laboratory testing, n (%)			
Elevated troponin level	2 (8)	0 (0)	2 (10)
Elevated BNP level	11 (44)	4 (80)	8 (40)

EF, ejection fraction.

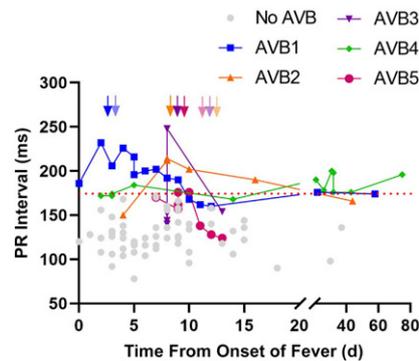
onset of fever (excluding patient with a previous history of Kawasaki disease and coronary aneurysm). Of those, 3 patients had coronary artery dilation (z score  $\geq 2$  but <2.5) and 2 patients had small coronary artery aneurysms (z score  $\geq 2.5$  but <5). One of the patients with coronary artery aneurysms had a previous diagnosis of Kawasaki disease and no significant change in coronary artery dimension after MIS-C diagnosis.

Troponin levels were elevated in 2 patients (13%), both of whom had ventricular dysfunction. BNP levels were elevated in 10 of 15 patients (67%) with ventricular dysfunction (median 395 [IQR 105–1008] pg/mL) and in only 1 of 10 patients (10%) with normal biventricular systolic function (median 35 [IQR 16–79] pg/mL).

### ECG Anomalies

ECGs were performed in all patients, and 20 (80%) patients had multiple ECGs to review. First-degree AVB was found in 5 (20%) patients admitted with MIS-C at a median of 6 (IQR 5–8) days after onset of fever (Fig 1, Supplemental Table 3). Of the 5 patients with first-degree AVB, 4 of 5 had a normal admission ECG and

subsequently developed AVB, and 1 of 5 had first-degree AVB on the admission ECG. AVB progressed to the second or third degree in 4 of 5 patients during the hospital admission (Mobitz type I in 2 patients, Mobitz type II in 1 patient [without QRS widening], and third-degree AVB in 1 patient) within 0 to 3 days after onset of first-degree AVB. No patient required acute resuscitation, pacing, or medication to improve atrioventricular conduction or increase the escape rate. Second- and third-degree AVB resolved in all patients within 1 to 6 days. First-



**FIGURE 1** PR interval in patients with and without AVB by days from onset of fever. Arrows reveal onset and resolution of higher-grade AVB (second and/or third degree). AVB1-5, individual patients with AVB.

degree AVB resolved in 4 of 5 patients between 10 and 14 days after onset of fever; 1 patient had persistent first-degree AVB on the latest outpatient follow-up (75 days after onset of fever).

All patients with AVB had ventricular dysfunction on the echocardiogram (mild in 4 patients, moderate in 1 patient). All were admitted to the ICU (unrelated to AVB), and 4 of 5 patients required inotropic support for hypotension or shock at the time of initial presentation. One patient was intubated because of cardiogenic shock, and another required positive pressure ventilation for COVID-19 pneumonia. Although second- and third-degree AVB occurred during the initial ICU admission in 2 of 4 patients, it occurred later in the course of the disease in the other 2 patients, requiring transfer back to the ICU or to a cardiology floor for closer monitoring. All patients who developed second- or third-degree AVB presented with hypotension or shock, gastrointestinal symptoms, and dermatologic manifestations. The other patient with first-degree AVB presented with COVID-19 pneumonia and hypotension responsive to fluid resuscitation but did not have gastrointestinal or dermatologic manifestations, as opposed to those who progressed to higher-grade AVB. None of the patients with AVB had elevated troponin levels. All patients with second- or third-degree AVB had elevated BNP levels (median 1407 [IQR 1127–1776] pg/mL), whereas the patient with first-degree AVB had a normal BNP level.

QTc prolongation was seen in 7 patients (28%) at a median of 6 (IQR 2–8) days after onset of fever (median QTc 484 [IQR 474–493] milliseconds). QTc prolongation was more often seen in patients with ventricular dysfunction (n = 6) compared with those with normal ventricular function (n = 1) and those with AVB (4 of 5 [80%] patients with AVB versus 3 of 20 [15%] patients

without AVB). Nonspecific ST segment changes were seen in 14 patients (56%), without a difference between those with and without ventricular dysfunction (9 of 15 vs 5 of 10 patients, respectively). All patients with AVB had nonspecific ST segment changes on the ECG, compared with only 9 (45%) patients without AVB.

Two patients had atrial ectopy, and another patient had sustained ectopic atrial tachycardia. No ventricular arrhythmias were seen. No patient required antiarrhythmic medication.

## DISCUSSION

In this series, ECG anomalies were found in 14 (56%) children with MIS-C and included PR prolongation, ST segment changes, and QTc prolongation. First-degree AVB was found in 5 children (20%) during hospital admission, with 4 of 5 patients progressing to second- or third-degree AVB. The incidence of AVB was highest among patients requiring ICU admission (4 of 14 patients; 29%). All patients with second- and third-degree AVB presented with hypotension or shock, gastrointestinal symptoms, and dermatologic manifestations and had evidence of ventricular dysfunction on the echocardiogram. ECGs should be monitored for evidence of PR prolongation throughout admission in patients with MIS-C. Patients who develop first-degree AVB may benefit from continuous telemetry because of the risk of progression to high-grade AVB.

Evidence of myocardial injury is common among adults hospitalized with COVID-19. Possible causes of myocardial injury in patients with COVID-19 include myocarditis, hypoxic injury, stress (takotsubo) cardiomyopathy, ischemic injury caused by cardiac microvascular damage or coronary artery disease, right heart strain (acute cor pulmonale), and systemic

inflammatory response syndrome.<sup>10-14</sup> Clinical presentation ranges from asymptomatic elevation of troponin levels to fulminant myocarditis requiring extracorporeal membrane oxygenation support. Atrial and ventricular arrhythmias have been reported in 3% to 17% of adults hospitalized with COVID-19.<sup>15-17</sup> Bradyarrhythmias have not been typically seen, but there was one reported case of transient complete heart block in a critically ill 54-year-old woman with COVID-19 pneumonia who required cardiopulmonary resuscitation for ~10 minutes until resumption of normal sinus rhythm.<sup>18</sup>

Initial reports suggested that children with COVID-19 have a much milder form of COVID-19 than adults.<sup>1,2</sup> However, there have now been multiple reports of cases of MIS-C in conjunction with recent SARS-CoV-2 infection. Published case series have revealed cardiovascular involvement in a significant proportion of patients, with reports of elevated troponin levels, elevated BNP levels, ventricular dysfunction, and coronary artery dilation and aneurysm.<sup>5,6</sup> No significant tachyarrhythmias have been reported in children, compared with adult patients (in whom a much higher prevalence has been seen).

There has been one recent report of transient complete heart block in a child after SARS-CoV-2 infection.<sup>19</sup> The etiology of the AVB remains unclear but may result from inflammation and edema of the conduction tissue as part of a more diffuse process of myocardial injury.

Authors of an earlier single-center series of children with non-COVID-19-related acute myocarditis reported a high incidence of arrhythmias, occurring in 38 patients (45%) and including supraventricular tachycardia in 9 patients, ventricular arrhythmia in 30 patients, and complete heart block in 11 patients.<sup>20</sup> The clinical course of AVB in patients

with MIS-C differs from the previous experience with myocarditis. In non-COVID-19-related myocarditis, complete heart block was generally present at the time of initial presentation and frequently required interventions, including pacing and extracorporeal membrane oxygenation. In comparison, AVB developed later in the hospital course in patients with MIS-C, and no patients required pacing or extracorporeal membrane oxygenation for AVB. However, this initial experience with MIS-C is based on a small number of patients, and our understanding will likely evolve as we learn more about the disease.

In contrast, AVB seen in patients with MIS-C appears more similar to the previous experience with Lyme carditis. In a surveillance study in the United States, cardiac manifestations were present in 84 of 875 patients (10%) with Lyme disease, including conduction abnormalities in 16 patients (1.8%).<sup>21</sup> Similarly, patients with Lyme carditis presented with first-degree AVB that progressed to high-grade AVB, with the highest risk of progression in patients with a PR interval >300 milliseconds.<sup>22-24</sup> This is similar to findings in our cohort, in which most patients had initially normal ECGs and developed first-degree AVB before higher-grade AVB (although the progression occurred the same day in some cases). In MIS-C, patients with a prolonged PR interval for age were at high risk of progression of AVB, even with only mild PR prolongation (ie, <300 milliseconds; Fig 1).

The course of AVB remains unclear in patients with MIS-C. Although higher-grade AVB resolved within ~1 week in this series, some patient still had persistent first-degree AVB at the time of discharge. Antibiotic treatment has been shown to decrease the duration of cardiac manifestations in Lyme carditis.<sup>25</sup> Antiinflammatory treatment of patients with MIS-C with intravenous

immunoglobulin, steroids, or anakinra may help decrease the incidence of AVB in MIS-C; however, we were unable to assess the impact of therapy because of the empirical treatment of the most severe cases. Ongoing outpatient follow-up of patients with MIS-C will help us better understand the trajectory of AVB in patients with MIS-C. Until we know more about AVB in MIS-C, children should have frequent ECGs during admission to monitor for PR prolongation and have long-term follow-up after discharge. A 24-hour Holter monitor should be considered in patients with persistent first-degree AVB during outpatient follow-up.

This study should be interpreted in light of its limitations. This is a retrospective series of only a small number of patients from a single

institution. Moreover, there was no systematic protocol for ECG testing, and some patients without a follow-up ECG study or telemetry may have been missed. The limited follow-up on patients at the time of publication limits our ability to comment on long-term outcomes.

## CONCLUSIONS

In this series, MIS-C was associated with a high incidence of atrioventricular conduction disease in children, particularly in patients presenting with hypotension or shock and ventricular dysfunction. This experience highlights the importance of ECG monitoring throughout admission to identify patients with PR prolongation at risk for progression to high-grade AVB. Large multicenter studies are required to

better understand the pathophysiology, clinical presentation, and impact of treatment on atrioventricular conduction disease in MIS-C.

## ABBREVIATIONS

AVB: atrioventricular block  
BNP: brain natriuretic peptide  
COVID-19: coronavirus disease 2019  
ECG: electrocardiogram  
IQR: interquartile range  
MIS-C: multisystem inflammatory syndrome in children  
RT-PCR: reverse transcription polymerase chain reaction  
SARS-CoV-2: severe acute respiratory syndrome coronavirus 2

PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).

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**FINANCIAL DISCLOSURE:** The authors have indicated they have no financial relationships relevant to this article to disclose.

**FUNDING:** No external funding.

**POTENTIAL CONFLICT OF INTEREST:** The authors have indicated they have no potential conflicts of interest to disclose.

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