

# “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 ( $\beta$ -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;5:1650-6)

**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.<sup>1,2</sup> 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.”<sup>3,4</sup> 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).<sup>5</sup>

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.<sup>6,7</sup>

### 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<sub>1</sub>-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  $\gamma$ -glutamyltransferase ( $\gamma$ GT) 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  $\gamma$ GT 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

**TABLE I.** Classification and “danger signs” of delayed cutaneous drug reactions

|                                                    |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
|----------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Classification of delayed cutaneous drug reactions | <ol style="list-style-type: none"> <li>1. Uncomplicated maculopapular exanthema</li> <li>2. Morphological variants of cutaneous drug reactions: <ul style="list-style-type: none"> <li>Flexural exanthema (symmetrical drug-related intertriginous and flexural exanthema)</li> <li>Pustular exanthema (acute generalized exanthematous pustulosis)</li> <li>Fixed drug eruption</li> </ul> </li> <li>3. Drug-induced hypersensitivity syndrome</li> <li>4. Severe bullous skin reactions: Stevenson-Johnson syndrome, toxic epidermal necrolysis</li> </ol> |
| Clinical “danger signs”                            | <ul style="list-style-type: none"> <li>Intense facial involvement</li> <li>Atypical target or bullous lesions</li> <li>Widespread, dark-red erythema</li> <li>Extensive pustulosis</li> <li>Painful skin</li> <li>Mucosal involvement</li> <li>Generalized lymphadenopathy</li> </ul>                                                                                                                                                                                                                                                                        |
| Laboratory “danger signs”                          | <ul style="list-style-type: none"> <li>Hepatopathy: elevated liver enzymes</li> <li>Nephropathy: impaired renal function tests</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                    |

Clinical and laboratory “danger signs” are indicative of severe cutaneous drug reactions, that is, drug-induced hypersensitivity syndrome, Stevenson-Johnson syndrome, and toxic epidermal necrolysis.

MPE, and the skin condition had significantly improved in the remaining 3. All these outcomes were seen in the 6 patients who underwent a modification of antibiotic therapy. Patients 3, 13, 15, and 17 were free of skin symptoms, patient 11 had minor residues, and MPE had at least improved in patient 12.

## DISCUSSION

We herein present a case series of 18 patients with severe bacterial soft tissue infections (severe cellulitis) who developed MPE within a few days after initiation of intravenous antibiotic treatment. A decision to “treat through,” that is unchanged continuation of the antibiotic therapy despite the occurrence of MPE, was made for all patients. “Treating through,” however, had to be revised in 3 patients because of an increase of liver

enzymes ( $n = 2$ ), or because of clinical progression of MPE ( $n = 1$ ). In another 3 patients, it was deemed necessary to modify the initial antibiotic treatment because of insufficient improvement of the soft tissue infection. Therefore, “treating through” was successfully completed in 12 patients, meaning that a steady regression of skin symptoms was observed under continued antibiotic treatment, and no liver or kidney involvement occurred.

The immediate discontinuation of suspicious drugs is and remains a medical standard in patients experiencing exanthematous skin reactions during antibiotic treatment. In selected cases, however, that is whenever the benefits of a continued administration of the antibiotic outweigh the risks, “treating through” is an option worth to be considered. This is in accordance with observations from a limited number of studies and case series

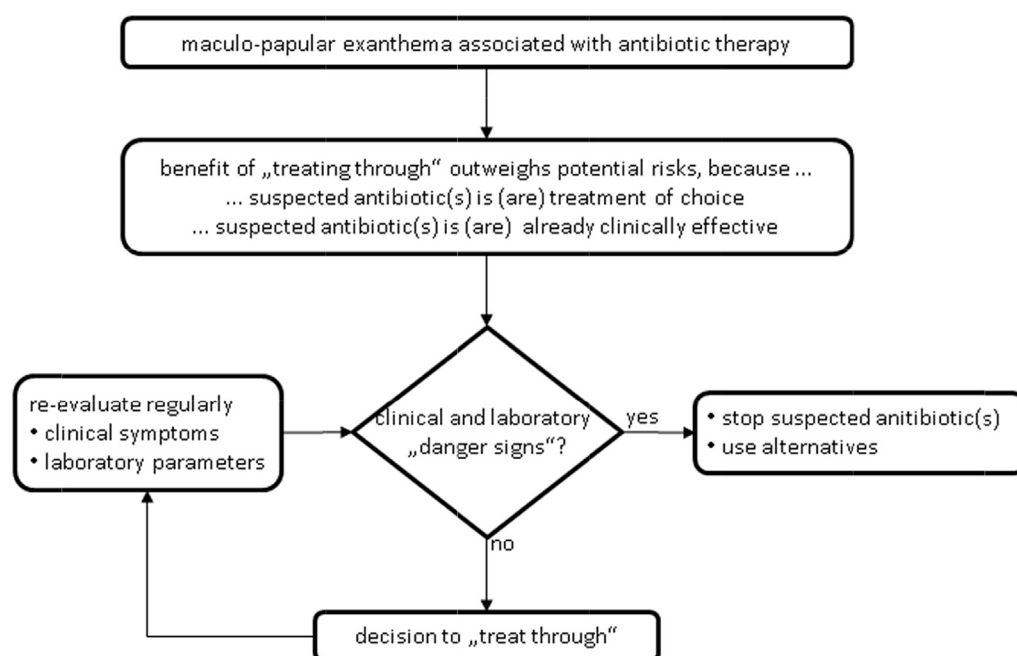
**FIGURE 1.** Decision algorithm for “treating through” in antibiotic therapy-associated maculopapular exanthema.

**TABLE II.** Clinical details and laboratory findings of 18 patients on admission and while “treating through”

| Patient no.,<br>age (y), sex | Lab results on<br>admission*                              | First-line antibiotic<br>therapy | Onset of<br>MPE | MPE<br>grading | Follow-up lab<br>results*                                 | Discontinuation<br>of antibiotics    | Alternative<br>antibiotics | MPE at discharge             |
|------------------------------|-----------------------------------------------------------|----------------------------------|-----------------|----------------|-----------------------------------------------------------|--------------------------------------|----------------------------|------------------------------|
| 1, 62, f                     | June 13<br>GPT 29.0<br>γGT 28.5<br>Crea 1.37<br>CRP 27.90 | Cefuroxime<br>Clindamycin        | June 22         | 2              | June 26<br>GPT 26.5<br>γGT 26.9<br>Crea 0.88<br>CRP 0.70  | No                                   | No                         | June 28<br>Minimal residues  |
| 2, 64, f                     | June 5<br>GPT 26.0<br>γGT 21.1<br>Crea 1.67<br>CRP 32.40  | Cefuroxime<br>Clindamycin        | June 8          | 1              | June 11<br>GPT 59.0<br>γGT 25.8<br>Crea 0.97<br>CRP 0.74  | No                                   | No                         | June 13<br>Healed            |
| 3, 76, m                     | Nov. 11<br>GPT 46.0<br>γGT 79.0<br>Crea 1.45<br>CRP 13.25 | Cefuroxime<br>Clindamycin        | Nov. 20         | 2              | Nov. 24<br>GPT 64.2<br>γGT 604.5<br>Crea 1.16<br>CRP 2.05 | Nov. 24<br>Cefuroxime<br>Clindamycin | Nov. 24<br>Meropenem       | Dec. 1<br>Healed             |
| 4, 51, m                     | Nov. 18<br>GPT 46.6<br>γGT 35.3<br>Crea 1.00<br>CRP 3.67  | Benzyl penicillin<br>Clindamycin | Nov. 25         | 2              | Nov. 29<br>GPT 67.5<br>γGT 34.3<br>Crea 1.10<br>CRP 0.62  | No                                   | No                         | Nov. 30<br>Minimal residues  |
| 5, 86, f                     | April 4<br>GPT 17.3<br>γGT 16.7<br>Crea 0.80<br>CRP 5.67  | Cefuroxime<br>Clindamycin        | April 12        | 2              | April 16<br>GPT 25.0<br>γGT 25.0<br>Crea 0.70<br>CRP 1.63 | No                                   | No                         | April 18<br>Minimal residues |
| 6, 46, f                     | Nov. 10<br>GPT 13.0<br>γGT 12.0<br>Crea 0.68<br>CRP 5.56  | Cefuroxime<br>Clindamycin        | Nov. 17         | 3              | Nov. 19<br>GPT 33.0<br>γGT 12.0<br>Crea 0.70<br>CRP 0.17  | No                                   | No                         | Nov. 22<br>Improved          |
| 7, 83, m                     | March 8<br>GPT 9.0<br>γGT 33.0<br>Crea 0.82<br>CRP 25.88  | Benzyl penicillin<br>Clindamycin | March 18        | 2              | March 20<br>GPT 11.7<br>γGT 45.6<br>Crea 0.76<br>CRP 5.34 | No                                   | No                         | March 25<br>Healed           |
| 8, 57, f                     | June 14<br>GPT 15.3<br>γGT 23.5<br>Crea 0.53<br>CRP 5.21  | Cefuroxime<br>Clindamycin        | June 16         | 1              | June 21<br>GPT 18.0<br>γGT 17.6<br>Crea 0.48<br>CRP 0.55  | No                                   | No                         | June 24<br>Healed            |
| 9, 32, m                     | Feb. 20<br>GPT 47.4<br>γGT 43.4<br>Crea 0.83<br>CRP 14.02 | Cefuroxime<br>Clindamycin        | Feb. 24         | 3              | Feb. 28<br>GPT 38.0<br>γGT 36.3<br>Crea 0.82<br>CRP 1.21  | No                                   | No                         | March 3<br>Improved          |
| 10, 64, m                    | Sept. 2<br>GPT 38.0<br>γGT 41.0<br>Crea 1.45<br>CRP 20.83 | Cefuroxime<br>Clindamycin        | Sept. 8         | 3              | Sept. 10<br>GPT 52.5<br>γGT 57.7<br>Crea 1.08<br>CRP 3.03 | No                                   | No                         | Sept. 17<br>Minimal residues |
| 11, 61, m                    | July 24<br>GPT 40.0<br>γGT 288.1<br>Crea 1.66<br>CRP 2.85 | Cefuroxime<br>Clindamycin        | July 30         | 3              | Aug. 3<br>GPT 137.7<br>γGT 666.3<br>Crea 1.29<br>CRP 0.19 | Aug. 3<br>Cefuroxime                 | No                         | Aug. 5<br>Minimal residues   |
| 12, 93, m                    | June 25<br>GPT 33.0<br>γGT 16.9<br>Crea 1.84<br>CRP 12.99 | Cefuroxime<br>Clindamycin        | June 29         | 3              | July 3<br>GPT 15.5<br>γGT 33.0<br>Crea 1.14<br>CRP 2.55   | July 2<br>Clindamycin                | No                         | July 10<br>Improved          |

(continued)

TABLE II. (Continued)

| Patient no.,<br>age (y), sex | Lab results on<br>admission*                               | First-line antibiotic<br>therapy | Onset of<br>MPE | MPE<br>grading | Follow-up lab<br>results*                                 | Discontinuation<br>of antibiotics | Alternative<br>antibiotics | MPE at discharge            |
|------------------------------|------------------------------------------------------------|----------------------------------|-----------------|----------------|-----------------------------------------------------------|-----------------------------------|----------------------------|-----------------------------|
| 13, 72, f                    | Nov. 11<br>GPT 24.0<br>γGT 90.2<br>Crea 2.59<br>CRP 4.22   | Clindamycin<br>Ciprofloxacin     | Nov. 20         | 2              | Nov. 24<br>GPT 30.0<br>γGT 115.7<br>Crea 2.50<br>CRP 3.74 | Nov. 21†<br>Clindamycin           | Nov. 21†<br>Ceftazidime    | Nov. 25<br>Healed           |
| 14, 75, m                    | Nov. 17<br>GPT 6.2<br>γGT 160.9<br>Crea 3.83<br>CRP 19.54  | Cefuroxime<br>Clindamycin        | Nov. 22         | 2              | Nov. 25<br>GPT 6.2<br>γGT 143.7<br>Crea 2.73<br>CRP 5.61  | No                                | No                         | Nov. 27<br>Minimal residues |
| 15, 62, f                    | Nov. 26<br>GPT 14.7<br>γGT 30.9<br>Crea 1.15<br>CRP 16.30  | Benzyl penicillin<br>Clindamycin | Nov. 29         | 2              | Dec. 8<br>GPT 13.0<br>γGT 64.7<br>Crea 0.94<br>CRP 8.27   | Nov. 29†<br>Benzyl penicillin     | Nov. 29†<br>Meropenem      | Dec. 16<br>Healed           |
| 16, 80, m                    | Feb. 2<br>GPT 27.0<br>γGT 151.9<br>Crea 1.51<br>CRP 2.41   | Cefuroxime<br>Clindamycin        | Feb. 9          | 2              | Feb. 12<br>GPT 23.3<br>γGT 135.4<br>Crea 1.35<br>CRP 1.54 | No                                | No                         | Feb. 17<br>Healed           |
| 17, 75, f                    | April 4<br>GPT 15.6<br>γGT 75.1<br>Crea 1.00<br>CRP 12.27  | Cefuroxime<br>Clindamycin        | April 12        | 1              | April 18<br>GPT 12.1<br>γGT 64.4<br>Crea 0.84<br>CRP 3.89 | April 15†<br>Cefuroxime           | April 15†<br>Meropenem     | April 25<br>Healed          |
| 18, 58, m                    | June 12<br>GPT 22.0<br>γGT 103.9<br>Crea 0.95<br>CRP 13.57 | Cefuroxime<br>Clindamycin        | June 17         | 1              | June 21<br>GPT 24.2<br>γGT 81.6<br>Crea 0.75<br>CRP 1.83  | No                                | No                         | June 24<br>Minimal residues |

Crea, Creatinine; CRP, C-reactive protein; γGT, γ-glutamyltransferase; GPT, glutamate-pyruvate transaminase; MPE, maculopapular exanthema.

\*Reference values: GPT male ≤50 U/L, female ≤35 U/L; γGT female ≤40 U/L, male ≤60 U/L; creatinine male ≤1.17 mg/dL, female ≤0.95 mg/dL; CRP ≤0.5 mg/dL.

†In patients 13, 15, and 17, modification of the initial antibiotic treatment was unrelated to MPE, but was caused by an insufficient improvement of the soft tissue infection.

stating that the reintroduction of a suspicious drug after an episode of MPE does not necessarily lead to a recurrence of the initial skin reaction, even if an allergic drug hypersensitivity reaction has been diagnosed or suspected. Trimethoprim-sulfamethoxazole (cotrimoxazole), for example, is a highly effective drug for the treatment and prophylaxis of *Pneumocystis jirovecii* infections in HIV-infected patients that is exceedingly hard to replace. At the same time, it is a common elicitor of drug hypersensitivity reactions. As a consequence, there are several studies describing protocols for desensitization or simple rechallenge. In a meta-analysis of 3 relatively small randomized trials, a desensitization protocol was compared with straightforward rechallenge in patients with suspected cotrimoxazole hypersensitivity.<sup>3</sup> In 2 of these studies, mild recurrences of exanthematous skin eruptions were described, but no severe symptoms were observed in any of the total 268 patients.<sup>8-10</sup> In the treatment of tuberculosis, there are virtually no alternatives to the first choice drugs, that is, isoniazid, rifampicin, ethambutol, and pyrazinamide. In a series of 11 patients, 23 of 25 cycles of sequential desensitization and rechallenge were completed without any serious symptoms.<sup>4</sup> There are a very small number of case reports describing strategies of “treating through” or rechallenge for suspected allergic hypersensitivity reactions associated with thalidomide, lamotrigine, or prasugrel.<sup>11-13</sup> On the

other hand, there are ample data confirming the benefits of “treating through” for exanthemas of nonallergic origin that are a common side effect of antitumor treatment with tyrosine kinase inhibitors. As acneiform rash was found to predict increased survival rates, “treating through” strategies have been incorporated in international guideline recommendations on the management of adverse events from epidermal growth factor receptor tyrosine kinase inhibitors.<sup>14</sup> Similar recommendations have been made for patients treated with the BRAF inhibitor vemurafenib.<sup>15</sup> However, the cutaneous adverse reactions of these biologics probably reflect pharmacological antitumor effectiveness rather than allergic drug hypersensitivity.

Within the morphologically and clinically heterogeneous spectrum of delayed cutaneous drug hypersensitivity reactions, 4 main groups can be differentiated (Table I): uncomplicated MPE, morphological variants of cutaneous drug reactions, drug-induced hypersensitivity syndrome (DIHS), and severe bullous skin reactions.<sup>16</sup> Whenever “treating through” is considered, every effort should be made to rule out the differential diagnoses of DIHS and generalized bullous skin reactions as both may take a severe or even life-threatening course and therefore require immediate discontinuation of the culprit drug. The diagnosis of DIHS is based on a protracted course with severe hepatic and renal involvement,<sup>17-19</sup> whereas cutaneous symptoms may range

from a mild MPE to severe pustular exanthema. We recently described a patient with morphologically typical MPE who subsequently developed acute renal failure due to DIHS.<sup>20</sup> On cessation of all suspected antibiotics and under therapy with high-dose steroids for 6 weeks, his renal function slowly returned to normal. We conclude that regular laboratory controls are essential while “treating through” even in clinically unsuspected MPE as it may turn out to be a “wolf in sheep’s clothing.” Accordingly, 2 patients of our series developed a relevant increase of liver enzymes during follow-up investigation. Moreover, it is important to bear in mind that severe bullous skin reactions may likewise resemble MPE in a very early stage.<sup>21</sup>

In view of our observation of a relatively benign course of antibiotic-associated MPE despite “treating through,” the question of causality needs to be addressed. First, it is highly unlikely that we have efficiently suppressed a persistence or progression of MPE by H<sub>1</sub>-antihistamines and topical steroids alone. Second, we might have induced a temporary desensitization or short-time tolerance towards immune-mediated hypersensitivity reactions by the continued administration of the culprit drug.<sup>22,23</sup> Third, the temporal relation between administration of one or several antibiotics and the onset of MPE is not necessarily indicative of a causal relationship. In other words, it remains unclear whether MPE was really caused by the suspected antibiotics and whether or not it was the result of a delayed-type immune-mediated hypersensitivity reaction. The most important differential diagnosis of drug-induced MPE is viral exanthema that was considered unlikely in our patients because of the whole clinical context. However, in severe bacterial infections, circulating immune complexes consisting of antibodies and bacterial antigens deposited in dermal capillary loops might possibly cause MPE. The hypothesis of a nonallergic cause of MPE during antibiotic therapy is supported by the observation that allergic drug hypersensitivity, though commonly suspected, is rarely confirmed by subsequent allergy testing.<sup>2,24,25</sup>

Whether and to which extent our experiences from “treating through” in patients with soft tissue infections and antibiotic-associated MPE can be extrapolated to other clinical situations, different drugs, or drug classes, remains open to speculation. For example, “treating through” may be an important, if not the only option for critically ill, septic patients in an intensive care setting with the culprit drug being both vital and difficult to identify because of multiple medications. In contrast, “treating through” should be avoided if any of the common triggers of DIHS or severe bullous skin reactions are suspected as the cause of MPE, for example, sulfonamide antibiotics, dapsone, the anticonvulsants carbamazepine and phenytoin, and allopurinol.

“Treating through,” the continued administration of a drug despite a suspected allergic hypersensitivity reaction, is a risky procedure. It may, however, be considered in selected patients whenever the benefits are likely to outweigh the risks. Three questions should be considered in the decision process. First, are the suspicious drugs commonly associated with DIHS or severe bullous skin reactions (such as anticonvulsants, dapsone, sulfonamide antibiotics, or allopurinol)? Second, is the suspected drug the treatment of choice for this patient? Third, can an unequivocal diagnosis of uncomplicated MPE be established because of the absence of clinical and laboratory “danger signs”? Once the decision to “treat through” is made, close monitoring comprising both the clinical re-evaluation of skin and mucous

membranes and regular controls of liver enzymes and renal function parameters is essential.

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