

Incidence of Rash After Amoxicillin Treatment in Children With Infectious Mononucleosis



WHAT'S KNOWN ON THIS SUBJECT: Antibiotics-induced rash in Epstein-Barr virus acute infectious mononucleosis, especially the aminopenicillins-induced type, was first described during the 1960s, with a reported incidence of 80% to 100%. This phenomenon was not further investigated but is well-established in pediatric textbooks.



WHAT THIS STUDY ADDS: The main observation of this study is that rash induced by amoxicillin in confirmed Epstein-Barr virus acute infectious mononucleosis was found at a rate of ~30%, which is much lower than previously reported.

abstract

BACKGROUND: "Ampicillin rash," a phenomenon unique to patients with Epstein-Barr virus acute infectious mononucleosis (AIM) treated with ampicillin, was first reported in the 1960s. The incidence was estimated as being between 80% and 100%, and the figures have not been reviewed since those first accounts. We sought to establish the current incidence of rash associated with antibiotic treatment among children with AIM.

METHODS: A retrospective study of all hospitalized children diagnosed as having AIM based upon positive Epstein-Barr virus serology in 2 pediatric tertiary medical centers in Israel.

RESULTS: Of the 238 children who met the study entry criteria during the study period, 173 were treated with antibiotics. Fifty-seven (32.9%) of the subjects treated with antibiotics had a rash during their illness compared with 15 (23.1%) in untreated patients ($P = .156$; not significant). Amoxicillin was associated with the highest incidence of antibiotic-induced rash occurrence (29.5%, 95% confidence interval: 18.52–42.57), but significantly lower than the 90% rate reported for ampicillin in past studies. Age, gender, ethnicity, and atopic or allergic history were not associated with the development of rash after antibiotic exposure. Among the laboratory data, only increased white blood cell counts were more prevalent among subjects who did not develop an antibiotic-induced rash.

CONCLUSIONS: The incidence of rash in pediatric patients with AIM after treatment with the current oral aminopenicillin (amoxicillin) is much lower than originally reported. *Pediatrics* 2013;131:e1424–e1427

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KEY WORDS

infectious mononucleosis, antibiotic treatment, ampicillin/amoxicillin rash, clinical and laboratory disease characteristics

ABBREVIATIONS

AIM—acute infectious mononucleosis

EBV—Epstein-Barr virus

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Dr Reif conceptualized and designed the study, critically reviewed the article, and approved the final article as submitted; Dr Chovel-Sella carried out the main data collection and analysis, drafted the initial article, and approved the final article as submitted; Dr Ben Tov supervised and contributed to acquisition of the data and the statistical analysis, reviewed and revised the article, and approved the final article as submitted; and Drs Mor, Lahav, Ms Rudich, and Dr Paret contributed to acquisition of the data, reviewed the article, and gave final approval for the article to be published.

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The Epstein-Barr virus (EBV) is a widespread human γ -herpes virus that infects over 95% of the world population by adulthood.¹ Primary infection, usually asymptomatic in children,² is commonly associated with acute infectious mononucleosis (AIM) in adolescents and young adults. It is a benign self-limiting lymphoproliferative disease involving the typical triad of fever, pharyngeal inflammation, and cervical lymphadenopathy.³ Several serologic tests are available for the detection of acute EBV infection, including heterophile antibodies, early antigens, and immunoglobulin M viral capsid antigens.⁴ The latter is considered definitive and is frequently detected at disease presentation, disappearing within 4 to 8 weeks.¹ A rash, which can be macular, petechial, scarlatiniform, urticarial, or erythema multiforme, is present in 3% to 15% of patients with AIM.⁵ The typical eruption is morbilliform, involving mainly the trunk and sparing the extremities.⁶ It emerges during the first days of the disease and disappears within 1 to 6 days.⁷

In the 1960s, Patel et al,⁸ Pullen et al,⁹ and Brown et al¹⁰ drew attention to a unique phenomenon in pediatric patients with EBV-related AIM, the “ampicillin rash.” As many as 90% to 100% of those children developed a rash upon being treated with ampicillin. This rash can be distinguished from the spontaneous eruption associated with AIM in that the former is more severe and generalized, involving the face, neck, trunk, extremities, and occasionally the palms and soles.⁷ Other antibiotics, such as penicillin (14%) and tetracyclines (9%), had also been linked to a similar rash, however, with a much lower incidence.^{8–10} No consistent relation has been shown for antibiotic dose, duration of treatment, atopic history, or previous exposure to penicillin. The incidence of the rash has not been reviewed since these studies

that were conducted in the 1960s. The Nelson Textbook of Pediatrics⁵ quotes that the incidence of ampicillin or amoxicillin rash in AIM is up to 80%.

Our current study was designed to verify the current incidence of antibiotic-associated rash among children with AIM treated with antibiotics. We also looked for clinical differences between children with and without an antibiotic-induced rash.

METHODS

Setting

We conducted a retrospective study of all children hospitalized in 2 large tertiary medical centers in Israel with a diagnosis of AIM attributed to EBV as confirmed by serology. Data for 1999–2009 were collected from the “Dana-Dwek” Children’s Hospital, Tel-Aviv Medical Center, and for 2002–2009 from The Edmond and Lily Safra Children’s Hospital, Chaim Sheba Medical Center. The study was reviewed and approved by the local institutional review board of each institution.

Subjects

Eligible study participants were children aged 0 to 18 years diagnosed as having AIM and a positive serology for immunoglobulin M viral capsid antigens. Children with congenital immunodeficiency, malignancy, or lacking adequate clinical follow-up were excluded. Clinical and demographic parameters, including age, gender, history of chronic disease, drug sensitivity, presenting symptoms, signs on physical examination, antibiotic treatment, and laboratory results, were extracted from personal hospitalization records for all subjects. A rash was attributed to antibiotic treatment if it developed after administration of the first dose and up to 48 hours after treatment ended. To compare total rash incidence, we included all children who developed a rash during their illness

either before or after antibiotic exposure. These children were included in the analysis of overall rash development, but they were not included in the analysis of antibiotic-associated rash.

Statistical Analyses

All statistical analyses were conducted by using SPSS 15.0 (SPSS Inc, Chicago, IL). The χ^2 test for categorical variables and the *t* test analysis of variance for continuous variables were performed to determine significant differences between study groups. The McNemar test was used to compare the studied antibiotics’ association with rash. The level of significance was set at 5%.

RESULTS

During the study period, a total of 273 children were diagnosed as having AIM with positive EBV serology, and 238 of them met the inclusion criteria. The average age of the cohort was 6.13 ± 5.17 years, and there were 106 (44.54%) boys. Forty-two children in the study population (17.65%) had an atopic history, including asthma, food allergies, atopic dermatitis, or allergic rhinitis.

We identified 173 patients who were treated with antibiotics during the course of their disease, and the remaining 65 were not. Fifty-seven (32.9%) of the treated patients developed a rash, compared with 15 (23.1%) of the untreated patients ($P = .156$, not significant). It should be noted that there were only 41 (23.6%) cases of an antibiotic-induced rash as defined by study protocol. The highest incidence of an antibiotic-induced rash was associated with amoxicillin (29.5%, 95% confidence interval: 18.52–42.57). All other antibiotics were associated with a lower rash incidence (Table 1). Comparison of amoxicillin with other included antibiotics revealed that the incidence of a rash after treatment with

amoxicillin was significantly higher than after treatment with penicillin (8%), with amoxicillin and clavulanate (15%), with cephalosporins (15%), or with macrolides (9%) ($P < .001$). A significantly higher overall rate of rash was observed in subjects treated with amoxicillin compared with subjects not treated by any antibiotics (39.3% vs 23.1%, $P < .05$).

Evaluation of clinical and laboratory characteristics in antibiotic-treated patients who did and did not have an antibiotic-induced rash revealed that an enlargement of submandibular lymph nodes on physical examination (50.0% vs 31.7%, $P = .04$), dysphagia (60.6% vs 41.46%, $P = .031$), and higher white blood cell counts (21 428 vs 13 758, $P = .013$) were more prevalent among subjects who did not develop an antibiotic-induced rash compared with those who did. There were no significant differences in age, gender, ethnicity, atopic background, known allergies, and other laboratory findings between these 2 subgroups.

DISCUSSION

The incidence of a rash induced by amoxicillin in our study population was 29.5%, compared with a rate of 23% that we observed in patients with AIM not

treated with any antibiotics and a rate of 5% to 10% associated with regular ampicillin/amoxicillin use in the general population.^{11–13} Our main finding is that an amoxicillin-induced rash is significantly lower than the 90% incidence rate reported in the original studies on ampicillin rash^{8–10} (Table 2). However, it should be noted that the incidence of rash among our untreated patients was slightly higher than that typically associated with AIM,⁵ possibly reflecting a selection bias due to more complicated disease presentations in hospitalized children.

Patel et al⁸ reported that all 38 children diagnosed with AIM without a previous history of allergy developed a rash in association with ampicillin. They also observed a relationship between dosage and duration of ampicillin treatment with rash severity. In another report published in 1967, Pullen et al⁹ described a rash in 18 of 19 adolescent patients with AIM treated with ampicillin. In the same year, Brown et al¹⁰ reported their results revealing a 69% rate of rash in university students treated with ampicillin. They have also described higher rash incidence in patients treated with penicillin or tetracycline compared with their untreated colleagues although to a much

lesser extent than those treated with ampicillin (23%).

The pathogenesis behind the aminopenicillin-associated rash has yet to be fully elucidated. Some authors have suggested that it is an allergic reaction, whereas others have proposed a transient immunostimulation by the EBV. Positive lymphocyte transformation tests,¹⁴ drug-specific IgE antibodies, and positive skin prick and patch tests¹⁵ all support an allergic etiology among patients who develop this rash. On the other hand, several investigators have shown that ampicillin can be readministered after viral resolution without any adverse effect,^{16,17} suggesting a toxic etiology. A prospective study of 933 patients with infectious disease documented a high incidence of ampicillin-induced rash in patients with viral diseases, particularly AIM, and there was no correlation with previous use of penicillin or an atopic family or personal history.¹⁸ The latter is in line with the findings of the current study.

Previous cohort studies of antibiotic-induced rash in patients with AIM investigated ampicillin, with little attention having been given to amoxicillin. An association of the development of a rash with the use of amoxicillin has been mentioned in only a few case reports, and the rash was similar in appearance to that of ampicillin, possibly due to their chemical similarity.^{6,7} In spite of their similar structure, however, there are differences between the 2 compounds that may partially explain our observation of a decreased incidence in the rash among our

TABLE 1 Rate of Antibiotic-induced Rash by Antibiotic Type

Antibiotic	Total Treated	Antibiotic-Induced Rash	Rate, %	95% Confidence Interval
Penicillin	35	3	8.57	1.80–23.06
Amoxicillin	61	18	29.51	18.52–42.57
Amoxicillin + clavulanate	45	7	15.56	6.49–29.46
Cephalosporins	65	10	15.38	7.63–26.48
Macrolides	33	3	9.09	1.92–24.33

TABLE 2 The Original Studies on Ampicillin Rash

Author(s)	Year	Subjects	Methods	Infectious Mononucleosis Definition	Rate of Ampicillin Rash	Rate of Rash in Untreated Patients
Patel ⁸	1967	38 hospitalized patients	Retrospective analysis	Diagnosis at discharge	100% (13/13)	9% (1/11)
Pullen et al ⁹	1967	184 hospitalized patients	Retrospective analysis	Typical blood count or positive Paul-Bunnell test	95% (18/19)	16% (10/63)
Brown and Kanwar ¹⁰	1967	150 hospitalized patients	Retrospective analysis	Typical blood count or positive Paul-Bunnell test	69% (20/29)	13% (3/24)

patients. For example, the absorption and urinary excretion of amoxicillin have been shown to be better than ampicillin.¹⁹ We therefore believe that our results, based solely on the use of amoxicillin, can be taken to reveal that the assumption that both antibiotics are similar in their propensity for rash may not be valid.

A plausible alternative explanation for our finding could be that ours was a homogenous population with a lower propensity toward rash development. Our study cohort is representative of the Israeli population, which is heterogeneous insofar as Israel is an immigration country mainly from European, North African, and Arab countries. As such, the ethnicity of our study population is mainly Ashkenazi and

Sephardic Jews, and includes some non-Jewish patients of Arabic origin as well. We encourage others to carry out similar studies in other ethnic and racial populations to validate our findings.

A second objective of the current study was to identify clinical markers associated with antibiotic-induced rash. We examined a large range of intrinsic demographic and clinical parameters (age, gender, atopic background, fever peak and duration, disease symptoms, physical signs, and laboratory values) and identified a significant ($P < .05$) association only for a few parameters, including complaints of dysphagia or sore throat, submandibular lymphadenopathy, and higher leukocyte counts, all of which were more prevalent in the children who did not develop

an antibiotic-induced rash. We cannot offer a reasonable biological explanation for these observations.

CONCLUSIONS

The main important finding of the current study indicates that the incidence of amoxicillin-induced rash in pediatric patients with EBV infection is significantly lower than previously reported.

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