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Use of broad-spectrum antibiotics in children diagnosed with multisystem inflammatory syndrome temporarily associated with SARS-CoV-2 infection in Poland: the MOIS-CoR study

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ABSTRACT

Objectives: Multisystem inflammatory syndrome in children (MIS-C) is the result of an immune response triggered by a previous exposure to SARS-CoV-2. The clinical presentation of MIS-C overlaps with other life-threatening bacterial infections, in which antimicrobials are the mainstay therapy. The aim of study was to describe the use of antibiotics in children with MIS-C in Poland.
Methods: The analysis of 345 children reported from 42 Polish cities to the national MultiOrgan Inflammatory Syndromes COVID-19 Related Study (MOIS-CoR Study) from June 2020 to April 2021.
Results: At least one antibiotic was used in 310 (90%) children, mainly third-generation cephalosporin (251/310). Broad-spectrum antibiotics were used in 258 (75%) children and 224 (87%) received this treatment for more than 3 days. Concentrations of serum procalcitonin >2 µg/l and the presence of lower respiratory symptoms were associated with increased odds of receiving any antibiotic.
Conclusion: Although bacterial infections in patients with MIS-C are uncommon, we show that MIS-C poses a challenge to clinicians who are faced with the decision to start, continue, or stop antimicrobial therapy. Antibiotic stewardship in patients with MIS-C should be improved to ensure that likely pathogens are treated and that antimicrobials are stopped when bacterial infections are excluded and the diagnosis of MIS-C is made.

Introduction

Since April 2020, after the first wave of the COVID-19 pandemic, many reports have documented a new hyperinflammatory condition in children, manifesting with a persistent fever, fatigue, and a variety of symptoms, including multiorgan involvement and elevated inflammatory markers (Belot *et al.*, 2020; Davies *et al.*, 2020; Verdoni *et al.*, 2020). The first definition of pediatric inflammatory multisystem syndrome temporally associated with COVID-19 (PIMS-TS) was announced by the Royal College of Pediatrics and Child Health on May 1 (Health Policy Team, 2020). The alternative name for this disease proposed in the United States was multisystem inflammatory syndrome in children (MIS-C), and it was adopted by the World Health

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Organization (WHO) (Centers for Disease Control and Prevention, 2020).

Since mid-May 2020, the CDC has been tracking case reports of MIS-C. According to the CDC, as of March 28, 2022, in the United States, the total number of patients with MIS-C who met the definition was 7880. The total number of children who had died of MIS-C was 66. The median age of children with MIS-C was 9 years, with half of the children with MIS-C being between the ages of 5 and 13 years; 60% of reported patients were male (Centers for Disease Control and Prevention, 2022).

PIMS monitoring reports are also being conducted in Europe. Since May 25, 2020, Poland has been conducting nationwide surveillance of pediatric inflammatory syndromes in the MultiOrgan Inflammatory Syndromes COVID Related Study (MOIS-CoR)(Okarska-Napierała et al., 2020). Such monitoring enables the exchange of experiences between treatment centers and the development of common rules of conduct based on national and international experience.

Current evidence indicates that MIS-C is the result of an exaggerated innate and adaptive immune response, characterized by a cytokine storm, and that it is triggered by previous SARS-CoV-2 exposure. Pathogenically, it is associated with immune-mediated postinfectious hyperinflammation, involving fever, severe inflammation, and multiorgan dysfunction, leading to vasoplegic shock, requiring vasopressor therapy. Cardiovascular involvement is apparently marked by acute myocardial injury/myocarditis and the development of coronary artery aneurysms (Mahase, 2020). A characteristic element is a significant increase in inflammatory markers: C-reactive protein (CRP), erythrocyte sedimentation rate, procalcitonin, and ferritin. Therapy essentially consists of anti-inflammatory and immunomodulatory medications, such as intravenous immunoglobulins and steroids, based on the knowledge that the disorder is induced by postinfectious immune dysregulation (Henderson et al., 2021)(Henderson *et al*., 2020). The course of the disease is characterized by a strong inflammatory reaction, which requires differentiation from a septic state, and many clinicians also implement empirical antibiotic therapy.

The aim of this study was to assess the frequency of, clinical reasons for, and type of antibiotics prescribed in children with MIS-C.

Methods

Patient data

We analyzed data from the Polish MOIS-CoR. Children aged 0-18 years with features of MIS-C from 42 cities in Poland were voluntarily reported. Anonymized patients' data were collected through an online questionnaire developed for that purpose (Ludwikowska et al., 2021).

For the purpose of this study, the WHO MIS-C case definition criteria were adopted (World Health Organization 2020). The case definition included the following criteria: children aged 0-18 years with fever >3 days and two of the following: (i) rash or bilateral nonpurulent conjunctivitis or signs of mucocutaneous inflammation (oral, hands, or feet); (ii) hypotension or shock; (iii) features of myocardial dysfunction, pericarditis, valvulitis, or coronary abnormalities, including echocardiography findings or elevated troponin/N-terminal pro-B-type natriuretic peptide; (iv) evidence of coagulopathy by prothrombin time, partial thromboplastin time, elevated D-dimers; (v) acute gastrointestinal problems (diarrhea, vomiting, or abdominal pain) and elevated markers of inflammation (e.g., erythrocyte sedimentation rate, CRP, or procalcitonin) and no other obvious microbial cause of inflammation, including bacterial sepsis, staphylococcal, or streptococcal shock syndromes and evidence of COVID-19 by reverse transcription polymerase chain reaction, antigen test or serology positive, or likely contact with patients with COVID-19. Cases not meeting the WHO criteria and cases with incomplete crucial data were excluded from the analysis.

Statistical methods

The summary statistics for continuous variables are presented as a median with interquartile range, and categorical variables are presented as frequencies. The continuous variables were compared using the Mann-Whitney U test, and categorical variables were compared between groups using chi-square tests. Binary logit regression models were used to identify variables that were associated with the probability of using antibiotics in patients with MIS-C. The results were considered statistically significant when the *P*-value was less than 0.05. The statistical analysis was conducted using TIBCO Software Inc. (2017) Statistica, version 13 (Palo Alto, CA, USA).

Ethical considerations

Ethical approval was obtained from the bioethics committee at Wroclaw Medical University (CWN UMW BW: 313/2020). A waiver of written informed consent was obtained with only deidentified data transmitted and analyzed.

Results

Among the 437 pediatric patients who reported to MOIS-CoR with suspected MIS-C, 345 cases fulfilled the WHO criteria for MIS-C associated with SARS-CoV-2 and were eligible for study inclusion. All cases were registered between June 2020 and April 2021. The majority of children (n = 293, 85%) were admitted over a 3-month period from November 2020 to January 2021 during the second COVID-19 wave in Poland. There were 214 boys and 131 girls in the study group. All children were of European White ethnicity, and the median age was 8.6 years (range 4 months-17 years). There were nine children under the age of 1 year, and 82 children aged between 1 and 5 years. Characteristics of the study group are shown in Table 1.

The use of antibiotics was common in the analyzed group. A total of 310 (90%) children diagnosed with MIS-C were administered at least one antibiotic (Figure 1). A total of 49 (14%) children received antibiotics from at least three different classes. The most commonly used antibiotics were third generation cephalosporins, being used in 251/310 (81%) children who were treated with antibiotics.

Overall, the use of broad-spectrum antimicrobials (third-generation cephalosporins, meropenem, vancomycin, aminoglycosides) in monotherapy or combination therapy was common. These antibiotics were administered to 258 (75%) of all children diagnosed with MIS-C. Of those 258, 224 (87%) children were treated with these regimens for more than 3 days, whereas 34 (13%) received the treatment for less than 3 days. Figure 2 shows that antimicrobial treatment did not change over time. Polish guidelines on the treatment of MIS-C were published in December 2020; however, this had no effect on the duration and type of antimicrobials used in these patients (Okarska-Napierała *et al*., 2021).

Compared with those who did not receive antimicrobials, children treated with antibiotics were characterized by higher concentrations of inflammatory markers and the presence of respiratory tract symptoms. Using a binary logit regression model, we aimed to identify variables that were associated with the risk of using antibiotics in patients with MIS-C. In the univariable analysis, we found that children with signs of upper and lower respiratory tract infections were over twice as likely to receive any antibiotic

Table 1
Characteristics of the study group

	All	Not treated with Abx (n = 35)	Treated with Abx (n = 310)	*P*
Age, years	8.6 (4.9-12.0)	8.6 (5.6-12.3)	8.6 (4.8-11.9)	0.57
<1 year	9 (3%)	0	9	
1-5 years	82 (23%)	6	76	
6-12 years	168 (49%)	19	149	
>12 years	86 (25%)	10	76	
Sex, female/male	131/214 (38%/62%)	13/22 (37%/63%)	118/192 (38%/62%)	0.92
Underlying chronic health condition	47/263 (18%)	1/24	46/239	0.07
Symptoms:				
Rash	264/332 (80%)	27/35(77%)	237/297 (80%)	0.71
Mucocutaneous or lymphadenopathy	320/339 (94%)	30/34 (88%)	290/305 (95%)	0.99
Gastrointestinal	294/333 (88%)	29/34 (85%)	265/299 (89%)	0.57
Upper respiratory	128/320 (40%)	7/32 (22%)	121/288 (42%)	**0.03**
Lower respiratory	157/315 (50%)	10/31 (32%)	147/284 (52%)	**0.04**
Osteoarticular and muscular	131/311 (42%)	12/31 (39%)	119/280 (43%)	0.69
Neurologic	266/320 (83%)	27/32 (84%)	239/288 (83%)	0.84
Decreased level of consciousness	20/325 (6%)	2/31 (6%)	18/294 (6%)	0.94
Hypotension	35/268 (13%)	2/23 (9%)	33/245 (13%)	0.52
Laboratory workup				
Positive SARS-CoV-2 PCR	49/290 (17%)	7/31 (23%)	42/259 (16%)	0.37
CRP, mg/l	129 (72-190)	85 (33-152)	134 (77-193)	**0.02**
CRP > 100 mg/l	216/337 (64%)	14/32 (44%)	202/305 (66%)	**0.01**
Lactate, mmol/l	2.0 (1.6-3.0)	1.9 (1.3-2.4)	2.0 (1.6-3.1)	0.09
Lactate >2 mmol/l	54/111 (49%)	7/16 (44%)	47/95 (49%)	0.68
WBC, 10^3/µl	9.5 (6.6-13.5)	7.9 (6.3-11.6)	9.6 (6.7-13.6)	0.23
Blood neutrophils, 10^3/µl	8.6±6	6.2 (4.4-9.6)	7.6 (4.8-11.0)	0.16
Blood neutrophils >10 000/ µl	87/314 (28%)	5/32 (16%)	82/282 (29%)	0.11
Procalcitonin, µg/;	2.3 (0.9-7.0)	1.0 (0.2-2.8)	2.7 (1.0-7.8)	**<0.001**
Procalcitonin >2 µg/l	164/311 (53%)	9/31 (29%)	155/280 (55%)	**0.005**
Leukocyturia	53/319 (17%)	3/31 (10%)	50/288 (17%)	0.27
Lung consolidations on chest X-ray or CT	67/305 (22%)	6/26 (23%)	61/218 (22%)	0.60
Pericardial effusion	20/287 (7%)	1/28 (4%)	19/259 (7%)	0.19
Treatment				
Treatment in PICU	31/341 (9%)	1/34 (3%)	30/307 (10%)	0.19
Mechanical ventilation	14/326 (4%)	0/30 (0%)	14/296 (5%)	-
Treatment with antibiotics	310/345 (90%)	0	310 (100%)	-
Broad-spectrum antibiotics	259/345 (75%)	0	258 (83%)	-
Other antibiotics	52(17%)	0	51 (16%)	-
IVIG (first-line)	282/308 (92%)	22/25 (88%)	260/283 (92%)	0.50
Glucocorticoids (first-line)	119/237 (50%)	2/17 (12%)	117/220 (53%)	**0.001**

Continuous data are presented as medians with interquartile range, categorical data are presented as frequencies. Denominators lower than the sample size indicate missing data.
Abbreviations: CRP, C-reactive protein; CT, computed tomography; IVIG, intravenous immune globulin; PCR, polymerase chain reaction; PICU, pediatric intensive care unit; WBC, white blood cell.

(Figure 3). Also, increased serum concentrations of CRP >100 mg/l, and procalcitonin >2 µg/l were associated with an increased risk of receiving antibiotics. Age, comorbidities, and treatment in an intensive care unit were not associated with the odds of using antibiotics in this study group. Importantly, however, all infants with MIS-C were given antimicrobial treatment. A multivariable analysis revealed that increased procalcitonin and signs of lower respiratory tract infection were the only two variables that were significantly associated with around three-fold higher odds of using antibiotics in children with MIS-C.

Discussion

Treatment of MIS-C involves an immunomodulatory approach, that is, the application of an intravenous infusion of immunoglobulin, glucocorticosteroid, and, in some specific cases, biological treatment, the use of acetylsalicylic acid to prevent an increased clotting tendency, as well as symptomatic treatment. Because of the complex clinical picture of MIS-C, which resembles the initial stadium of a serious bacterial infection, such as sepsis, toxic shock syndrome, or bacterial intestinal infection, doctors must consider the use of broad-spectrum antibiotic therapy in the initial treatment (Gharbi *et al.*, 2016; Harwood *et al.*, 2021; McMurray et al., 2020).

Pediatricians worldwide, including during the COVID-19 pandemic, have raised concerns about the numerous threats associated with the use of broad-spectrum antibiotics—from individual complications, such as adverse reactions and intestinal microbiota disorders, to the selection of antibiotic-resistant bacterial strains, which cause a particular problem in the hospital environment. There have been few studies analyzing the irrelevant use of antibiotic therapy in children; however, the available data estimate that antibiotic therapy was used improperly in up to 20% of hospitalized pediatric patients (Gharbi *et al.*, 2016; Tan et al., 2021; Tribble *et al.*, 2020). The problem of inadequate antibiotic therapy is noticeable in both children and adults as early as in the treatment of SARS-CoV-2 infection itself. With respect to the MIS-C treatment, antibiotic treatment should be terminated as soon as the MIS-C diagnosis is established or when negative results of the microbiological examination are obtained (Harwood *et al.*, 2021).

A limited number of studies analyzing the frequency of antibiotic application in MIS-C have been published to date, many of which analyzed groups of patients with COVID-19 and those with MIS-C.

In a multicenter analysis comprising 990 children being treated for COVID-19 and MIS-C in seven hospitals in Latin America, it was stated that antibiotic therapy was used in 24.5% of children within the whole group (MIS-C was diagnosed in 7% and was a

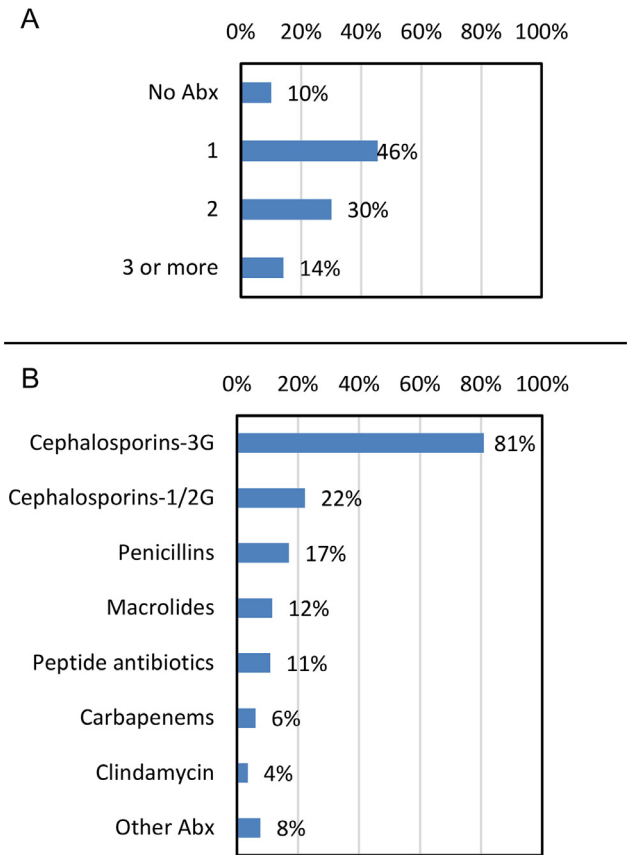

Figure 1. Use of antibiotics in children diagnosed with MIS-C in Poland, registered in the database, presented as the total number of different antibiotics used (A) and a percentage of children treated with a specific group of antibiotics (B). The total percentage in (B) does not sum up to 100% because children were treated with different combinations of listed antibiotics. Abbreviations: Abx, antibiotics; Cephalosporins-3G; third-generation cephalosporins; Cephalosporins-1/2G, first and second-generation cephalosporins.

significant factor increasing the use of antibiotics) (Yock-Corrales et al., 2021b). British authors associated with Paediatric Research Across the Midlands provided data from hospitals in the United Kingdom, which also showed a high percentage of antibiotic prescriptions for patients diagnosed with COVID-19 and MIS-C (antibiotics were used in 64% of children, almost half of whom were given broad-spectrum antibiotics, and in 84% of children diagnosed with MIS-C) (Tan *et al.*, 2021). Significantly lower use of antibiotics was noted in Italian clinics, where an antibiotic was used in only 10 of 117 children with COVID-19 or MIS-C; five of them were diagnosed with MIS-C, and one patient had sepsis (Papadopoulou *et al., 2021*). In a study of children diagnosed with PIMS-TS in the United Kingdom and Ireland, antibiotics were used in 92.9% (249/268) of children (Flood et al., 2020).

It is noteworthy that in previous years, the dilemma concerning the use of antibiotics in multisystem inflammatory syndrome was considered with respect to Kawasaki disease. In a study analyzing 140 patients with Kawasaki disease, the prevalence of antibiotic therapy before establishing the diagnosis was estimated at 54.3% (Han and Lee, 2018). In a study concerning the course and treatment of Kawasaki disease in comparison with that of MIS-C in Italy, it was stated that antibiotics were used in 72.7% of the entire analyzed group, whereby the frequency of taking them in MIS-C was significantly higher than in Kawasaki disease (73.6% vs 35.4%) (Cattalini *et al.*, 2021). The difficulties in establishing the optimal initial treatment were also highlighted by the authors of a study carried out in one of the London hospitals. In this study, a group of experts made therapeutic decisions in the case of MIS-C suspicion. All patients received broad-spectrum antibiotics (Papadopoulou *et al.*, 2021). The authors of a Turkish study, analyzing the treatment of 20 children diagnosed with MISC-C who were hospitalized in Istanbul, also reported the use of empiric antibiotic therapy in all patients (Öcal Demir *et al.*, 2021).

The majority of the cited publications did not analyze the profile of antibiotics used in detail but concentrated on other aspects of the MIS-C treatment. The authors of the cited studies stated that, given the concern over the increasing number of multidrug-resistant strains of bacteria, it is crucial to develop clear guidelines concerning the use of antibiotic therapy in both COVID-19 and MIS-C.

The previously mentioned reports are consistent with the results of our study, describing the frequency of antibiotic use in Polish patients diagnosed with MIS-C. We have shown that the majority of children diagnosed with MIS-C were given antibiotic therapy in the course of their treatment. Third-generation cephalosporins were the most commonly used antibiotics, followed by first- and second-generation cephalosporins, penicillin and macrolides, polypeptide antibiotics, and others, and as many as 14% of children were given antibiotics from three different groups.

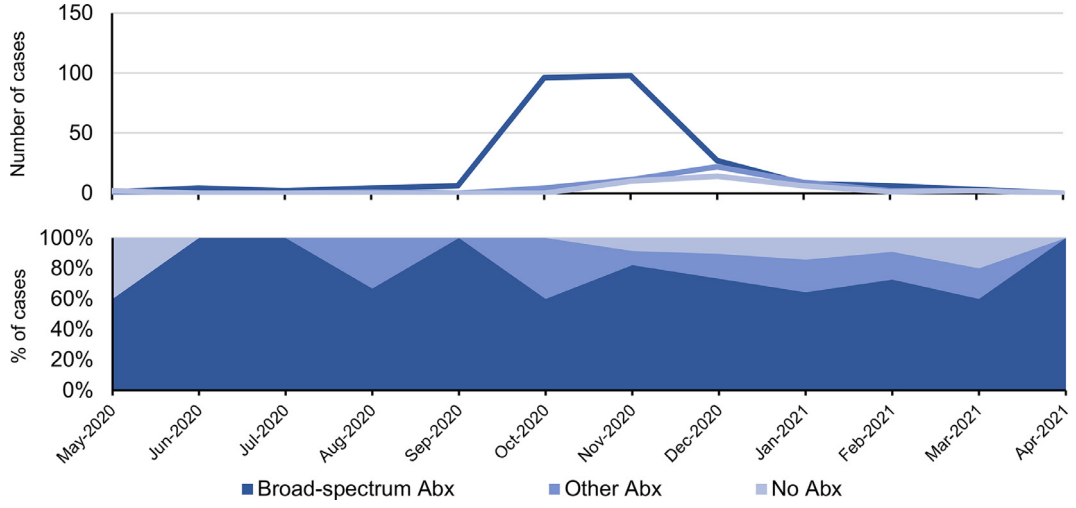

Figure 2. Children registered in the database, hospitalized with pediatric inflammatory multisystem syndrome, divided by the type of antimicrobial treatment. The upper graphs show the monthly number of cases. The lower stack area chart shows how antimicrobial treatments changed over time in relation to each other.

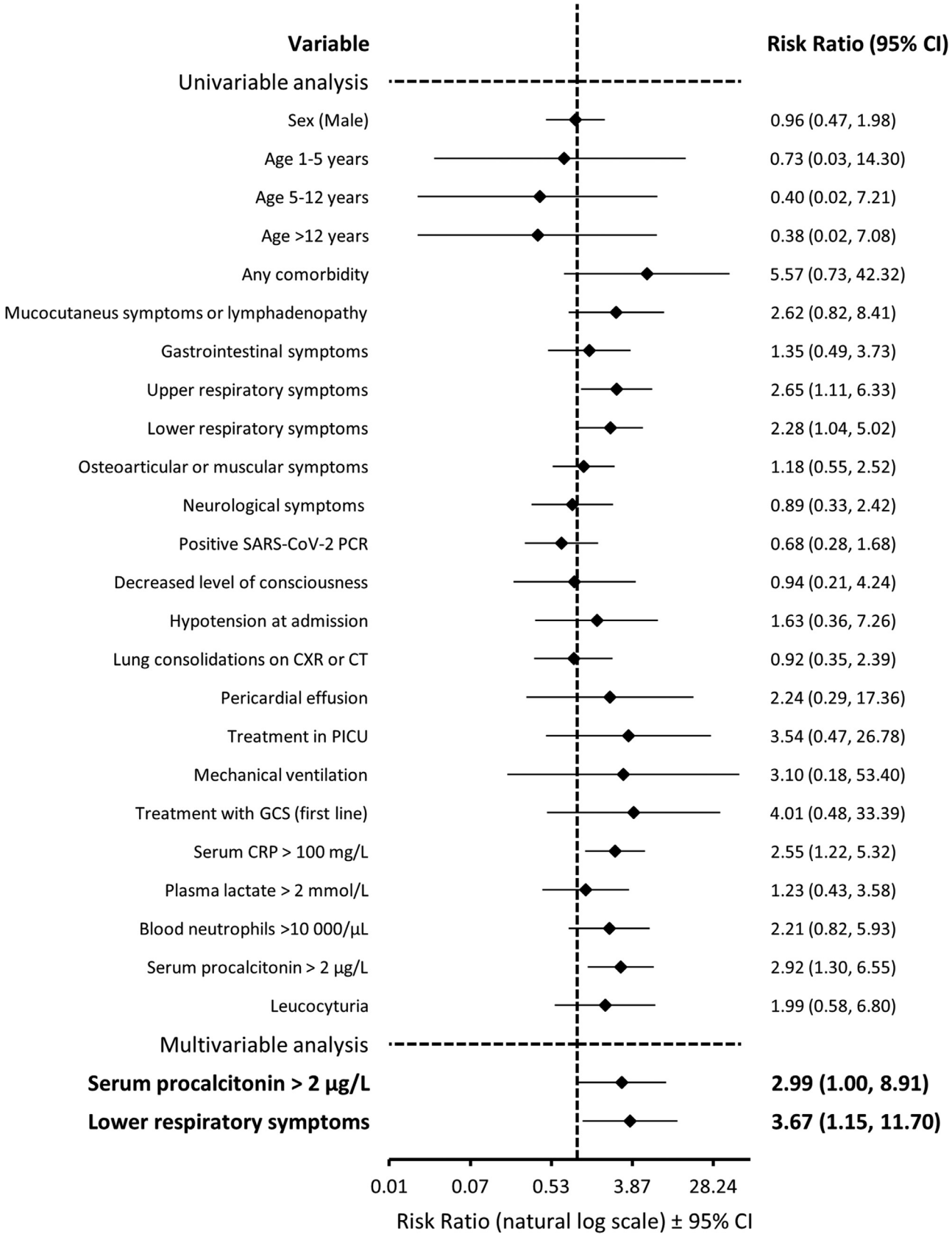

Figure 3. Binominal logistic regression analysis of variables associated with the risk of receiving antimicrobial treatment. The age-related risk was calculated with reference to age under 1 year. Abbreviations: CXR, chest X-ray; CT, computed tomography; PICU, pediatric intensive care unit; CRP, C-reactive protein.

Most of the treated children were given antibiotics for more than 3 days. The frequency of antibiotic application did not change significantly during the almost 12 months of data gathering, even after publishing and updating the Polish procedure guidelines for treating children with MIS-C (Okarska-Napierała *et al*., 2021). This observed high antibiotic use in Polish children with MIS-C, in particular, broad-spectrum antibiotics, is alarming. This observation is consistent with the reports of other authors and indicates the need to educate medical personnel about rational antibiotic therapy (Yock-Corrales et al., 2021a)

The publications we analyzed as well as the data from our study indicate an urgent need to provide the most accurate diagnostic criteria for the identification of MIS-C and to promote them widely to avoid the prolonged use of broad-spectrum antibiotics in children with this complex disease entity. It seems that because of the disease pattern and the similarity of symptoms to serious bacterial infections, it will be difficult to avoid antibiotic use in the initial phase of treatment. The emphasis should be placed on early withdrawal of antibiotics after the diagnosis is made. Databases run by expert assemblies in various countries and meta-analyses summarizing multiple studies as well as international cooperation may be particularly useful for optimization of treatment in the case of MIS-C.

Our study had some limitations. Because of the voluntary participation in the register, the number of reported MIS-C cases might have been an underestimate or biased by nonrandom sampling. However, it is important to note a major strength of this study. We included data from across 42 Polish cities; hence, our study provides a good overview of clinical practices in the management of patients with MIS-C throughout Poland.

Conclusion

Our study shows that MIS-C poses a challenge to clinicians who are faced with the decision to start, continue, or stop antimicrobial therapy. Signs of MIS-C overlap with other life-threatening conditions, for the majority of which antimicrobials are the mainstay therapy. Although bacterial infections in patients with MIS-C are uncommon, proper antimicrobial stewardship is difficult, especially when inflammatory markers are significantly elevated or lower respiratory tract infection signs are present. These complex patients should be discussed with pediatric infectious disease or microbiology specialists to ensure that likely pathogens are treated and that antimicrobials are stopped when they are no longer necessary. Our study shows that MIS-C presents a challenge for clinicians who must make the decision to start, continue, or stop antimicrobial therapy. The symptoms of MIS-C overlap with other life-threatening conditions, most of which antimicrobial drugs are the primary therapy. Although bacterial infections in patients with MIS-C are rare, proper management of antimicrobials is difficult, especially when markers of inflammation are markedly elevated or symptoms of a lower respiratory tract infection are present. These complex patients should be discussed with pediatric infectious diseases or microbiology specialists to ensure treatment of possible pathogens and the discontinuation of antimicrobials when no longer needed. It is of utmost importance that emergency pediatricians provide rational, empirical antibiotic therapy, and endeavor to terminate it early upon confirmation of MIS-C.

Conflict of interest

The authors have no competing interests to declare.

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Ethical approval

Ethical approval was obtained from the bioethics committee at Wroclaw Medical University (CWN UMW BW: 313/2020). A waiver of written informed consent was obtained with only deidentified data transmitted and analyzed.

Author contributions

KT (conception and design of the study, analysis and interpretation of the data, drafting the article, revising the article, final approval of the version to be submitted); JŁ-Z conception and design of the study, drafting the article), IP-B (conception and design of the study, drafting the article), KML (conception and design of the study, acquisition of data), MO-N (conception and design of the study, acquisition of data), ND (acquisition of data, analysis and interpretation of the data), AA (acquisition of data, analysis and interpretation of the data), CS (acquisition of data, analysis and interpretation of the data), MBK (acquisition of data, analysis and interpretation of the data), TJ (conception and design of the study), EK (conception and design of the study), LS (conception and design of the study), KM-M (conception and design of the study, analysis and interpretation of the data, drafting the article, revising the article, final approval of the version to be submitted.

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