Multisystem Inflammatory Syndrome in Children After Breakthrough Infection in a COVID-19–vaccinated Child

To the Editors:

Multisystem Inflammatory Syndrome in Children (MIS-C) is a rare hyperinflammatory condition requiring a high index of suspicion, as the differential diagnosis is broad, and patients often present critically ill.[1] MIS-C has not been reported after breakthrough infection in children who have completed mRNA coronavirus disease 2019 (COVID-19) vaccination.

A 13-year-old male who received 2 doses of the Pfizer/BioNTech vaccine (BNT162b2) 13 weeks before admission presented with 3 days of fever, abdominal pain, nausea, and vomiting. Six weeks earlier, following a family exposure, he had tested positive for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) by nasopharyngeal nucleic acid amplification test while asymptomatic. On arrival, he was febrile to 100.8°F, hypotensive, and ill appearing with diminished capillary refill time. Despite 2 normal saline boluses, his blood pressure remained, and he was started on epinephrine before being admitted to pediatric intensive care unit. An abdominal ultrasound to evaluate the appendix was ordered, and further workup for possible MIS-C diagnosis was performed (Table 1). His abdominal ultrasound showed a normal appendix. His EKG and echocardiogram were normal. Despite the improvement in his blood pressure after 24 hours, he remained tachycardic with elevated D-dimer levels. His chest computed tomography was negative for a pulmonary embolus. He remained febrile with abdominal pain and subsequently developed an erythematous macular rash on his chest and palms, nonexudative conjunctivitis, and periorbital edema and erythema. Given his negative cultures and development of mucocutaneous signs, he was given the diagnosis of MIS-C and treated with intravenous immune globulin and methylprednisolone. His fever and mucocutaneous signs resolved, and his C-reactive protein improved. Two weeks after his discharge, he only had mild fatigue. His cardiac magnetic resonance imaging demonstrated mild biventricular dilation with normal function, a trivial pericardial effusion and no myocarditis. His coronary arteries were normal. Written parental consent for this report was obtained.

Vaccination against SARS-CoV-2 infection has been one of the most effective tools to bring the pandemic under control, lowering the risk of infection, hospitalization, and death.[2] The possibility of MIS-C following COVID-19 vaccination in children has been carefully considered and, to our knowledge, has not been reported to this date, whereas multisystem inflammatory syndrome in adults has been reported in 2 patients following vaccination.[3,4] One of these patients received the BBIBP-CorV (Sinopharm) inactivated vaccine shortly after COVID-19 infection and 6 weeks later presented with multisystem inflammatory syndrome in adults symptoms within hours after their second vaccine dose.[3] The second patient developed symptoms 2 days after the first dose of Pfizer/BioNTech mRNA vaccine and was also diagnosed with pulmonary embolism and acute kidney injury.[4] Our patient was diagnosed with MIS-C 6 weeks after an asymptomatic breakthrough SARS-CoV-2 infection and 13 weeks after completing Pfizer/BioNTech vaccination, suggesting that the mild infection, rather than the vaccination, triggered the hyperinflammatory response.

This case highlights the critical need for reporting symptoms associated with breakthrough infections and monitoring for symptoms of MIS-C. Clinicians should continue to be vigilant of signs and symptoms of MIS-C irrespective of vaccination status.

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Searching High and Low: Call for a Joint European Society for Paediatric Infectious Diseases-European Committee on Antimicrobial Susceptibility Testing Survey on Dosage of Antibacterial Agents in Children—Part One

To the Editors:

In the past decades, most European clinical microbiology laboratories have adopted susceptibility testing methods and clinical breakpoints issued by the European Committee on Antimicrobial Susceptibility Testing (EUCAST) for reporting whether an isolated microorganism is susceptible or resistant to a given antimicrobial agent.[1,2] In 2019, EUCAST introduced a new definition of the old categories susceptible, intermediate and resistant, namely susceptible, standard dosing regimen, susceptible, increased exposure and resistant. Central to this concept is the principle of exposure, which is

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TABLE 1. Laboratory Parameters at Outside Hospital, on Admission to Our Center, on the Day of Discharge and at 2 Weeks Follow-up Evaluation

Laboratory Tests*	Outside Hospital	Admission	1 Day Before Discharge	2-Week Follow-up
WBC (4.5–13.5 10^9/L)	4.93	3.4	8.8	5.7
Hemoglobin (12.5–16.4 g/dL)	13.1	12.5	11.4	12.6
Hematocrit (37.0%–49.0%)	38.1	37.1	33.3	38.2
Platelets (142–508 10^9/L)	188	162	367	380
Absolute lymphocyte count (10^9/L)	0.31	0.5	2.8	1.5
CRP	89.4 (0.0–10.0 mg/L)	21.7 (<1.0 mg/dL)	5.8 (<1.0 mg/dL)	<0.5 (<1.0 mg/dL)
Procalcitonin (<0.5 ng/mL)		2.4	<0.5	
Sedimentation rate (<13 mm/h)		15	33	35
Interleukin 6 (<10 pg/mL)		211.2		
Ferritin (7–142 ng/mL)		218		128
Quantitative D-dimer [<0.50 µg(FEU)/mL]		1.96	3.28	0.44
Fibrinogen (170–410 mg/dL)		429	302	
Sodium	130	133	136	137
AST (15–50 U/L)		46	90	40
ALT (<36 U/L)		22	57	40
BNP (<60.0 pg/mL)		160.7	280.9	
Troponin (<0.029 ng/mL)		<0.010	<0.010	<0.010
SARS-CoV-2 NC IgG antibody [<1.40 (Index S/C)]		3.12		

*Normal values are given in parenthesis.

ALT indicates alanine transaminase; AST, aspartate aminotransferase; FEU, fibrinogen equivalent units; NC, nucleocapsid; WBC, white blood cell count.

described as the function of the antimicrobial agent's pharmacokinetics, the mode of administration, the individual dose, and the dosing interval.[3] To account for the differential exposure between susceptible, standard dosing regimen and susceptible, increased exposure, EUCAST published a table alongside the annual breakpoint tables (https://www.eucast.org/clinical_breakpoints/), listing the standard and increased dosages of antibiotic agents resulting in minimum levels of exposure which were behind EUCAST breakpoints. This offers healthcare practitioners a standard dosage and a high dosage of some antibacterial agents for the treatment of patients.[4]

However, the dosages in the current table were based on data from adult patients, leaving a need for pediatricians. To translate the table to pediatric use is complicated by the scarcity of high-quality evidence in terms of pharmacokinetics/pharmacodynamics for children. With an increasing demand from the pediatric community, EUCAST and the European Society for Paediatric Infectious Diseases (ESPID) have decided to form a joint task force, with the aim of developing a dosage table for pediatric patients beyond the neonatal age. The Task Force recognizes the wide variation in dosing regimens used globally and the need for harmonization of existing recommendations as expressed by others.[5]

In a preliminary search for existing pediatric dosage recommendations, the Task Force identified existing dosing recommendations, dosage tables or drafts thereof from the following sources: Kinderformularium (Nederlands Kenniscentrum Farmacotherapie bij Kinderen, the Netherlands), SwissPedDose (Association SwissPedDose, Switzerland), the British National Formulary for Children (National Institute for Health and Care Excellence, United Kingdom), Sociedad Española de Infectología Pediátrica (Spain), as well as feedback from the national antimicrobial susceptibility testing committees of Germany, Denmark, the Russian Federation, Montenegro, Finland, Estonia, Sweden, Norway and Australia.

These dosage recommendations were compiled, and the ranges are shown in Table 1. In this table, we focus on standard dosage only, with a lower and upper range found in the source materials. As demonstrated the dosage ranges vary, with some being very narrow, and others rather wide. We wish to emphasize that we have created these ranges without modification from the sources described above.

We now invite all pediatricians, pharmacists, and healthcare practitioners who are involved in the antibacterial treatment of children from all over the world to participate in the first part of a survey which is linked here:

www.ukbb.ch/eucastsurvey

The survey will close on April 22, 2022.

Briefly, the questions that we aim to answer are the following:

1. Do the dosage ranges shown in the table align with what you are using in your daily practice as standard dosing regimens?
2. To what extent does your practice differ from the ranges given in the table?
3. What are the clinical indications that you use different (higher or lower than standard) dosages for?
4. What sources are you using to derive antibacterial dosages in children?

The dosages shown in the table are not meant as a recommendation, but they reflect the ranges from a selection of sources and national antimicrobial susceptibility testing committees. In a first step, we aim to investigate if these ranges correspond with what is being prescribed in clinical practice. Thus, we strongly encourage you to take part in this process. This endeavor depends greatly on your help and active participation.

We acknowledge that clinical responsibilities during these dire pandemic times are part of our reality. Therefore, we have kept this first part of the survey as lean as possible. Further survey rounds with increased dosages and more antibacterial agents will follow in due course. We aim to further refine these dosages after the survey period has ended. The objective is to create a full dosage table for children with both standard and increased dosage, aligning as much as possible with exposures achieved in adult patients. The ultimate goal is to improve efficacy and safety in the antimicrobial treatment of pediatric patients.

This letter is being published simultaneously in *Clinical Microbiology and Infection*.