Original Article

"Treating Through" Decision and Follow-up in Antibiotic Therapy-Associated Exanthemas

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What is already known about this topic? Replacement of the offending drug is considered standard medical care in acute exanthematous skin reactions. This is straightforward in uncomplicated clinical situations, but may be a problem if no equivalent alternatives are available.

What does this article add to our knowledge? Continued administration of suspected antibiotic(s) despite an exanthema may enable effective treatment of severe bacterial soft tissue infections (severe cellulitis). "Treating through" does not necessarily lead to a progression of the skin lesions.

How does this study impact current management guidelines? "Treating through" is an option for carefully selected patients experiencing maculopapular exanthema during antibiotic therapy. Thereby, close monitoring of clinical and laboratory findings is mandatory.

BACKGROUND: Immediate discontinuation or replacement of suspected drugs is considered standard medical care in acute exanthematous skin reactions. In the treatment of bacterial infections, structurally different alternative antibiotics, however, are commonly second choice options due to a suboptimal antimicrobial activity or an unfavorable side effect profile. Nonetheless, "treating through," the continuation of antibiotic treatment despite an objective exanthema, is practiced only rarely.

OBJECTIVE: We aimed to assess whether "treating through" is an option for patients with severe bacterial soft tissue infections (severe cellulitis) who experience maculopapular exanthema (MPE) during antibiotic therapy.

METHODS: We retrospectively reviewed clinical data from 18 patients who developed MPE within a few days after initiation of intravenous antibiotic treatment. A decision to "treat through" was made when the suspected antibiotics (β-lactams, clindamycin, ciprofloxacin) were clinically effective and the benefits of continued treatment outweighed potential risks. Clinical and laboratory findings were closely monitored in an inpatient setting.

RESULTS: In 2 patients, a modification of antibiotic therapy was deemed necessary due to a significant increase of liver enzymes within 4 days after the initial decision to "treat through." Because of a progression of MPE under ongoing treatment with cefuroxime and clindamycin, clindamycin was discontinued in 1 patient. In another 3 patients, antibiotic treatment was modified because of insufficient improvement of the soft tissue infection. In the remaining 12 "treated through" cases, the skin symptoms improved despite unchanged continued antibiotic treatment, and relevant laboratory parameters remained within the normal range.

CONCLUSIONS: Careful risk-benefit assessment may enable the continuation of antibiotic therapy despite MPE, provided that patients are under close medical observation. © **2017 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2017;■:■-■)**

Key words: *Desensitization; Drug reaction; Adverse drug reaction; Allergy; Hypersensitivity; Rash; Rechallenge*

Maculopapular exanthema (MPE) is both the most common and the most obvious clinical manifestation of nonimmediate allergic antibiotic hypersensitivity.[1,2] The discontinuation of suspicious antibiotics and treatment with alternative structurally different drugs are straightforward in uncomplicated clinical situations, for example, in amoxicillin-associated MPE during the treatment of a respiratory tract infection. In more complex and more serious bacterial infections, however, the benefit of unaltered continuation of an effective antibiotic regimen needs to be weighed against the risk of exanthema progression.

In patients with antibiotic therapy-associated MPE, a number of individual considerations should precede the decision to "treat through."[3,4] First, a serious bacterial infection has clinically improved under the initial antibiotic treatment. Second, structurally different alternative antibiotics are likely to have a suboptimal antimicrobial activity or unfavorable side effects. Third, close monitoring of clinical findings and laboratory parameters is

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Abbreviations used
DIHS- Drug-induced hypersensitivity syndrome
MPE- Maculopapular exanthema

warranted, which is generally guaranteed in an inpatient setting. Fourth, and most importantly, an unequivocal diagnosis of uncomplicated MPE has been made. It is not sufficient to diagnose a rash. Every effort should be made to differentiate MPE from other, more serious types of delayed cutaneous drug reactions by thorough clinical and laboratory investigations (Table I).[5]

In this article, we describe an algorithm to decide between the discontinuation of antibiotic therapy and "treating through" in inpatients with soft tissue infections and MPE during antibiotic therapy. Clinical and laboratory follow-up investigations under ongoing antibiotic treatment were evaluated.

PATIENTS AND METHODS

Patients

We retrospectively evaluated medical records of 18 patients treated during the time period from July 2014 until July 2016. Inclusion criteria were inpatient antibiotic therapy for bacterial soft tissue infections (severe cellulitis), the occurrence of MPE within a few days after the initiation of treatment, and the intention to "treat through." The institutional review board of the University Hospital Würzburg consented to the retrospective review and publication of anonymized clinical data.

Diagnosis of antibiotic therapy-associated exanthema

In all patients, exanthematous lesions and latency time between the initiation of antibiotic treatment and the onset of skin symptoms were compatible with delayed allergic hypersensitivity reactions. The extent of MPE was semiquantitatively graded as mild (<25% body surface area), moderate (25% to 50%), or severe (>50%). For the classification of the cutaneous reaction as uncomplicated MPE, both clinical and laboratory parameters were used (Table I). All patients had classical MPE without mucosal involvement. Liver and kidney function parameters were evaluated by routine laboratory testing. Because of severe bacterial infections, leukocytosis and an elevated C-reactive protein were detected in most patients. As a consequence, these criteria of potentially severe drug reactions could not be taken into account.[6,7]

Decision to "treat through"

The decision to "treat through" was made by the authors in their function as senior hospital physicians in charge (SB, MG, and JS) or consulting allergist (AT). First, continuation of the incriminated antibiotics was deemed necessary because of their clinical effectiveness and a more favorable side effect profile compared with structurally different alternatives. Second, an unequivocal diagnosis of MPE was made by exclusion of any clinical and laboratory "danger signs" indicating a potentially severe drug reaction (Table I). In every individual case, the benefit of continued antibiotic therapy was considered to outweigh potential risks (Figure 1). After thorough information and consideration of advantages and disadvantages, patients and relatives gave their approval to "treat through."

Follow-up while "treating through"

Close and careful monitoring of patients was ensured in the inpatient setting. In addition to cutaneous and overall clinical symptoms, liver and kidney function parameters were regularly evaluated during follow-up. The frequency of laboratory testing in this retrospective study varied considerably from daily to every fourth day, depending on the whole clinical situation and whether elevated values were measured. MPE was invariably treated with topical preparations containing either 0.05% clobetasol propionate, or 0.1% betamethasone valerate. Various H_1-antihistamines (eg, desloratadine, cetirizine, clemastine, dimetindene) were given for symptomatic relief of pruritus. At hospital discharge, patients' skin condition was classified as "improved" if MPE was still visible and as "minimal residues" if only residual desquamation was detectable; "healed" means that MPE has completely resolved.

RESULTS

Patients

All 18 patients had severe bacterial soft tissue infections of the legs (severe cellulitis) necessitating intravenous antibiotic treatment in an inpatient setting. Details of the patients' age and gender, laboratory results on hospital admission, and the antibiotic therapy are listed in Table II. At the time of hospitalization, elevated serum creatinine levels were recorded in 11 patients. This was attributed to a combined effect of fever/infection and dehydration in 6 cases. Five patients had a history of chronic renal insufficiency. Seven patients presented with an elevated γ-glutamyltransferase (γGT) on admission, which was considered to result from alcohol-induced liver damage or biliary tract disease. Viral hepatitis was ruled out serologically.

Antibiotic therapy-associated exanthema

The latency time between initiation of antibiotic therapy and the onset of MPE ranged from 2 days (patient 8) to a maximum of 10 days (patient 7). In 11 of the 18 patients, it was more than 5 days (Table II). The extent of MPE was classified as mild to moderate in 13 patients, and as severe in 5. None of the patients had a conclusive history of preexisting antibiotic allergy. Inquiries concerning the previous administration of antibiotics were either unsuccessful or of no relevance.

Follow-up while "treating through"

Within 4 days after the decision to "treat through," 2 patients (patients 3 and 11) had a significant increase of liver enzymes (Table II). As a consequence, cefuroxime and clindamycin were replaced by meropenem in patient 3, and cefuroxime was stopped without substitution in patient 11. We decided to discontinue clindamycin despite normal liver parameters in patient 12 because a considerable improvement of the soft tissue infection was paralleled by a temporary worsening of MPE. The decision to "treat through" has thus been revised in 3 cases (patients 3, 11, and 12), twice due to an increase of liver enzymes, once because of progressive MPE.

In spite of "treating through," a steady regression of MPE was observed in all other patients. In 5 cases (patients 2, 4, 10, 13, and 15), a mild increase of liver enzymes returned to normal under continued antibiotic therapy (Table II). A preexisting elevation of γGT and/or creatinine values was considered unrelated to the current clinical situation in patients 13, 14, 16, 17, and 18. In patients 13, 15, and 17, the decision to modify the initial antibiotic treatment was unrelated to the MPE, but was triggered by an insufficient improvement of the soft tissue infection. On the day of discharge, 8 patients were completely free of cutaneous symptoms, 7 had only minimal residues of