

The Ampicillin Rash as a Diagnostic and Management Problem: Case Reports and Literature Review

John P. Geyman, MD, and Steven Erickson, RPh
Seattle, Washington

Ampicillin is the most commonly prescribed antibiotic in the United States, and causes skin reactions in five to ten percent of patient populations. These reactions are considerably more frequent in patients with a viral illness, infectious mononucleosis, and lymphocytic leukemia. Skin reactions to ampicillin are usually of two types: a maculopapular rash in about two thirds of cases, and urticaria in about one third of cases. There is strong evidence that the maculopapular rash is a benign, nonallergic phenomenon.

Patients with the maculopapular ampicillin rash are often incorrectly labeled as allergic to ampicillin/penicillin. Ampicillin can be continued and administered again in the future in these patients, and this kind of skin reaction resolves spontaneously in a few days without sequelae. Skin tests are neither required nor recommended to document the nonallergic basis of the maculopapular ampicillin rash.

Since ampicillin was introduced into medical practice in 1961, it has become the most commonly prescribed antibiotic in the United States, and is second only to Valium in frequency of use according to a national prescription survey.¹ Skin reactions to this drug have been reported in five to

ten percent of patient populations, and occur with considerably greater frequency in patients with a viral illness, infectious mononucleosis, or lymphocytic leukemia.²⁻⁴ These skin reactions are usually of two types: a maculopapular rash in about two thirds of cases, and urticaria angioedema in about one third of affected patients.⁵ Although the mechanism for the maculopapular rash remains unclear, there is strong evidence that the rash is not on an immunologic or allergic basis.⁵⁻¹¹ Despite the fact that the maculopapular rash has been widely described and documented in the medical literature as a benign, nonallergic

From the Department of Family Medicine, School of Medicine, University of Washington, Seattle, Washington. Requests for reprints should be addressed to Dr. John P. Geyman, Department of Family Medicine RF-30, University of Washington, Seattle, WA 98195.

reaction to ampicillin, there is evidence (particularly in the pediatric literature¹²) that many physicians unnecessarily consider such patients allergic to ampicillin and other penicillins, an unwarranted lifetime label with unfortunate implications.

In view of these problems and the lack of attention to them in the family practice literature, an effort was made to learn how patients are managed with ampicillin rash at the Family Medical Center at the University of Washington. The purpose of this paper is fourfold: (1) to present brief case reports of patients seen with maculopapular rash secondary to ampicillin therapy; (2) to review the literature concerning the incidence, etiology, diagnosis, and management of ampicillin-related skin rashes; (3) to discuss the implications of inappropriate management of the maculopapular rash as an allergic phenomenon; and (4) to suggest effective approaches to the diagnosis and management of this common problem which can be used by family physicians in everyday clinical practice.

Case Reports

In order to readily identify patients in the Family Medical Center who were given ampicillin, charts were retrieved and reviewed for children treated for otitis media during the previous two years. One hundred charts were reviewed for children receiving ampicillin. Four of these patients were found to have had skin rash appearing during ampicillin therapy. Each patient was seen by a different resident.

Since the clinical picture of each of the four patients was almost identical, these patients can be considered collectively. All four patients were between one and two years of age and presented with otitis media, presumably on a bacterial basis, without other associated illnesses. None of the patients had known allergic diathesis or history of allergic reactions to any drug. Two of the four had previously received ampicillin without incident for treatment of acute otitis media. Each of the patients was given a ten-day course of oral am-

picillin, and each developed a maculopapular skin rash after four to eight days of treatment.

In each instance, the physician became aware of the skin rash by telephone, and managed the problem without seeing the patient. In all cases, ampicillin was discontinued, another antibiotic was substituted (usually erythromycin), and the patient was labeled "Allergic to Ampicillin/Penicillin." No further follow-up was carried out for the acute problem as the rash cleared spontaneously in several days without specific therapy, and the otitis media resolved on alternative drug therapy. In one case, ampicillin was given during a subsequent bout of otitis media, and the patient did not develop a rash.

Literature Review

Incidence

The overall incidence of cutaneous reactions to ampicillin ranges from five to ten percent in most studies of patient populations without associated illness or drugs known to increase this incidence.^{2,3,10} The great majority of ampicillin rashes are of the maculopapular type. Urticarial skin rashes secondary to ampicillin therapy occurred in approximately one percent of all patients in two large series (each with 400 patients receiving ampicillin).^{9,13} The incidence of true penicillin allergy, as suggested by urticarial rashes, approximates that of other preparations of orally administered penicillin.¹⁴

The incidence of ampicillin rash is greatly increased in patients with infectious mononucleosis. Several studies have shown that a skin rash develops after the administration of ampicillin in more than 90 percent of cases in the presence of infectious mononucleosis.¹⁵⁻¹⁸

An increased incidence of ampicillin rash has also been documented in females and in association with acute viral respiratory tract infections.^{7,11} For example, in a prospective study in England of 933 patients being treated with ampicillin, the incidence of skin rash was 13.4 percent for females

(3.7 percent for males), and 16.6 percent in patients with proved viral respiratory tract infection (7.3 percent overall incidence of rash in all patients studied).⁷ No correlation was established in that study between an ampicillin rash and a history of previous penicillin treatment, skin disease, or atopic illness in the patient or his/her family.

A high incidence (90 percent) of skin rash has also been reported in patients with lymphatic leukemia treated with ampicillin.¹⁹

One large study has shown at least a threefold increase in incidence of ampicillin rash in patients taking allopurinol.²⁰

Etiology

The etiology of the maculopapular ampicillin rash is unknown. There is strong evidence against any allergic basis for the maculopapular skin rash resulting from administration of ampicillin.⁵⁻¹¹ Bierman and his associates, for example, studied 30 cases of patients who developed a maculopapular ampicillin rash and found no positive skin tests when tested with benzylpenicillin G, sodium penicilloate, penicilloyl-polylysine (PPL), and ampicillin. They also found no other allergic manifestations in these patients.⁸ Skin biopsy and eosinophil counts were conducted on 61 patients with maculopapular ampicillin rash in the large prospective study in England mentioned earlier.⁷ Biopsy of all of these rashes showed perivascular and perifollicular aggregates of mononuclear cells, especially lymphocytes, in the dermis, and blood eosinophil counts were normal.

Two studies have demonstrated a significant reduction in the incidence of ampicillin rash in patients receiving purified ampicillin free of protein impurities, suggesting that the rash may be due to protein impurities in the ampicillin.^{21,22}

There is some evidence suggesting that the maculopapular ampicillin rash is dose related.²³ In a study of 78 patients with pneumonia treated with 1 gm of ampicillin daily, four percent of patients developed skin rashes.²⁴ In another group of 80 patients treated with up to 3 gm of ampicillin daily, seven percent of patients developed skin rashes.²⁵

In a third study of 80 patients with paratyphoid fever treated with 4 to 6 gm of ampicillin daily, 22 percent developed skin rashes.²⁶

Diagnosis

The typical nonallergic maculopapular ampicillin rash usually appears on the trunk and spreads peripherally, or may often appear first on the extensor aspects of the limbs. This rash occurs after four or more days (usually seven to ten days) of ampicillin therapy, does not become worse when ampicillin is continued, and generally disappears spontaneously after three to five days whether or not ampicillin is continued.^{5,7,11} The typical rash is most abundant on the trunk, and is usually only slightly pruritic. The mucous membranes, palms, and soles are not affected. No urticaria or systemic symptoms are associated with this rash.

In view of the importance of making a correct diagnosis of a skin rash developing during ampicillin therapy, the patient should be seen, and a careful history and physical examination taken. The features of the rash should be recorded in the patient's chart. An unqualified diagnosis of "ampicillin rash" is inadequate.

Management

As made explicit by the preceding discussion, the important point in management of the ampicillin rash is to differentiate the benign maculopapular rash from urticaria and other potentially allergic skin reactions. Once this is accomplished, no specific treatment is required for the maculopapular rash, and the course of ampicillin therapy can be completed.^{5,7,9-11} Just as it is essential to exercise appropriate caution in the event of a potentially allergic skin reaction to ampicillin, so it is important to avoid labeling the patient incorrectly as "Allergic to Ampicillin/Penicillin."

In the event of an urticarial or other potentially allergic type of ampicillin rash, the drug should be discontinued and the patient considered a likely candidate for ampicillin/penicillin allergy. Further administration of any penicillin should be avoided unless penicillin sensitivity can be disproved.⁵

Skin tests are not ordinarily recommended or useful as a means to confirm the absence of an allergic basis for the maculopapular ampicillin rash.²⁷ The most effective and practical way to confirm the benign nature of this rash is to observe and document the spontaneous disappearance of the rash while ampicillin therapy is continued. Skin testing may be of some value in assessing risk of ampicillin/penicillin allergy in patients who have recently experienced an urticarial reaction while taking a number of sensitizing drugs, including ampicillin or penicillin.²⁷

Implications of Incorrect Label of Ampicillin Allergy

In view of the frequency of use of ampicillin in everyday clinical practice and the incidence of the benign maculopapular rash developing during treatment, misdiagnosis of this rash as allergic can inappropriately label large numbers of patients as allergic to ampicillin and all penicillins. Such an outcome prevents all future use of an important, potentially lifesaving drug, and raises the problem of selection of alternative antibiotic regimens for common infectious diseases. In the treatment of otitis media in children less than five years of age, for example, erythromycin and a sulfonamide become a recommended alternative approach to therapy²⁸ (erythromycin alone is not effective against *Hemophilus influenzae*)²⁹; the cost to the pharmacist of this combination of drugs is almost four times that of the more effective ampicillin³⁰ and complicates the drug regimen which may lead to decreased medication compliance.

Attention to the essential details which have been described concerning the history and physical examination of patients developing a skin rash during ampicillin therapy can prevent these avoidable sequelae and at the same time protect the patient from the risks of allergic drug reactions.

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