Received: 14 February 2022 | Revised: 13 April 2022 | Accepted: 20 May 2022

DOI: 10.1111/apa.16416

ACTA PÆDIATRICA NURTURING THE CHILD WILEY

BRIEF REPORT

Antibiotic use in children with multisystem inflammatory syndrome associated with SARS-CoV-2

Multisystem inflammatory syndrome in children (MIS-C) is a new diagnosis discovered as a result of the global SARS-CoV-2 pandemic. MIS-C presents as a shock-like syndrome, therefore initial management often includes antibiotics.[1,2] There is a lack of data to guide medical providers regarding antibiotic duration in this newly described disease state. We examined antibiotic use among children with confirmed MIS-C and correlated changes in practice with stewardship activities.

Using an internal database, we identified hospitalised children and young adults 0–21 years old from May 2020 through June 2021 who met criteria for MIS-C based on the Centers for Disease Control and Prevention (CDC) definition.[3] We collected age, gender, race, date of presentation, hospital length of stay (LOS), need for intensive care, in-house mortality, inflammatory markers, culture results, and antibiotic data from the electronic health record. We excluded patients with an alternative diagnosis to explain use of antibiotics beyond the initial 48 h sepsis rule out period. Outcomes (antibiotic use and hospital LOS) were compared before and after stewardship interventions, with data presented as weighted means. Proportions of patients with various characteristics among those who received antibiotics versus those who did not were compared using chi-square or Fisher's exact tests. Continuous/numeric variables were compared using Mann–Whitney tests. Non-parametric tests were used due to skewed distribution of many variables. Logistic regression was performed to evaluate the odds ratio for children in the intensive care unit (ICU) receiving antibiotics compared to children not in the ICU. Statistical analysis was performed using IBM SPSS Statistics version 20.0. This project was reviewed by our Institutional Review Board and determined not to be human subject research.

Ninety-one patients presented with symptoms consistent with MIS-C; 75 met the CDC definition. Sixteen were excluded due to an alternative diagnosis to explain antibiotic use. The median age at diagnosis was 6.4 years. The median LOS was 4 days; 68% required intensive care within the first 24 h of admission. Most presented with fever (median temperature 39.3 Celsius) and elevated inflammatory markers (median C-reactive protein 17.9 mg/dL, procalcitonin 7.3 ng/mL). The prevalence of patients starting antibiotics was 51% (95% confidence interval 38%–63%). All antibiotic use was intravenous. Children who received antibiotics had longer hospital stays (6 versus 3 days, $p < 0.001$) and higher procalcitonin values (median 12.4 versus 4.3 ng/mL, $p = 0.014$) compared to those who did not receive antibiotics. Children in the ICU were 4.7 times more likely to start antibiotics (95% confidence interval 1.4–15.6; $p = 0.012$) compared to the general wards. Among those receiving antibiotics, the median length of therapy was 2 days. Most (97%) received a cephalosporin (ceftriaxone) and one-third (33%) received an anti-staphylococcal antibiotic (clindamycin, vancomycin, or linezolid). There were no deaths during hospitalisation.

Trends in antibiotic administration were compared to the onset of antimicrobial stewardship activities. Two interventions occurred during Quarter 3, 2020: development of a guideline and

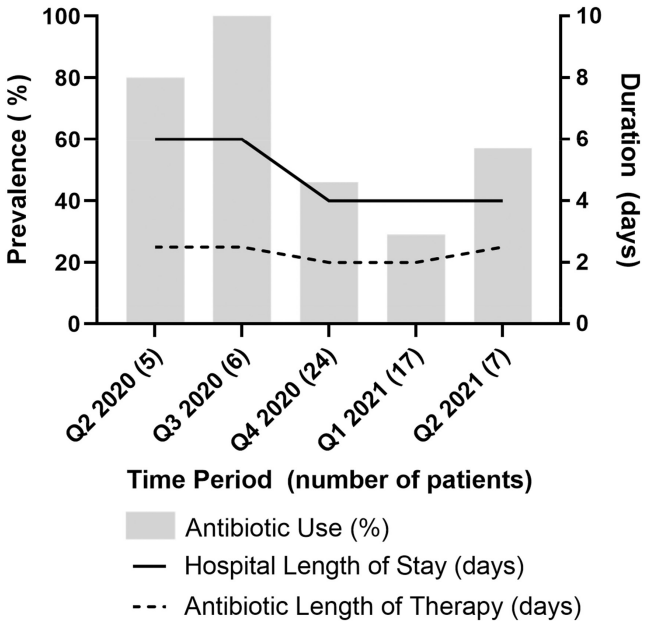

FIGURE 1 Antibiotic use, length of therapy, and hospital length of stay over time. Prevalence of antibiotic use is represented by the grey bars. Median hospital length of stay (in days) is represented by the solid black line. Median antibiotic length of therapy (in days) is represented by the dotted black line. Data is presented by quarter of the evaluation period. Number of patients per quarter is indicated

Abbreviations: CDC:, Centers for Disease Control and Prevention; ICU:, intensive care unit; LOS:, length of stay; MIS-C:, multisystem inflammatory syndrome associated with SARS-CoV-2 in Children.

re-institution of in-person antimicrobial stewardship rounds which had been paused at the start of the pandemic. The weighted mean of antibiotic use pre-intervention was 90.9% compared to 41.7% post-intervention (Figure 1). The median length of antibiotic therapy remained steady at 2 days, though when evaluated pre- and post- intervention, the absolute number of courses exceeding 2 days declined from 5/10 (50%) to 6/20 (30%) and hospital LOS declined from 6 to 4 days.

Our data reveal a high rate of antibiotic initiation with the first cases of confirmed MIS-C that declined over time and did not impact adverse outcomes. Reports from Latin America and Europe described similar rates in the initial waves of the pandemic but did not evaluate trends over time.[4,5] Despite lack of bacterial disease, high initial use of antibiotics is not unexpected since MIS-C symptoms mimic sepsis. In fact, nearly 70% of our patients were ill enough to require ICU admission within the first 24 h, which was statistically associated with a higher frequency of antibiotic administration. Fortunately, most children received only 2 days of therapy, consistent with the use of antibiotics for a "rule out sepsis" period.

During the evaluation period, our institution developed an MIS-C treatment guideline, which recommended ceftriaxone for ill/toxic appearing patients and no anti-staphylococcal coverage. Adherence to the guideline may explain the decline in antibiotic use. Additionally, the decline could be attributed to accumulated knowledge and confidence of medical providers who diagnose and treat MIS-C. LOS also decreased over time, which is likely due to improved guideline-based care and not decreased severity of illness. Finally, our antimicrobial stewardship team resumed in-person rounding, which may have had an additional effect. A frequent stewardship intervention is active promotion for antibiotic discontinuation in patients with negative culture results and no signs of bacterial infection. Though antibiotic selection was largely driven by the guideline, durations of therapy were at the discretion of the medical provider. After re-instituting stewardship rounds, there were fewer courses exceeding the typical rule out sepsis period without change in outcomes.

Children with MIS-C and no evidence of bacterial infection can safely receive a limited duration of antibiotics. Our data support continued integration of antimicrobial stewardship and development of clinical practice guidelines to direct antibiotic selection and duration of therapy for treatment of children with MIS-C during the COVID-19 pandemic.

ACKNOWLEDGEMENTS

None.

FUNDING INFORMATION

None.

CONFLICT OF INTEREST

All authors have nothing to disclose.

Tracy N. Zembles[1]
Katie M. Ray[1]
Evelyn M. Kuhn[2]
Anna R. Huppler[3]

[1]*Department of Enterprise Safety, Children's Wisconsin, Milwaukee, Wisconsin, USA*
[2]*Department of Business Intelligence and Data Warehousing, Children's Wisconsin, Milwaukee, Wisconsin, USA*
[3]*Department of Pediatrics, Medical College of Wisconsin, Milwaukee, Wisconsin, USA*

Correspondence
Tracy Zembles, PharmD, BCPS, BCIDP Children's Wisconsin, Department of Enterprise Safety 9000 West Wisconsin Ave Milwaukee, WI 53226, USA.
Email: tzembles@chw.org

ORCID

Tracy N. Zembles https://orcid.org/0000-0003-3727-7970

REFERENCES

1. Whitaker E, Bamford A, Kenny J, et al. Clinical characteristics of 58 children with a pediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2. Jama. 2020;324(3):259-269.
2. American Academy of Pediatrics. Multisystem Inflammatory Syndrome in Children (MIS-C) Interim Guidance. American Academy of Pediatrics; 2021. Available at: https://www.aap.org/en/pages/2019-novel-coronavirus-covid-19-infections/clinical-guidance/multisystem-inflammatory-syndrome-in-children-mis-c-interim-guidance/. Accessed October 18, 2021.
3. Centers for Disease Control and Prevention Health Advisory. Multisystem Inflammatory Syndrome in Children (MIS-C) Associated with Coronavirus Disease 2019 (COVID-19). CDC Health Alert Network; 2020. Available at: https://emergency.cdc.gov/han/2020/han00432.asp. Accessed October 18, 2021.
4. Yock-Corrales A, Lenzi J, Ulloa-Gutierrez R, et al. High rates of antibiotic prescriptions in children with COVID-19 or multisystem inflammatory syndrome: a multinational experience in 990 cases from Latin America. Acta Paediatr. 2021;110(6):1902-1910.
5. Velasco-Arnaiz E, Lopez-Ramos MG, Simo-Nebot S, et al. Pediatric antimicrobial stewardship in the COVID-19 outbreak. Infect Control Hosp Epidemiol. 2021;42(5):642-644.