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Antibiotic therapy in adult patients with infectious mononucleosis in the prehospital period – a single-center experience

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ABSTRACT:

Introduction: Some viral pharyngitis can mimic *streptococcal pharyngitis*. The clinical similarity of infectious mononucleosis (IM) and *streptococcal pharyngitis* makes differential diagnosis based on the clinical picture alone tricky, and patients with IM may be treated empirically with antibiotics (ATBs).

Aim: To assess prehospital ATB use in adult patients with IM admitted to the hospital. In addition, to compare antibiotic-treated individuals and patients not treated with ATBs using selected demographic, clinical, and laboratory parameters.

Materials and methods: Medical records of patients with a laboratory-confirmed IM diagnosis (2006–2023) from one center in Poland were analyzed.

Results: Out of one hundred and forty-four patients, 119 (82.6%) were treated with ATBs in the prehospital period. Many patients (n = 59) received more than one ATB. The most common choices were amoxicillin/clavulanate (46.2%), cefuroxime (27.7%), and macrolides (26.1%). One-fourth of patients had palpebral edema (more commonly in subjects treated with ATBs). The enlarged spleen was found in almost 90% of individuals with an available abdominal ultrasound assessment (113/127). A significant proportion of patients (43.1%) were given steroids (more commonly in subjects treated with ATBs).

Conclusions: More severe IM in young adults is a common cause of ATB therapy. Broad-spectrum ATBs are often prescribed. Meticulous clinical evaluation supported by simple and widely available diagnostic tools could reduce the use of antimicrobials in such a patient population.

KEYWORDS: antibiotics, antimicrobials, EBV, Epstein-Barr virus, hepatitis, infectious mononucleosis, lymphocytosis, pharyngitis, steroids, treatment

STRESZCZENIE:

Wprowadzenie: Niektóre wirusowe zapalenia gardła mogą naśladować stany zapalne wywołane paciorkowcami. Podobieństwo kliniczne mononukleozy zakaźnej (IM) i paciorkowcowego zapalenia gardła sprawia, że diagnostyka różnicowa oparta wyłącznie na obrazie klinicznym jest trudna, a pacjenci z IM mogą być poddawani antybiotykoterapii empirycznej.

Cel: Celem badania była ocena przedszpitalnego stosowania antybiotyków u dorosłych pacjentów z IM przyjętych do szpitala. Dodatkowym celem było porównanie pacjentów leczonych i pacjentów nieleczonych antybiotykami w oparciu na wybranych parametrach demograficznych, klinicznych i laboratoryjnych.

Materiały i metody: Przeanalizowano dokumentację medyczną pacjentów z potwierdzonym laboratoryjnie rozpoznaniem IM (2006–2023) z jednego ośrodka w Polsce.

ORIGINAL ARTICLE

Received: 27.02.2025
Accepted: 20.11.2025
Published: 03.03.2026

CITE THIS ARTICLE AS:
Bura M., Michalak M., Dachowska S., Haraj J., Sochacki K., Woźniak K.et al.: Antibiotic therapy in adult patients with infectious mononucleosis in the prehospital period – a single-center experience; Otolaryngol Pol 2026; 80 (2): 1–5; DOI: 10.5604/01.3001.0055.4889

AUTHORS' CONTRIBUTION:
A. Conceptualization
B. Data Curation
C. Formal Analysis
D. Funding Acquisition
E. Investigation
F. Methodology
G. Project Administration

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COMPETING INTERESTS:
The authors declare that they have no competing interests.

Wyniki: Na 144 pacjentów, 119 (82,6%) było w okresie przedszpitalnym leczonych antybiotykami. Wielu pacjentów (n = 59) otrzymywało więcej niż jeden antybiotyk. Najczęściej wybieranymi antybiotykami były amoksycylina/klawulanian (46,2%), cefuroksym (27,7%) i makrolidy (26,1%). U 1/4 pacjentów wystąpił obrzęk powiek (częściej u osób leczonych antybiotykami). Powiększenie śledziony stwierdzono u niemal 90% osób z dostępnym badaniem USG jamy brzusznej (113/127). U znacznej części pacjentów (43,1%) zastosowano sterydoterapię (częściej u osób leczonych antybiotykami).

Wnioski: Cięższy przebieg IM u młodych dorosłych jest częstą przyczyną wdrażania antybiotykoterapii. Często przepisywane są antybiotyki o szerokim spektrum działania. Skrupulatna ocena kliniczna wsparta prostymi i powszechnie dostępnymi narzędziami diagnostycznymi mogłaby ograniczyć stosowanie środków przeciwdrobnoustrojowych w takiej populacji pacjentów.

SŁOWA KLUCZOWE: antybiotyki, EBV, leczenie, limfocytoza, mononukleoza zakaźna, sterydy, środki przeciwdrobnoustrojowe, wirus Epsteina-Barr, zapalenie gardła, zapalenie wątroby

ABBREVIATIONS

ALAT – alanine aminotransferase
AST – aspartate aminotransferase
ATB – antibiotic
CI – confidence interval
EBV – Epstein-Barr virus
IM – infectious mononucleosis
ITP – idiopathic thrombocytopenic purpura
LR– – negative likelihood ratio
LR+ – positive likelihood ratio
LYMPH – lymphocytes
OR – odds ratio
PLT – platelets
RADT – rapid antigen diagnostic test
RSV – respiratory syncytial virus
TMP-SMX – trimethoprim-sulfamethoxazole
VCA – viral capsid antigen
WBC – white blood cells

INTRODUCTION

Respiratory tract infections are among the most common reasons for patient visits to primary care practice and emergency departments. Pharyngitis is a significant part of them. It is usually caused by viruses. The most common etiologies of pharyngitis include adenoviruses, coronaviruses, enteroviruses, human metapneumovirus, influenza and parainfluenza viruses, respiratory syncytial virus (RSV), and rhinoviruses [1]. Infections with viruses of the *Herpesviridae* family or HIV are less common. Some of them may imitate the bacterial (*streptococcal*) etiology of pharyngitis. Such causes include primary infection with the Epstein-Barr virus (EBV), one of the clinical forms of which is infectious mononucleosis (IM).

EBV infections are prevalent. They most often occur in childhood when they are asymptomatic or nonspecific. In children, a significant minority of these infections cause classic IM [2]. In contrast, in adolescents and young adults, most primary EBV infections cause typical IM, with fever, pharyngitis (or pharyngotonsillitis), lymphadenopathy, headache, and potentially long-lasting fatigue. Some patients experience the Hoagland sign (palpebral edema), palatal petechiae, and skin eruptions. Common laboratory abnormalities in IM include lymphocytosis on a complete blood count with differential, the presence of atypical lymphocytes (LYMPH), mild hepatitis (elevated transaminases), and the presence of heterophile antibodies (less common in young children) and/or EBV-specific anti-VCA (viral capsid antigen) IgM antibodies. Abdominal ultrasound shows splenomegaly (and much less common enlarged liver); it can sometimes be identified during abdominal palpation.

The clinical similarity of IM and *streptococcal pharyngitis* (fever, cervical lymphadenopathy, pharyngeal exudates, and palatal petechiae) makes differential diagnosis of these two entities based on the clinical picture alone tricky [2, 3]. The above facts mean that patients with IM may be treated empirically with antibiotics (ATBs).

AIM

The main objective of this study was to assess prehospital ATB use in adult patients with IM admitted to the hospital. In addition, antibiotic-treated individuals and patients not treated with ATBs were compared using selected demographic, clinical, and laboratory parameters.

MATERIALS AND METHODS

Medical records of all patients hospitalized in the Department of Infectious Diseases at Józef Struś Multidisciplinary Municipal Hospital in Poznań (Greater Poland Region) during eighteen years (2006–2023) were analyzed. There were no structured criteria for hospitalization. The decision regarding hospitalization was made by the physician assessing the patient in the emergency unit of the Department of Infectious Diseases.

Only patients with a laboratory-confirmed IM diagnosis were included in the study. IM was defined as the presence of a clinical triad of fever, pharyngitis, and cervical lymphadenopathy, and the positivity for anti-VCA IgM and/or heterophile antibodies (assays of different manufacturers, depending on period). Some other routine laboratory data (complete blood count with differential and transaminase levels) and abdominal ultrasound (for spleen size assessment) were also considered. All patients tested negative for HIV infection (HIV Ag/Ab assay), anti-CMV IgM, and (in case of

Tab. I. A list of antimicrobials taken by 119 out of 144 patients in the prehospital period.

ANTIMICROBIAL MEDICATION	n (%)*
Amoxicillin	14/119 (11.8%)
Amoxicillin/clavulanate	55/119 (46.2%)
Azithromycin	14/119 (11.8%)
Cefuroxim	33/119 (27.7%)
Doxycycline	8/119 (6.7%)
Clarithromycin	13/111 119 (10.9%)
Clindamycin	19/119 (16%)
Penicillin V	12/119 (10.1%)
Cefadroxil	6/119 (5%)
TMP-SMX	5/119 (4.2%)
Metronidazole	5/119 (4.2%)
#Other antimicrobial	13/119 (10.9%)

TMP-SMX – trimethoprim-sulfamethoxazole.

*59 patients received more than one antibacterial medication; therefore, the sum of n and % exceeds 119 and 100%, respectively.

#Other antimicrobials include: gentamicin (n = 3), spiramycin (n = 3), cefaclor (n = 2), ceftriaxone (n = 1), roxithromycin (n = 1), ciprofloxacin (n = 1), levofloxacin (n = 1), and acyclovir (n = 1).

increased transaminases) for primary hepatotropic viruses (anti-HAV IgM, HBsAg ±anti-HBc IgM, and anti-HCV) (Architect or Alinity platform, Abbott).

Ethics

It was a retrospective, non-interventional study; therefore, the Bioethics Committee approval was not required.

Statistics

Interval data were presented as medians and interquartile ranges, Me [Q1–Q3], while categorical data were presented as frequencies and corresponding percentages. Comparisons between groups receiving and not receiving ATBs were performed using the Mann-Whitney test, as the variables did not follow a normal distribution (Shapiro-Wilk test). When comparing more than two groups (no ATBs, one ATB, and more than one ATB), the Kruskal-Wallis test was used. For significant differences, Dunn's post-hoc tests with the Benjamini-Hochberg correction for multiple comparisons were applied. Categorical variables were compared using the Chi-square independence test, and in cases where Cochran's conditions were not met, Fisher's exact test was used. All tests were considered significant at $p<0.05$. Statistical analysis was performed using PQStat Software (2022), PQStat v.1.8.4.164.

RESULTS

One hundred and forty-four eligible patients (88 men and 56 women) aged 18-40 (median 21 years; Q1–Q3: 19–23 years) were identified. The duration of their hospitalization ranged from 2 to 43 days (median: 9 days; Q1–Q3: 6–14 days).

There were no significant differences in the seasonality of hospitalization of those persons with IM: January–March *vs.* April–June *vs.* July–September *vs.* October–December, that is, n = 35 (24.3%), n = 43 (29.9%), n = 36 (25%), n = 30 (28.8%), respectively ($p>0.05$ for all comparisons).

Tab. II. Transaminase levels and hematologic parameters in the study participants.

PARAMETER*	VALUES
ALAT [IU/L], n = 144	
Range; median (Q1–Q3)	15–1055; 184.5 (114.7–337.2)
ALAT >40 IU/L, n (%)	136/144 (94.4%)
ALAT >80 IU/L, n (%)	123/144 (85.4%)
ALAT >120 IU/L, n (%)	104 (72.2%)
AST [IU/L], n = 143	
Range; median (Q1–Q3)	17–816; 124 (76–213)
AST >40 IU/L, n (%)	132 (92.3%)
AST >80 IU/L, n (%)	103 (72%)
AST >120 IU/L, n (%)	74 (51.7%)
WBC [G/L], n = 144	
Range; median (Q1–Q3)	5.2–40.5; 13.7 (11.2–16.2)
WBC >10 G/L, n (%)	119 (82.6%)
WBC >20 G/L, n (%)	16 (11.1%)
LYMPH [% of WBC], n = 139	
Range; median (Q1–Q3)	47–86; 65.4 (59–72.1)
LYMPH >45%, n (%)	139 (100%)
PLT [G/L], n = 144	
Range; median (Q1–Q3)	19–389; 186 (150–227)
PLT <130 G/L, n (%)	23 (16%)
PLT <100 G/L, n (%)	10 (6.9%)
PLT <50 G/L, n (%)	2 (1.4%)

*Reference ranges for ALAT: <40 IU/L, for AST: 4–40 IU/L, for WBC: 4–10 G/L, for LYMPH: 25–45% of WBC, for PLT: 130–400 G/L.
ALAT – alanine aminotransferase; AST – aspartate aminotransferase; WBC – white blood cells; LYMPH – lymphocytes; PLT – platelets.

One hundred and nineteen patients (82.6%) were treated with ATBs in the prehospital period. Almost half of them (59/119, 49.6%) received more than one antibacterial drug.

Tab. I. shows the antimicrobials this study participants received prior to hospitalization.

Selected laboratory parameters of patients with IM are summarized in Tab. II.

Palpebral edema (the Hoagland sign) was identified in 37 patients (25.7%). Data on spleen size were available in 127 cases (88.2%). Splenic enlargement (defined as the length of the spleen exceeding 120 mm) was found in 113 of these patients (89%). In 14 cases, the size of the organ was normal. One patient had a splenectomy in the past due to idiopathic thrombocytopenic purpura (ITP).

Out of the 144 patients, 62 (43.1%) were treated with glucocorticoids (hydrocortisone or dexamethasone, different duration of treatment, and different dosages of glucocorticoids). The indication for the use of glucocorticoids in this study subjects was airway obstruction,

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Tab. III. A comparison of people with IM not treated with antibiotics, those receiving one antibiotic, and patients treated with more than one antibiotic during the prehospital period.

	NO ATB n = 25	ONE ATB n= 60	MORE THAN ONE ATB n = 59
Men / Women	16 (64%) / 9	36 (60%) / 24	36 (61%) / 23
Median age (Q1–Q3) [years]	21 (19–23)	20 (19–23)	21 (19–24)
Median WBC, white blood cells [G/L]	13.7 (11.5–16.2)	14.1 (10.9–16.8)	13.3 (11.2–16.3)
Median LYMPH (Q1–Q3) [% of WBC]	66.6 (59.8–74.2)	65.1 (58.6–72.2)	65.2 (58.9–71.6)
Median PLT (Q1–Q3) [G/L]	183 (127–214)	186 (141.25–214)	195 (158.5–238)
Median ALAT (Q1–Q3) [U/L]	323 (167–541.5)[a,b]	172.25 (109–322)[a]	183 (124–297)[b]
Median AST (Q1–Q3) [U/L]	179 (114–286)[c]	127 (73.8–233.3)	108 (68.5–163.8)[c]
Enlarged spleen, n (%)	132 (92.3%)	46/54 (85.2%)	47/51 (92.2%)
No data[#]	3	6	8[#]
Glucocorticoids, n (%)	4/25 (16%)[d,e]	24/60 (40%)[d,*]	34/59 (57.6%)[e,*]
Palpebral edema, n (%)	1/25 (4%)[f,g]	18/60 (30%)[f]	18/59 (30.5%)[g]
Median duration of hospitalization (Q1–Q3) [days]	7 (6–10)[h]	7 (5–10)[i]	12 (7.5–14)[h,i]

ATB – antibiotic; ALAT – alanine aminotransferase; AST – aspartate aminotransferase; WBC – white blood cells; LYMPH – lymphocytes; PLT – platelets.
[a-i] – Values followed by the same letters differ significantly at $p < 0.05$;
[*] – $p = 0.0544$;
[#] – including one patient after splenectomy.

most often resulting in significant sleeping problems due to breathing difficulties and/or significant problems with food intake.

A comparison of subjects treated and not treated with ATBs prior to their hospital admission is presented in Tab. III.

DISCUSSION

The vast majority of hospitalized patients with IM were treated with ATBs in the pre-hospital period. Only 17.4% of them did not receive any antibacterial drug. This is most likely because primary care physicians and other practitioners suspected bacterial pharyngitis in those persons with a more severe course of IM. The more severe course of IM in the participants of this study is indicated by the fact that they were hospitalized and by the frequent use of glucocorticoids for symptomatic treatment (43.1%) in the hospital. Several factors should be noted here. First, differentiating IM from bacterial (in practice most often *streptococcal*) pharyngitis based only on the clinical picture can be difficult, especially in the early stage of the disease [4]. Second, in Poland, at the time of this study, *streptococcal* rapid antigen diagnostic tests (RADTs) were rarely performed in patients with pharyngitis, while other useful laboratory tests, apart from being associated with additional costs, require more time. Third, the patient's expectation of receiving ATBs may have also played a role.

The widespread use of antibacterials in patients with IM has also been reported by other authors. In a German study of family physicians' practices, the frequency of ATB therapy in patients with IM was almost half lower than in our analysis, but still high (319/731, 43.6%) [4]. In a 15-year analysis by Danish authors from the otolaryngology department of 257 patients with IM and acute tonsillitis and/or peritonsillar abscess, a similar frequency of ATB therapy (45%) was found in the prehospital period [5], and in a study from Spain covering a period of 23 years, it was 51.3% [6].

The above data indicate that diagnostic difficulties with the correct determination of the viral etiology of pharyngitis in the case of IM are common in everyday practice.

However, another phenomenon is even more disturbing. Namely, the profile of the antibacterials used and treating patients with multiple ATBs instead of deepening the diagnosis. Unlike in the aforementioned study from Denmark [5], antimicrobials with a narrow antibacterial effect were rarely used (amoxicillin/clavulanate combination was the most common choice). In our patients, penicillin V (phenoxymethylpenicillin) was given to only 10% of them (*vs.* 86% in the analysis by Danstrup et al.) [5]. Amoxicillin or cefadroxil were also rarely used. Moreover, taking into account the knowledge of the epidemiology and etiology of pharyngitis (the most common cause justifying ATB therapy is *streptococci*), some of the therapeutic choices for the treatment of pharyngitis were surprising. The above situation is primarily unfavorable from an epidemiological point of view as it promotes the development of ATB resistance in potentially pathogenic bacteria. In addition, it results in an increased risk of adverse effects and generates additional, unnecessary costs.

Spleen enlargement was often found by ultrasound (90%), and eyelid edema was observed in a quarter of patients (interestingly, significantly more often in those treated with ATBs).

It should be noted that there is a significant difference in the frequency of spleen enlargement detected on physical examination (from less than 10% to 65%) *versus* ultrasound evaluation (even in all patients) [2, 7–9], and that rapid access to abdominal ultrasound is often limited in primary care settings. The incidence of eyelid edema in patients with IM is difficult to estimate. Small studies show that it can reach 34–54% [10, 11].

It should be emphasized that in patients with pharyngitis, enlargement of the spleen (and/or liver) and swelling of the eyelids

are clinical abnormalities firmly against a bacterial etiology of this clinical syndrome and suggestive of IM.

It is worth noting that in one-fifth of the patients, there was no leukocytosis, while in all study participants with an available blood count differential, relative lymphocytosis (>45% of white blood cells [WBC]) was found. This is an important practical hint in differentiating IM-related pharyngitis from the bacterial etiology of the observed clinical picture.

A recently published meta-analysis clearly shows that hematologic abnormalities are more accurate in establishing a diagnosis of IM than symptoms and signs [12]. For the parameters assessed in our study (i.e., leukocytosis >10 G/L and lymphocytosis >45%) positive likelihood ratio (LR+), negative likelihood ratio (LR–), and diagnostic odds ratio (OR) (and their 95% confidence interval [CI]) (for IM) found in that meta-analysis were 2.55 (1.58–3.99), 0.68 (0.56–0.82), and 3.85 (1.93–7.01) for leukocytosis >10 G/L and 9.46 (6.76–13.1), 0.38 (0.34–0.42), and 25.2 (16.5–36.8) for lymphocytosis >45%, respectively.

Increased transaminase activity was found more commonly than leukocytosis. In other studies of this type, such biochemical abnormalities were observed less frequently – in about 80% [13], or – as in a recently published systematic review – in about 60% of patients with IM [9]. We think that the higher frequency of hepatitis in our patients may be due to the interaction of three factors. First, our analysis includes more severely ill people with IM who were hospitalized. Second, a significant percentage of them were treated with ATBs such as amoxicillin/clavulanate, azithromycin, clindamycin, and doxycycline, which may induce hepatitis. Finally, symptomatic treatment in the pre-hospital period (e.g., analgesics and anti-inflammatory drugs) could have contributed to abnormal liver function tests to some extent.

In our opinion, higher transaminase levels in people not treated with ATBs indicate that they were probably hospitalized earlier in the natural course of primary EBV infection (those who were treated with antimicrobials before admission to the hospital were more likely to have already had the peak of transaminase activity).

Our study has several limitations.

First of all, it applies only to hospitalized patients with IM, that is, those most seriously ill. Therefore, the observations from our analysis may not describe all adult patients with primary EBV infection presenting as IM. Secondly, it is a retrospective survey from only one center. Third, there is no data on the duration of symptoms before hospitalization. Four, there were no structured criteria for hospitalization of IM patients. Finally, the detailed clinical picture and other laboratory abnormalities of the participants in this study are incomplete. However, the study presented here included the most common symptoms, hematological and biochemical tests, and imaging useful in diagnosing IM.

Despite the above-mentioned limitations, we believe this analysis provides some valuable information for practitioners.

CONCLUSIONS

Overall, this study shows that more severe IM in young adults is a common cause of unnecessary ATB therapy. *Streptococcal* RADT, lymphocytosis, elevated transaminase activity, and ultrasound-confirmed spleen enlargement are crucial in the differential diagnosis when there is limited access to rapid serological testing for EBV infection. Accurate clinical evaluation supported by simple and widely available diagnostic tools could reduce the proportion of antimicrobial use in such a patient population.

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